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**Editor's Choice**

Optimized formulation of Mallotus oppositifolius extract reverses cognitive decline and beta amyloid deposition in a murine Alzheimer's disease-like dementia model kkekukuia@ug.edu.gh
Pewee et al., 2025. Pages 1102 - 1113
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**About the cover portrait**

The painting, Odikro's Wife, draws inspiration from Ghanaian tradition, where the Odikro, a title bestowed upon a chief in the Ashanti region, serves as the custodian of law and order. The Odikro is often perceived as the ultimate authority, embodying the essence of leadership and ownership within the village.

# Summary Author Information

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# Contents


## Editorial



## Commentary



## Original Research Articles

## Review Article



## Feature Article



## Clinical Image



## Medical Case Report

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The HSI Journal Logo

The Logo is an *Adinkra* symbol rendered in the Akan language as ***Nea onnim no sua a, ohu***. It is loosely translated into English as "the one who does not know but learns, gets to know."

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# Editorial

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## Welcome message from the Editor-in-chief

Professor Andrew Anthony Adjei
Email: hsijournal@ug.edu.gh

It is with much pleasure that I welcome you to Volume 7 Issue 1 of the Health Sciences Investigations Journal (HSI Journal). The Journal remains committed to reaching the global community with open-access publications from basic and clinical health sciences. HSI Journal therefore places a high premium on the quality of research articles published and the impact of outcomes on health (complete physical, mental and social well-being) and thus consistently provides an avenue for communication of research findings in health, the science of well-being. During the 2023-2024 calendar year, HSI Journal experienced a substantial increase in manuscripts submitted for consideration in publishing and a corresponding rise in requests for indexing from Medical and Health-related Websites. As I reflect on the HSI Journal's accomplishments in 2024, I am encouraged by the fortitude, passion, dedication and commitment of our Editors, Editorial and Administrative Teams who persevered through economic times for the University of Ghana and The College of Health Sciences. The current issue of the HSI Journal we have featured 22 manuscripts, comprising 20 original articles, and two case-control studies. The substantial increase in the number of articles published in this issue indicates the level of visibility attained and acceptance of the HSI Journal by the scientific and clinical communities. The current issue of the Journal contains a case study on the atypical intestinal serosal granulomatous lesions of Schistosoma haematobium and Schistosoma mansoni coinfection presenting in a surgical unit in an obstructed hernia. The intraoperative findings pose a clinical dilemma and difficult management decision. This presentation of extensive serosal and omental granulomatous lesions is uncommon. This is a rare condition that surgeons must know in cases of parasitic infestations with schistosomiasis. In this issue, we also present a case of unilateral fused kidney (inferior ectopia). The incidence is said to be 1 in 2000 births and more common in males compared to females. A left-to-right positioning is about three times more common compared to right-to-left. This case of a right-to-left is therefore rarer, and clinically most cases present in the paediatric age group. There is also an interesting article on lessons for future pandemics following the recent COVID-19 episode. The COVID-19 pandemic had overwhelming effects on global health, with a complex interaction between socioeconomic factors and mental health outcomes. The pandemic introduced new stressors, including economic instability, job loss, and social isolation, disproportionately affecting vulnerable populations. Future pandemic preparedness therefore depends on successful interventions that incorporate socioeconomic policy with mental health considerations. This paper indicated that addressing these socioeconomic determinants is essential for improving mental health and resilience after the pandemic. I am grateful to the hardworking Editorial Team, the Reviewers and the Proofreaders for their effort in ensuring that the Journal publishes good articles for our cherished readers. The Advisory Board, Authors and Publishers are also acknowledged for their contributions. I welcome suggestions, complaints, discussions, and thoughts from authors and readers to help us maintain high standards. I look forward to receiving your high-quality manuscripts for publication.

Adjei et al., 2025. https://doi.org/10.46829/hsijournal.2025.6.7.1.1036-1037


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About the Editor-in-chief

Professor Andrew Anthony Adjei is a Professor of Immunology with over thirty years of biomedical and allied health sciences training and research experience. He is a Fellow of the following: Ghana Academy of Arts and Sciences (FGA), African Academy of Sciences (AAS), Ghana Association of Medical Laboratory Scientists (GAMLS) and African Sciences Institute (ASI). Professor Adjei has been Head of Department, University of Ghana (UG) School of Biomedical and Allied Health Sciences, Deputy Provost, College of Health Sciences (CHS), Director of Research, Innovation and Development (UG), Acting Director, Institutional Research and Planning Office (UG), Coordinator of Research, University of Ghana Medical School (UGMS), Editor-in-Chief, Ghana Journal of Allied Health Sciences, President of Ghana Association of Medical Laboratory Scientists, Project Coordinator, Transdisciplinary Training for Resource Efficiency and Climate Change Adaptation in Africa, Project Coordinator, Building Stronger Universities (Partnership between UG and Universities in Denmark), Project Coordinator, Fogarty Global Health Fellows Training Programme (Partnership between UGMS and University of Morehouse School of Medicine, Atlanta, Georgia, USA), and Project Coordinator, Minority in Health Research Training (Partnership between UGMS and University of Morehouse School of Medicine). Professor Adjei was the immediate past Coordinator of the Worldwide Universities Network and the Australia-Africa Universities Network. Currently, he is the Chairman of the following: Ethics and Protocol Review Committee, CHS Public Lecture Series and Scientific Conference Planning Committee, CHS Newsletter (In Focus), CHS Library Refurbishment Committee, Member of Korle Bu Teaching Hospital Institutional Review Board and the Coordinator, MPhil Programme in Immunology, at the Department of Pathology, UGMS. Professor Adjei is a reviewer of several clinical and biomedical Journals globally. He has served on various UGMS and UG committees and currently serves on both the UG and CHS Academic Boards.

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# HSI Journal Celebrate CHS @ 25

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***UG-CHS 25th Anniversary logo: Transforming lives through excellence in education, research and healthcare.***

The College of Health Sciences (CHS) at the University of Ghana (UG), which hosts and funds the Health Sciences Investigations Journal marks 25 years of impactful contributions to health education, research, and service in Ghana and beyond. Established in 1999, UG-CHS brought together the University's health-related schools, institutes, and centres to promote interdisciplinary collaboration and drive innovation in health sciences training and research. Over the past two and a half decades, UG-CHS has become a hub of academic excellence, nurturing generations of medical, dental, nursing, pharmacy, and allied health professionals. Its institutions - including the University of Ghana Medical School, University of Ghana Dental School, School of Pharmacy, School of Nursing and Midwifery, and Noguchi Memorial Institute for Medical Research - have made significant strides in training world-class professionals and conducting cutting-edge research that addresses national and global health challenges. As it celebrates this milestone, the College reflects on its achievements and renews its commitment to shaping the future of health care through innovation, impactful research, and high-quality education. The 25th anniversary is not only a celebration of legacy but also a call to further excellence and collaboration in advancing health outcomes across Africa.

The ode, *Echoes of the Past, Seeds of the Future*, chronicles the journey of the College and commerates its 25th anniversary

**Echoes of the Past, Seeds of the Future: A History of Healing at Legon**

From the annals of time, a vision took hold, Sir Gordon Guggisberg, and a story unfolded. Nineteen twenty-three, the whispers began, A proposal for healing, a bold, forward plan. Korle Bu's foundation, a teaching so grand, the seeds of a college, sown in the land. Medical education began in the land of Ghana in 1984. Farquhar and Dr. Richard Cross, with a purpose so true, secured vital funding for dreams to break through. Nineteen sixty-five, a landmark we see, The University of Ghana, embraced destiny. Fifty-one students, a pioneering start, Home-grown physicians, playing a crucial part.

Challenges emerged, like shadows so deep, Economic downturn, and the progress to keep. Staffing shortages, resources so lean, but resilience and aid helped bridge the unseen. British Council support, a lifeline so strong, Restoring the balance, where they truly belong. Yet the path wasn't straight, detours arose, American models considered, as history shows. But a Ghanaian spirit began to ignite, a need for their own, burning ever so bright. The nineteen sixties stirred, a pivotal time, for a medical genesis, in its glorious prime.

Expansion unfolded, with steady increase, More students arriving, bringing inner peace. Dentistry's dawn, a parallel stride, with Manchester's guidance, their futures allied. Socio-economic hurdles, a temporary delay, but the spirit endured, lighting a brighter day.

From time's deep well, a '1993 vision began, sparked by Prof Archampong, the 5th Dean of the Medical School: health united. A Dean's bold dream, a College to rise; passed to Prof S.K. Owusu, through the winding hall it went. Debated, refined - Medicine joined the name. Voices converged, Public Health Research, Nursing's aim. Allied Health's promise then began to gleam. The Collegiate concept, a unifying thread, breaking down silos, knowledge widespread. Interdisciplinary learning, a powerful art where collaboration blossoms right from the start. A shared infrastructure, efficiency's gain, A stronger foundation, weathering every pain. The nineteen-eighties, a period of strain, Economic pressures, causing academic pain. But lessons were learned, adaptations were made, Sensitization grew, and no longer afraid. Logical opinions began to take hold. The collegiate structure, a story to be told.
Preliminary discussions, the idea took flight, disseminated widely, bathed in wisdom's light. Enthusiasm surged, a contagious desire, the Ghanaian Medical School, reaching ever higher. Objectives were drafted, with foresight and care, A vision for healing, beyond all comparison.

From Guggisberg's vision to Nkrumah's embrace, through trials and triumphs, they found their rightful place. The College of Health Sciences, a history defined, located in the heart of Ghana, for all humankind. Through process and pact, the University council's nod, at least, was affirmed on 18th July 1998. Provisional approval by the University Council on 4th August 1999, a day for the vision to begin. The College of Health Science was born with the elevation and upgrading of the departments of Nursing and the public health school, emerging into schools, and the Noguchi Memorial Institute for Medical Research was given Faculty status. On 10th December 1999, the university Council approved the establishment of the College of Health Sciences. The decision conveyed in a letter dated 17th December 1999 saw the conception of the College of Health Sciences with six (6) schools: University of Ghana Medical School, Noguchi Memorial Institute for Medical Research, School of Public Health, School of Nursing, and the newly established University of Ghana Dental School and School of Allied Health Sciences. The School of Pharmacy joined in 2007, and the West African Genetic Medicine Centre (WAGMC) in 2019.

A College established to be headed by a provost, supported by Deans of the Schools. A legacy to begin with the first provost, Rev. Prof. A.S. Ayettey's early might, then Prof. C.N.B. Tagoe's guiding tact. Through Prof. Aaron L. Lawson's steady hand, and Prof. Yao Tettey's focused aim, Rev. Prof. Patrick F. Ayeh-Kumi's vision bright, to Prof. Julius N. Fobil's respected name. And 25 years on, Prof Alfred Edwin Fiifi Yawson continues the legacy, celebrating 25 years of Transforming lives through excellence in education, research, and healthcare. To the vision bearers and founding fathers, we say "*yɛ da mo ase*", "*akpe na mi*" to the members of the first College Council, deputy provosts and registrars, and all who have made the College of Health Sciences a success. *Ayekooo!!!* College of Health Sciences a legacy for training scientists and healthcare professionals, not only healing Legon but the Nation Ghana and sending Stars to brighten the World.

***Authors:*** *Michelle Otuah Antwi, Gloria Addokwei,*
*School of Public Health, College of Health Sciences, University of Ghana.*

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# About the cover

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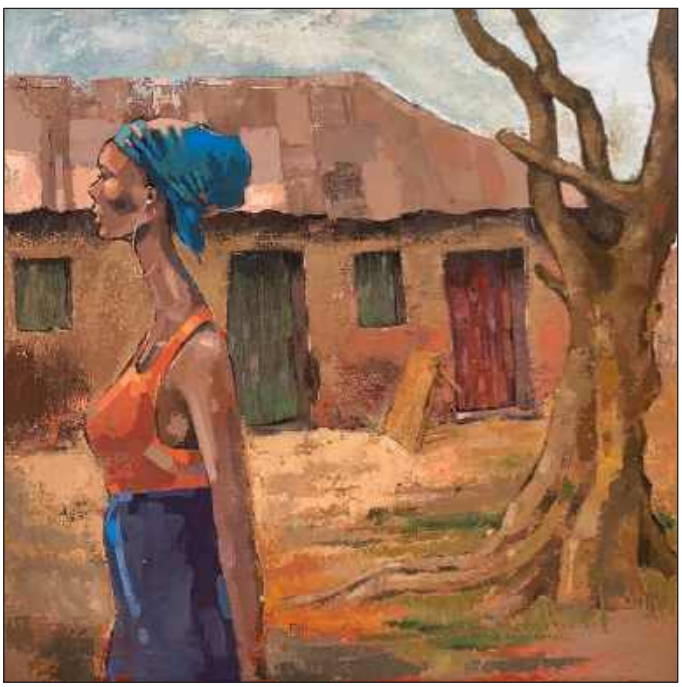

Tabi Crentsil (2025) Odikro's wife
*Art*

**Artist's Perspective**

The painting, Odikro's Wife, draws inspiration from Ghanaian tradition, where the Odikro, a title bestowed upon a chief in the Ashanti region, serves as the custodian of law and order. The Odikro is often perceived as the ultimate authority, embodying the essence of leadership and ownership within the village.

In the foreground stands a striking figure—the Odikro's wife. She exudes an aura of elegance and commanding authority, matching the stature of her husband. Her poised and imposing presence speaks volumes, suggesting that her influence and power are undeniable, even in a role traditionally overshadowed by the male figure.

The setting of the painting is stark, almost lifeless, evoking a profound sense of solitude. This atmosphere reflects a deeper truth: as one rises in status and authority, a sense of isolation often follows. Success can create an emotional distance, as others struggle to reconcile themselves with one's achievements, leaving the individual to navigate an increasingly lonely path.

The predominant use of earthy brown tones symbolizes fertile ground—endless opportunities for growth and flourishing. Despite the loneliness that may come with elevated status, the painting hints at the resilience and potential for renewal that lies within, waiting to be cultivated and nurtured.

This work masterfully captures themes of power, isolation, and the quiet strength required to thrive in the face of life's complexities

**Editors View**

Odikro's Wife is a compelling artistic meditation on leadership, resilience, and the often-unseen burdens of authority. Rooted in Ghanaian tradition, the painting elevates the Odikro's wife from a supporting role to a central, commanding presence, graceful, stoic, and undeniably influential. Her composed stillness evokes the quiet strength that upholds institutions, families, and communities.

The subdued backdrop and earthy tones convey both the solitude and the fertile ground that leadership often brings. Like scientific inquiry or institutional growth, leadership requires vision, patience, and the courage to persist through uncertainty. Odikro's wife becomes a powerful metaphor for those who shoulder great responsibility, often uncelebrated, yet foundational.

As the College of Health Sciences marks 25 years of advancing health education and research, Odikro's wife reflects the College's own journey: a legacy of steady impact built through dedication, service, and leadership.

For this journal, the painting resonates deeply. Editors, reviewers, and contributors labor behind the scenes to safeguard the integrity of science, ensuring accuracy, transparency, and truth. In this quiet but essential role, we too are custodians of trust. Odikro's wife calls us to honour those who lead with discipline and vision, in science, in art, and in life.

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**Original Research Article**

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# Knowledge, attitude and practice on breast cancer screening among female nurses in a tertiary hospital in Ghana

**Josephine NSAFUL [1,2], Yaw B APPIAH [2], Edmund T NARTEY [3*]**

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**Abstract**

***Background:*** Breast cancer is the most common female malignancy worldwide. In Sub-Saharan African countries, there are no national screening programmes for BC. In the absence of sufficient mammograms, breast self-examination and clinical breast examination play an important role. Nurses educate the general public on BC screening.

***Objective:*** The study aimed to evaluate the knowledge, attitude and practices with regard to BC among female nurses at a tertiary hospital in Ghana.

***Methods:*** This was a cross-sectional descriptive study utilising a self-administered close-ended questionnaire carried out among full-time nurses. This assessed knowledge of BC risk factors, signs and symptoms of BC, the attitude one should develop towards BC and the practice of breast self-examination (BSE), clinical breast examination (CBE) and mammography. The level of knowledge was categorised into good (≥ 75%), satisfactory (50 - 74%) and poor (< 50 %). A logistic regression analysis was carried out to determine factors associated with inadequate knowledge (level of knowledge < 50%) and the practice of BSE, CBE and agreeing to mastectomy.

***Results:*** This study found that the knowledge of nurses in BC was adequate. A total of 67% of nurses regularly practised BSE, 39% had previously had a CBE, and 85% of those 40 years and above had never had a mammogram. A total of 60% of nurses admitted they would disagree with a mastectomy in the event of being diagnosed with BC.

***Conclusion:*** This study found that the knowledge of BC among nurses did not translate into good BC screening practices, and they had an overwhelming fear of mastectomy. There is a need for training programs to be directed at improving breast screening practices, also focusing on the curability of BC, its treatment options and survivorship to help overcome the fear and stigma associated with mastectomy.

**Keywords:** Breast cancer; Breast screening; Mammogram; Nurses

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## INTRODUCTION

Breast cancer (BC) is the most common female malignancy. According to the Global Cancer Observatory (GLOBOCAN), about 2.3 million new cases of BC were diagnosed in 2020, and there were 685,000 BC deaths [1]. The incidence is highest in Australia, Europe, and North America, but the mortality rate is highest in Melanesia, West Africa, Polynesia, and the Caribbean. In these less developed countries, women have a 17% higher mortality rate than in developed countries. The differences in global distribution of incidence and mortality have been attributed to differences in socioeconomic development across the globe [1]. GLOBOCAN reports 4,500 new cases of BC diagnosed in Ghana annually, with about 2,000 deaths, thus making it the leading cause of cancer mortality in the country [2]. BC has a 5-year survival rate exceeding 90% in high-income countries (HICs) and 40% - 66% in low-to-middle-income countries (LMICs) [3]. Although BC awareness and education have improved in Ghana, a

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study has revealed that late presentation still characterises BC among Ghanaian women, mostly reporting at stage 3 or 4 of the disease with an average symptom duration of 10 months [4]. Early detection is achieved through screening. In Ghana and all over Sub-Saharan Africa, mammograms are not readily available, being mostly limited to urban areas. Consequently, breast self-examination (BSE) and clinical breast examination (CBE) continue to play an important role, although such options are not as clinically sensitive as mammography and are no longer recommended in advanced countries [5]. Therefore, the BC screening tools accepted in Ghana are BSE, CBE, and mammography.

In Ghana, there is no national screening programme for BC. Individuals are, therefore, encouraged to be "breast aware" and engage in breast screening. Recent years have been characterised by an increase in the activities of some governmental and non-governmental organisations in creating awareness about BC and advocating the benefits of early detection through breast screening and early treatment. Yet more than half of those with BC report late to the hospital [4]. Findings from a study indicate that the late presentation of these BC cases is due to various reasons, including ignorance [6]. A systematic review has revealed a paucity of publications in the sub-Saharan region on the knowledge, attitudes and practices concerning BC. These reviews have discovered varying levels of knowledge among various populations and various categories of women. The resounding trend, however, is the rather poor breast screening practices throughout the sub-region [7].

A few studies conducted among Ghanaian women have further revealed a deficiency in knowledge about the disease [8,9]. Studies conducted in LMIC on the knowledge, attitude and practice of BC screening among healthcare workers have shown that female health professionals need more education on the practice of BC screening [10-16]. To the best of our knowledge, little research has been conducted in Ghana on the knowledge, attitude and practice of BC screening among practising female nurses [1]. One study conducted among Ghanaian nursing students found that good knowledge about BC and BSE is attributable to its inclusion in their curriculum and professional training. However, it was found that the actual practice of BSE by these students was poor [17]. Similarly, two available studies among practising nurses reveal a good knowledge base but a poor uptake of breast screening [18,19].

Nurses, who are mostly the first point of contact for patients, are strategically front-lined to educate patients on BC and BC screening. Well-informed nurses can create breast awareness and encourage community members within and outside of the hospital environment to get involved in health-promoting behaviours, including regular breast screening. Invariably, this results in early detection and appropriate treatment, eventually leading to reduced BC-related mortality [20,21]. Nurses are, therefore, major stakeholders in this quest. Bailey [20] and Harmer [21] have illustrated the important role of the practising nurse in BC awareness and empowerment of patients. The knowledge base of nurses in Ghana needs to be explored as a basis for developing programmes targeted at equipping nurses to be front liners in BC awareness creation. The aim of this study was to evaluate the knowledge of BC risk factors and symptoms, attitudes towards BC and the BC screening practices among female nurses at a tertiary hospital in Ghana. This study expands the repository of emerging literature on BC awareness and screening practices among healthcare professionals in LMICs.

## MATERIALS AND METHODS

### Study design and sites

This was a cross-sectional descriptive study utilising a self-administered closed-ended questionnaire including only full-time female nurses at Korle-Bu Teaching Hospital (KBTH) from the departments of Surgery, Medicine, Child Health and Obstetrics and Gynaecology. The study was carried out from October to November 2022. It was pretested among female nurses at the Korle-Bu Polyclinic. Written informed consent was obtained from each participant after the procedure had been explained, and the option was given to withdraw at any stage. Nursing students and male nurses were excluded. The questionnaire comprised four main sections: 6 questions on demography, 15 questions on knowledge of BC risk factors, 7 questions on signs and symptoms of BC, and 5 questions on attitude should a person develop BC and the practice of BSE, CBE and mammography.

### Statistical analysis

Stata® 14 software was used to analyse the data. Continuous variables were reported as median with interquartile range (IQR), and categorical variables were presented as frequency and percentages. Knowledge of the signs and symptoms of BC was based on the correctness of a set of 7 non-weighted questions, whilst knowledge of the risk factors of BC was based on a set of 15 non-weighted questions. Descriptive analysis was used to determine the level of knowledge of BC (BC) and breast self-examination (BSE) and the practice of BSE among the study participants. The level of knowledge and practice was categorised into good (≥ 75%), satisfactory (50 - 74%) and poor (< 50%). For the logistic regression analysis, adequate knowledge was determined by correct answers of ≥ 50% (i.e. categories "good" and satisfactory") and inadequate knowledge by category "poor" (< 50%). A logistic regression analysis was carried out to determine the socio-demographic factors associated with inadequate knowledge of the signs and symptoms of BC and the risk factors of BC. In addition, a logistic regression analysis was carried out to determine the socio-demographic factors associated with the practice of BSE, CBE and agreeing to mastectomy. A two-tailed p-value < 0.05 was considered statistically significant.

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## RESULTS

A total of 287 nurses were interviewed, with a median age of 30.0 (IQR: 26.0 - 36.0) years. Table 1 shows the socio-demographic characteristics of the study participants.

### Knowledge of whether BC is curable

The majority of the nurses (68.6%, n = 197) believed that BC is curable. A total of 106 nurses have experience working with BC patients, of which 64% (n = 68) believed BC to be curable. Of the 181 nurses who had never worked with BC patients, 71% (n = 129) also believed BC to be a curable disease, with no significant statistical difference between the two groups (p = 0.210).

### Knowledge of the signs and symptoms of BC

Table 2 shows the knowledge levels on the signs and symptoms of BC, which were mostly good (> 75% correct answers), with breast lump being the most common symptom identified (95.5%). Knowledge was satisfactory (50 – 74% correct answers) for the presence of a lump in the armpit (71.8%) and that BC is not usually associated with pain in its initial stage (70.7%). Table 3 shows an analysis of factors associated with inadequate knowledge of the signs and symptoms of BC among the study participants. The increasing age of the study participants was associated with decreasing odds of inadequate knowledge of the signs and symptoms of BC (OR = 0.91 [95% CI, 0.84 - 0.97], p = 0.006). In addition, study participants with a Nursing Diploma as the highest professional qualification were at increased odds (OR = 3.9 [95% CI, 1.69 - 8.98], p = 0.001) of having inadequate knowledge of the signs and symptoms of BC compared with those with a Nursing Degree (Table 3).

### Knowledge of risk factors for developing BC

Table 2 shows the knowledge levels of the risk factors for developing BC. A total of 93.7% correctly identified family history as a risk factor. Knowledge of late menopause (47%), nulliparity (39%) and childbirth after age 35 (40.8%) risk factors was poor (< 50% correct answers). Knowledge of increasing age (58.9%), early menarche (50.5%), obesity (56.4%), not breastfeeding (50.5%), and oral contraceptive use (58.2%) as risk factors were all on the lower border of satisfactory. A proportion of nurses had a misconception that putting objects such as money (42.2%) and mobile phones (47.4%) in brassiere are risk factors, as well as wearing underwire brassieres (20.9%), sleeping with brassieres (26.8%) and using deodorant (8.4%) could also cause BC.

Logistic regression analysis indicated that increasing age was marginally associated with decreased odds of inadequate knowledge of the risk factors for BC (OR = 0.97 [95% CI, 0.97 - 1.00], p = 0.045) (Table 3). Further analysis

Table 1. Demographic characteristics of study participants

| Characteristic | Frequency (N= 287) | Percentage (%) |
|---|---|---|
| Age, median [IQR], years | 30.0 [26.0-36.0] | |
| Age groups (years) | | |
| 20 – 30 | 138 | 50.5 |
| 31 – 40 | 98 | 35.9 |
| 41 – 50 | 18 | 6.6 |
| >50 | 19 | 7.0 |
| Marital Status | | |
| Married | 149 | 51.9 |
| Single | 132 | 46.0 |
| Widowed/divorced | 6 | 2.1 |
| Religion | | |
| Christianity | 274 | 96.1 |
| Islam | 10 | 3.5 |
| Traditional | 1 | 0.4 |
| Nursing Qualification | | |
| Nursing Diploma | 138 | 48.1 |
| Nursing Degree | 149 | 51.9 |
| BC OPD | | |
| Yes | 106 | 36.9 |
| No | 181 | 63.1 |
| Working years | | |
| < 10 years | 222 | 77.4 |
| 11 – 20 years | 40 | 13.9 |
| 21 – 30 years | 13 | 4.5 |
| > 30 years | 12 | 4.2 |

IQR=Interquartile range; BC=BC; OPD=Out-patient department

Table 2. Knowledge on signs and symptoms and risk factors of BC

| Characteristic | Correct answer n, %[1] | Incorrect answer n, %[1] |
|---|---|---|
| Signs and Symptoms of BC | | |
| Usually painful | 203 (70.7) | 84 (29.3) |
| Breast lump | 274 (95.5) | 13 (4.5) |
| Lump in armpit | 206 (71.8) | 81 (28.2) |
| Ulcer on breast | 220 (76.7) | 67 (23.3) |
| Swelling of breast | 230 (80.1) | 57 (19.9) |
| Bloody nipple discharge | 233 (81.2) | 54 (18.8) |
| Deformation of breast shape | 237 (82.6) | 50 (17.4) |
| Risk factors of BC | | |
| Family history | 269 (93.7) | 18 (6.3) |
| Increasing age | 169 (58.9) | 118 (41.1) |
| Early menarche | 145 (50.5) | 142 (49.5) |
| Late menopause | 135 (47.0) | 152 (53.0) |
| Nulliparity | 112 (39.0) | 175 (61.0) |
| Obesity | 162 (56.4) | 125 (43.6) |
| Not breastfeeding | 145 (50.5) | 142 (49.5) |
| Oral contraceptive pill | 167 (58.2) | 120 (41.8) |
| Hormone replacement therapy | 178 (62.0) | 109 (38.0) |
| First childbirth after 35 years | 117 (40.8) | 170 (59.2) |
| Money in brassiere | 166 (57.8) | 121 (42.16) |
| Mobile phone in brassiere | 151 (52.6) | 136 (47.4) |
| Use of deodorant | 263 (91.6) | 24 (8.4) |
| Brassiere with underwire | 227 (79.1) | 60 (20.9) |
| Sleeping with brassiere | 210 (73.2) | 77 (26.8) |

[1] Row percentage

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Table 3. Factors associated with inadequate knowledge on signs & symptoms and risk factors of BC

| Characteristic | Knowledge status on signs and symptoms of BC | | Odds ratio [95% CI] | p-value | Knowledge status on risk factors of BC | | Odds ratio [95% CI] | p-value |
|---|---|---|---|---|---|---|---|---|
| | Inadequate n, %[1] | Adequate n, %[1] | | | Inadequate n, % | Adequate n, %[1] | | |
| Age, median [IQR], years | 26.0 [25.0-33.0] | 31.0 [27.0-36.0] | 0.91 [0.84-0.97] | 0.006 | 30.0 [27.0-34.0] | 31.0 [26.0-37.0] | 0.97 [0.93-1.00] | 0.045 |
| Age groups, years | | | | | | | | |
| 21 – 30 | 21 (15.2) | 117 (84.8) | 1.00 | | 53 (38.4) | 85 (61.6) | 5.30 [1.18-23.87] | 0.030 |
| 31 – 40 | 6 (6.1) | 92 (93.9) | 0.36 [0.14 – 0.94] | 0.036 | 29 (29.6) | 69 (70.4) | 3.57 [0.78-16.47] | 0.102 |
| 41 – 50 | 1 (5.6) | 17 (94.4) | 0.33 [0.04 – 2.60] | 0.291 | 5 (27.8) | 13 (72.2) | 3.27 [0.54-19.62] | 0.195 |
| >50 | 0 (0.0) | 19 (100.0) | N.E | 0.078* | 2 (10.5) | 17 (89.5) | 1.00 | |
| Marital Status | | | | | | | | |
| Married | 15 (10.1) | 134 (89.9) | 1.00 | | 51 (34.2) | 98 (65.8) | 1.00 | |
| Single | 18 (13.6) | 114 (86.4) | 1.41 [0.68 – 2.92] | 0.355 | 45 (34.1) | 87 (65.9) | 0.99 [0.61 – 1.63] | 0.981 |
| Widower/ divorced | 0 (0.0) | 6 (100.0) | NE | 1.000* | 1 (16.7) | 5 (83.3) | 0.38 [0.04 – 3.38] | 0.389 |
| Religion | | | | | | | | |
| Christianity | 32 (11.7) | 242 (88.3) | 1.00 | | 94 (34.3) | 180 (65.7) | 1.00 | |
| Islam | 1 (10.0) | 9 (90.0) | 0.84 [0.10 – 6.85] | 0.871 | 2 (20.0) | 8 (80.0) | 0.48 [0.10 -2.30] | 0.358 |
| Traditional | 0 (0.0) | 1 (100.0) | NE | 1.000* | 1 (100.0) | 0 (0.0) | N.E | 0.346* |
| Nursing qualification | | | | | | | | |
| Nursing Degree | 8 (5.4) | 141 (94.6) | 1.00 | | 41 (27.5) | 108 (72.5) | 1.00 | |
| Nursing Diploma | 25 (18.1) | 113 (81.9) | 3.90 [1.69 – 8.98] | 0.001 | 56 (40.6) | 82 (59.4) | 1.80 [1.10 – 2.95] | 0.020 |
| BC OPD | | | | | | | | |
| Yes | 11 (10.4) | 95 (89.6) | 1.00 | | 28 (26.4) | 78 (73.6) | 1.00 | |
| No | 22 (12.2) | 159 (87.8) | 1.19 [0.55 – 2.57] | 0.649 | 69 (38.1) | 112 (61.9) | 1.72 [1.01 – 2.90] | 0.044 |
| Working years | | | | | | | | |
| < 10 years | 30 (13.5) | 192 (86.5) | 1.71 [0.53 – 5.47] | 0.368 | 82 (36.9) | 140 (63.1) | 2.93 [0.63-13.69] | 0.172 |
| 11 – 20 years | 2 (5.0) | 38 (95.0) | 1.50 [0.41 – 5.48] | 0.540 | 12 (30.0) | 28 (70.0) | 2.14 [0.41-11.29] | 0.369 |
| 21 – 30 years | 1 (7.7) | 12 (92.3) | 0.63 [0.13 – 3.07] | 0.562 | 1 (7.7)) | 12 (92.3) | 0.42 [0.03 – 5.30] | 0.500 |
| > 30 years | 0 (0.0) | 12 (100.0) | 1.00 | | 2 (16.7) | 10 (83.3) | 1.00 | |

*Fisher's two-sided exact test; [1]Row percentages; NE=Not estimable; IQR=Interquartile range; BC=BC; OPD=Out-patient department

Table 4. Factors associated with disagreeing to mastectomy if diagnosed with BC

| Characteristic | Will disagree to Mastectomy n, %[1] | Will agree to Mastectomy n, %[1] | Odds ratio [95% CI] | p-value |
|---|---|---|---|---|
| Age, median [IQR], years | 30.0 [26.0-35.0] | 32.0 [27.0-37.0] | 0.97 [0.96-1.00] | 0.083 |
| Age groups, years | | | | |
| 21 – 30 | 93 (67.4) | 45 (32.6) | 2.30 [0.87 – 6.05] | 0.092 |
| 31 – 40 | 46 (46.9) | 52 (53.1) | 0.98 [0.37 – 2.63] | 0.973 |
| 41 – 50 | 12 (66.7) | 6 (33.3) | 2.22 [0.59 – 8.41] | 0.240 |
| >50 | 9 (47.4) | 10 (52.6) | 1.00 | |
| Marital Status | | | | |
| Married | 81 (54.4) | 68 (45.7) | 1.00 | |
| Single | 86 (65.2) | 46 (34.9) | 1.57 [0.97-2.54] | 0.067 |
| Widowed/divorced | 5 (83.3) | 1 (16.7) | 4.20 [0.48-36.80] | 0.195 |
| Religion | | | | |
| Christianity | 164 (60.1) | 109 (39.9) | 1.00 | |
| Islam | 5 (50.0) | 5 (50.0) | 0.66 [0.19 – 2.34] | 0.520 |
| Traditional | 0 (0.0) | 1 (100.0) | N.E | 0.402* |
| Nursing Qualification | | | | |
| Nursing Degree | 77 (51.7) | 72 (48.3) | 1.00 | |
| Nursing Diploma | 95 (68.8) | 43 (31.2) | 2.07 [1.27 – 3.35] | 0.003 |
| BC OPD | | | | |
| Yes | 61 (57.5) | 45 (42.5) | 1.00 | |
| No | 111 (61.3) | 70 (38.7) | 1.16 [0.72 – 1.95] | 0.529 |
| Working years | | | | |
| < 10 years | 138 (62.2) | 84 (37.8) | 1.64 [0.51 – 5.26] | 0.403 |
| 11 – 20 years | 20 (50.0) | 20 (50.0) | 1.00 [0.28 – 3.63] | 1.000 |
| 21 – 30 years | 8 (61.5) | 5 (38.5) | 1.60 [0.33 – 7.85] | 0.562 |
| > 30 years | 6 (50.0) | 6 (50.0) | 1.00 | |

*Fisher's two-sided exact test; [1]Row percentages; NE=Not estimable; IQR=Interquartile range; BC=BC; OPD=Out-patient department

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indicated that study participants with Nursing Diploma (OR = 1.80 [95% CI, 1.10 - 2.95], p = 0.020) and those who did not have any BC working experience (OR = 1.72 [95% CI, 1.01 - 2.90], p = 0.044) were significantly associated with increased odds of inadequate knowledge of the risk factors for BC (Table 3).

**Knowledge of BC screening methods**

The majority of nurses correctly identified the methods of BC screening as breast self-examination (95.8%), clinical breast examination (95.1%), and mammography (87.1%). Only 36.2% of the nurses correctly identified mammography as a diagnostic and screening tool, 48.4% thought it was purely for diagnosis, and 15.3% for screening. A total of 45.8% correctly knew the age to start mammographic screening to be 40 years. There was good knowledge of the technique for breast self-examination. A total of 95.1% knew the procedure involved standing in front of a mirror, 88.8% used the finger pads to examine the breast, 81.9% examined the armpit and 84.3% checked for nipple discharge. However, 55.4% wrongly identified fingertips for examination of the breast. Whilst 77% correctly knew BSE is done monthly, 79.4% also knew that BSE is done 1 week after the menses, and 11.8% believed the timing was unrelated to the menstrual cycle.

**Attitude to BC**

A total of 88.5% of nurses would see a doctor within a month of noticing a breast lump, and 10.1% within 3 months. A total of 80% of nurses admitted they would be scared if they were diagnosed with BC, and as much as 60% would refuse a mastectomy. However, 4% responded that they would not consult a doctor, 4% would go to a prayer house, and 3.5% would use traditional medicine. Further analysis revealed that nursing qualification was significantly associated with the acceptance of mastectomy (p-value 0.003), and Diploma Nurses were twice at increased odds of refusing mastectomy compared with Degree Nurses (Table 4).

**The practice of BC screening methods**

A total of 67.2% of nurses perform BSE regularly, and 32.7% do not. For those who do perform BSE, 64.5% do so monthly, 8.8% weekly, 6.2% daily, and 16.6% admit that the intervals vary. Most of the study participants who performed BSE (71%) did it one week after their menses, 22% did not time it with their menstrual cycle, 5% did so midcycle, and 2% did it during their menses. The analysis of data in Table 5 did not reveal any socio-demographic factors significantly associated with BSE performance. Regarding clinical breast examination, 39.3% (n = 112) had previously done a clinical breast examination. Young age (21 - 30 and 31 - 40 years) was found to have an increased odds of not having done a clinical breast examination compared with older study participants (> 50 years) (p < 0.05) (Table 5). A total of 58 nurses were aged 40 years and

Table 5. Factors associated with practice of BSE and CBE

| Characteristic | Do not perform BSE n, %[1] | Performs BSE n, %[1] | Odds ratio [95% CI] | p-value | Do not perform CBE n, %[1] | Performs CBE n, %[1] | Odds ratio [95% CI] | p-value |
|---|---|---|---|---|---|---|---|---|
| Age, median [IQR], years | 30.5 [26.0-35.3] | 30.0 [26.0-36.0] | 0.98 [0.95-1.01] | 0.249 | 30.0 [26.0-35.0] | 30.0 [27.0-38.0] | 0.97 [0.94-1.00] | 0.056 |
| Age groups | | | | | | | | |
| 21 - 30 | 45 (32.6) | 93 (67.4) | 2.58 [0.72 – 9.31] | 0.148 | 85 (61.6) | 53 (38.4) | 2.75 [1.02 – 7.42] | 0.046 |
| 31 - 40 | 37 (37.8) | 61 (62.2) | 3.23 [0.88-11.86] | 0.076 | 65 (66.3) | 33 (33.7) | 3.38 [1.22 – 9.38] | 0.020 |
| 41 - 50 | 5 (27.8) | 13 (72.2) | 2.05 [0.41-10.24] | 0.381 | 11 (61.1) | 7 (38.9) | 2.69 [0.71-10.18] | 0.144 |
| >50 | 3 (15.8) | 16 (84.2) | 1.00 | | 7 (36.8) | 12 (63.2) | 1.00 | |
| Marital Status | | | | | | | | |
| Married | 50 (33.6) | 99 (66.4) | 1.00 | | 90 (60.4) | 59 (39.6) | 1.00 | |
| Single | 44 (33.3) | 88 (66.7) | 0.99 (0.60 – 1.63) | 0.968 | 83 (62.9) | 49 (37.1) | 1.11 [0.69 – 1.80] | 0.670 |
| Widowed/divorced | 0 (0.0) | 6 (100.0) | N.E | 0.178* | 2 (33.3) | 4 (66.7) | 0.33 [0.06 – 1.85] | 0.206 |
| Religion | | | | | | | | |
| Christianity | 87 (31.7) | 187 (68.3) | 1.00 | | 164 (59.8) | 110 (40.2) | 1.00 | |
| Islam | 5 (50.0) | 5 (50.0) | 2.15 [0.61 – 7.62] | 0.236 | 9 (90.0) | 1 (10.0) | 6.04 [0.75-48.32] | 0.090 |
| Traditional | 1 (100.0) | 0 (0.0) | NE | 0.320* | 1 (100) | 0 (0.0) | N.E | 1.000* |
| Nursing Qualification | | | | | | | | |
| Nursing Degree | 48 (32.2) | 101 (67.8) | 1.00 | | 90 (60.4) | 59 (39.6) | 1.00 | |
| Nursing Diploma | 46 (33.3) | 92 (66.7) | 1.05 [0.64 – 1.72] | 0.840 | 85 (61.6) | 53 (38.4) | 1.05 [0.65 – 1.69] | 0.836 |
| BC OPD | | | | | | | | |
| Yes | 31 (29.3) | 75 (70.7) | 1.00 | | 60 (56.6) | 46 (43.4) | 1.00 | |
| No | 63 (34.8) | 118 (65.2) | 1.29 [0.77 – 2.17] | 0.333 | 115 (63.5) | 66 (36.5) | 1.34 [0.82 – 2.18] | 0.246 |
| Working years | | | | | | | | |
| < 10 years | 73 (32.9) | 149 (67.1) | 2.45 [0.52-11.47] | 0.255 | 140 (63.1) | 82 (36.9) | 1.71 [0.53 – 5.47] | 0.368 |
| 11 – 20 years | 14 (35.0) | 26 (65.0) | 2.69 [0.52-14.04] | 0.240 | 24 (60.0) | 16 (40.0) | 1.50 [0.41 – 5.48] | 0.540 |
| 21 – 30 years | 5 (38.5) | 8 (61.5) | 3.12 [0.47-20.58] | 0.236 | 5 (38.5) | 8 (61.5) | 0.63 [0.13 – 3.07] | 0.562 |
| > 30 years | 2 (16.7) | 10 (83.3) | 1.00 | | 6 (50.0) | 6 (50.0) | 1.00 | |

*Fisher's two-sided exact test; 1Row percentages; NE=Not estimable; IQR=Interquartile range; BSE=Breast self-examination; CBE=Clinical breast examination

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Table 6. Reasons for not screening breasts; BSE, CBE and Mammogram

| Reason for not screening breast | Frequency | Proportion (%) |
|---|---|---|
| Reason for not performing Breast Self-Examination | N=94 | |
| Do not have enough time | 4 | 4.3 |
| Forget to perform it | 56 | 59.6 |
| Do not know how to perform it | 9 | 9.6 |
| Think it is an unnecessary examination | 2 | 2.1 |
| No reason for not doing it | 21 | 22.3 |
| Do not have any risk factor for developing BC | 2 | 2.1 |
| Reason for not performing Clinical Breast Examination | N=174 | |
| Do not have enough time | 20 | 11.5 |
| Forget to get it done | 26 | 14.9 |
| Will be embarrassed to expose my breast | 19 | 10.9 |
| Think it is an unnecessary examination | 5 | 2.9 |
| No reason for not doing it | 97 | 55.8 |
| Do not have any risk factor for developing BC | 7 | 4.0 |
| Reason for not performing mammogram | N=49 | |
| Do not think I'm qualified | 2 | 4.2 |
| Do not have enough time to perform it | 2 | 4.2 |
| Forget to perform it | 11 | 22.9 |
| Think it is an unnecessary | 1 | 2.0 |
| Have no lump in my breast | 6 | 12.5 |
| No reason for not doing it | 26 | 54.2 |

above, and of these, 15.5% (n = 9) had done a mammogram previously, and the remaining 84.5% (n = 49) had never done a mammogram (Table 6). Reasons for not having had a mammogram done (for study participants with age ≥ 40 years), BSE and CBE are shown in Table 6.

## DISCUSSION

This study explored the knowledge, attitude and practices among female nurses at a tertiary hospital in Ghana. The study reports that nurses had good knowledge of BC signs and symptoms, good knowledge of risk factors and good knowledge of the practice of BSE. However, it revealed that there were poor BC screening practices, particularly mammography and also discovered that a large proportion of nurses would not consent to having a mastectomy in the event of being diagnosed with BC. This study has identified age, nursing qualification, and years of working experience with BC patients significantly influence knowledge (on signs and symptoms and risk factors of BC), attitude (towards agreeing to mastectomy if diagnosed with BC) and practices (of breast self-examination and clinical breast examination) of female nurses with regard to BC.

The median age of nurses in this study (30 years) was comparable with other investigations conducted in the western and eastern parts of Africa [11,19]. The nursing workforce is mostly of a young age group, with fewer older and experienced nurses in supervisory positions. In this study, 31% of nurses did not believe that BC is a curable disease, as similarly reported in other countries [10,11], but not as high as 60% of nurses in a Nigerian study [22]. This belief was irrespective of whether they had experience working with BC patients or not. The perception that BC is not curable could be due to the exposure of nurses to the countless late-stage diseases on admission in hospitals and their limited interaction with the very few BC survivors. It is ironic, though, that a smaller proportion (10%) of women in the Ghanaian public rather believe BC to be non-curable [9]. In Ethiopia, only 5.6% of nurses believed that BC was not curable [23].

Unsurprisingly, we found breast lumps to be the most commonly known symptom of BC (96% of respondents), as in other countries [23,24]. However, it should be common knowledge among nurses that early BC is usually painless, but this was so for only 71% of respondents, though it was better than for nurses in Ethiopia and Iran [23,24]. It is not surprising, then, that a cross-section of women in Ghana believed breast pain to be the most common symptom, second only to breast lump [9]. This widely held perception that cancer is a painful disease has misled numerous women to present with advanced disease. Like other studies, the commonest risk factor identified by respondents is family history [16,23]. In tandem with information in the non-hospital community, other risk factors were perceived to be due to putting objects such as money and mobile phones in a brassiere, wearing underwire brassieres, sleeping with brassieres and using deodorant. Other perceived risk factors were tight brassieres, prolonged breastfeeding, cracked nipples, spiritual causes, men sucking breasts [8,17,22,23,25] and trauma to the breasts [26]. In comparison to previous studies among the Ghanaian general public, nurses' knowledge of signs, symptoms and risk factors for BC was found to be higher [8,9].

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Almost all nurses successfully identified BSE, CBE and mammography as BC screening methods, which was higher than reported for student nurses [17]. However, less than half of the nurses in this study knew the recommended age to start screening mammograms (40 years), which was better than the 28% reported for Ethiopian nurses [23] but not comparable with the 73% reported for nurses in a Saudi Arabian study [27]. Knowledge of the technique of BSE was good, with the majority (77%) of nurses being aware that it is performed one week after menstruation (79%), similar to nurses' knowledge in previous publications [23,27]. Comparing the findings of this study with previous work done in Ghana, knowledge about BC is higher among nurses than the general public [8,9]. Research done in Nigeria clearly demonstrated that despite nurses being more knowledgeable on all aspects of BC, they did not have better breast screening practices than non-health professionals. Ironically, the non-health professionals had higher mammography uptake levels than nurses, but the difference was not statistically significant. In addition, it was found that approximately 40% of both groups of women shared the belief that prayer is a treatment option for BC [28]. It is encouraging that about 67% of nurses in this study do regularly perform BSE, mostly at monthly intervals and a week after menstruation, as did a cross-section of University nursing students (17); this finding was higher than the BSE rate in a cross-section of Ghanaian women [8,9,25]. A systematic analysis has revealed differing knowledge levels of BSE across sub-Saharan Africa and rather low levels of BSE practice [7]. The BSE rate in Poland is 56% [29].

A total of 39% of participants previously had a CBE, which was only a little higher than their counterparts in other Ghanaian hospitals (32%) [19] and even less in other studies [27]. Study participants above 40 years were aware they were candidates for screening mammograms, although the majority (85%) of them had not done so for no particular reason, or due to forgetfulness or because they were asymptomatic, as similarly reported among the general public [8] and similar to the behaviour of nurses in other Ghanaian hospitals [19], Nigeria [16] and Eritrea [11]. A study among female health professionals (doctors, nurses, and pharmacists) reported an impressive BSE uptake of 91%, but CBE was only 38% and none of those who qualified had done a mammogram [22]. The generally low levels of BSE, CBE and mammography practices among nurses in Ghana have been found to be due to their belief that BC screening is not beneficial, in addition to the reasons found in this study [19]. A recent publication from Sudan studied medical and non-medical female workers in a hospital. BC knowledge levels were higher in the medics. Positive attitude was comparable in both groups, the practice of BSE and CBE was very poor, and mammographic screening was not practised by either group [30].

By virtue of their professional training, it is a reasonable expectation that, unlike the public, nurses would report any breast symptoms promptly to the hospital and comply fully with treatment if diagnosed with BC. An unconventional metric introduced in this study was asking the respondents what their reaction would be if they were diagnosed with BC. This study discovered that approximately as much as 10% of nurses would wait for more than a month before reporting a breast lump to a doctor. This is similar to what has been reported to the general public [17]. Furthermore, an overwhelming 60% would refuse a mastectomy. The observation was in sharp contrast with 20% of nurses in an Eritrean study who would also not agree with a mastectomy [11]. This aversion to mastectomy may be attributed to the deeply held beliefs in the community, of which fear of mastectomy and spiritual beliefs are a significant cause of delayed presentation to the hospital and defaulting from treatment [6,8]. Unfortunately, this means nursing training/education has not transformed the fundamental beliefs and behaviour of female nurses regarding breast health. Nurses with diploma were twice as likely to refuse mastectomy (compared with degree nurses), even though a large proportion (52%) of degree nurses also would refuse mastectomy. This observation suggests the need for intensive BC education among nurses at all levels of nursing training institutions in the country. Anecdotally, in Ghana, it is known that various categories of health professionals have been known to hide huge breast lumps and refuse various treatment options, especially chemotherapy and mastectomy. It is not surprising that this study found that 4% of respondents would rather not see a doctor, would go to a prayer house and/or would use unapproved traditional medicine. An insightful study from Turkey revealed that there were high levels of fear in 72% of nurses, and this was not influenced by adequate knowledge levels about BC. Ninety-four (94%) of respondents admitted that spirituality was important in dealing with disease. The majority of nurses opted for spiritual coping mechanisms, and fewer opted for alternate coping mechanisms [31].

This study has identified age, nursing qualification, years of experience working with BC patients, and years of experience working with knowledge of BC signs, symptoms and risk factors among nurses (Tables 3 and 5). Older nurses were at increased odds of having had a clinical breast examination (compared with the younger nurses), which reflects their better knowledge of BC issues. We also found that diploma nurses had twice the odds of refusing mastectomy compared with degree nurses (Table 6), which is probably a likely reflection of their poor knowledge of BC. Nurses and other health professionals in the community are usually the first point of contact, and a person's next line of action is influenced by their opinion. Indeed, a study revealed that approximately 40% of newly diagnosed BC patients had already had a previous medical consultation before reporting to a treatment centre [6]. It is crucial, then, that nurses put out accurate, evidence-based information in order to guide decision-making. Publications by Bailey [20] and Harmer [21] highlight the

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pivotal role of nurses in BC screening and prevention through teaching breast awareness and health-promoting behaviours. They advocate that nurses play a central role in encouraging women to perform regular BSE, mammograms and other health-promoting behaviours [20,21]. In this study, we similarly align with the postulation that many female nurses render a unique opportunity to identify with women and empower them to be responsible for their health. Well-trained and well-informed nurses can teach (through demonstration) how to correctly perform BSE, give accurate information on signs, symptoms and risk factors of BC and what to do to find any relevant symptoms whilst emphasising the importance of CBE and mammograms. In the absence of national screening programs, this will lead to early detection, which gives the patient an excellent chance of getting a cure. In the event of a BC diagnosis, nurses are required to give the necessary counsel and support to encourage patients to comply with treatment and, hence, avert the myths and misconceptions surrounding treatment that have pervaded society.

The limitations of this present study include the fact that only female full-time nurses at a single facility were recruited, which may limit the generalizability of the study findings to the broader nursing population of Ghana. Additionally, a comparative analysis with other female health professionals and non-health professionals was not done. This study is also limited by the lack of a qualitative analysis to explore the underlying reasons for the poor screening practices, fear of mastectomy and possible systemic barriers to screening.

### Conclusion

This study found that the knowledge of nurses on BC regarding signs and symptoms, risk factors and the practice of BSE does not translate into good BC screening practices, particularly mammography. An overwhelming 60% of nurses admitted they would disagree with a mastectomy in the event of being diagnosed with BC. Accordingly, we recommend that nursing training programs include curricula to improve breast screening and overall breast health practices. In addition, hospital staff welfare/healthcare programs should include annual breast screening and mammography. Nursing education should focus on the curability of BC, its treatment options and survivorship to help overcome the fear and stigma associated with mastectomy.

Future research should include other health professional groups and in-depth interviews to explore the reasons for these findings.

## DECLARATIONS

### Ethical consideration

Ethical approval was obtained from the Institutional Review Board of Korle-Bu Teaching Hospital for Medical Research (KBTH-IRB) (protocol ID KBTH-STC/IRB/000158/2021). Written informed consent was obtained from each participant after the procedure had been explained, and the option was given to withdraw at any stage.

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest

### Author contribution

JN and YBA conceived and designed the study. JN and ETN gave conceptual advice. ETN and JN did the statistical analysis and drafted the manuscript. JN, YBA and ETN reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

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### Availability of data

Data is available upon request to the corresponding author

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# Prenatal care and maternal haemoglobin concentration at childbirth: insights from a district hospital

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**Abstract**

***Background:*** Antenatal care (ANC) encompasses clinical assessments, health advice, and medical guidance on maternal changes, nutrition, and supplements to promote maternal and fetal well-being and thus prevent pregnancy-related complications. Despite these efforts, maternal anaemia remains prevalent in resource-limited settings such as the Kwaebibirim district in the eastern region of Ghana.

***Objective:*** This study aimed to explore the link between the frequency of ANC visits and increased maternal haemoglobin concentration (mHgbc) levels.

***Methods:*** This study employed an analytical cross-sectional design using secondary data from birth registers in the district hospital's labour suite to assess variations in mHgbc levels across different ANC visit frequencies. Statistical analyses included descriptive analysis, one-way ANOVA and unpaired two-sample t-tests.

***Results:*** The mean number of ANC visits was 6.06 (SD 3.23), and the mean mHgbc was 10.34 g/dl (SD 1.42). ANC visits ranged from 0 to 16, while mHgbc levels ranged from 1.6 g/dl to 16.3 g/dl. Most women attended 4 - 8 ANC visits (54.7%), followed by 0 - 3 visits (23.25%) and ≥ 9 visits (22.1%). A higher frequency of ANC visits was associated with higher mHgbc levels. One-way ANOVA revealed significant differences in mean mHgbc among the 0 - 3, 4 - 8, and ≥ 9 ANC visit groups. Post hoc unpaired two-sample t-tests confirmed significant differences in mean mHgbc between 0 - 3 vs. 4 - 8 and 4 - 8 vs ≥ 9 visits. However, no significant differences were observed between 0 - 3 and 4 - 8 visits in women aged 21 – 30 years, those with senior high school education, formal occupations, and multiparae. Similarly, preterm or early-term deliveries and women with blood group A showed no significant differences between 4 - 8 and ≥ 9 visits.

***Conclusion:*** Increased ANC visit frequency is associated with higher mHgbc levels. However, further prospective studies are needed to identify which ANC components underlie this observation and further address the limitations of secondary data.

**Keywords:** Antenatal, maternal haemoglobin, anaemia

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## INTRODUCTION

Prenatal care or antenatal care (ANC) involves clinical assessments, health advice, and the provision of medical information on maternal physiological changes and prenatal nutrition, including vitamin supplements. This comprehensive approach aims to prevent potential health complications during pregnancy while promoting the well-being of both the pregnant woman and the developing foetus [1,2].

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In high-income countries, traditional ANC practices typically entail monthly consultations during the initial two trimesters, spanning from the 1st to the 28th week of gestation. From the 28th to the 36th week, appointments are scheduled bi-weekly, transitioning to weekly assessments from the 36th week until delivery, extending to the 38th to 42nd week. These protocols involve evaluating parental needs and family dynamics [3]. Despite the conventional development of ANC since the early 1900s, empirical evidence establishing its superiority as the optimal approach for prenatal care remains insufficient [3]. The World Health Organisation (WHO) recommends at least eight ANC visits during pregnancy, up from the previous

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minimum of four, to better identify and manage health issues and enhance immunisation opportunities. Despite ANC's critical role in maternal and infant health, many pregnant women do not adhere to the recommended eight visits, and evidence supporting its frequency and content is limited [3,4].

Proposals to reduce ANC visits for low-risk pregnancies have been countered by trials suggesting fewer visits may lead to increased Neonatal Intensive Care Unit admissions and longer hospital stays, though chance may influence outcomes [3]. A 2015 Cochrane Review suggested that in resource-limited settings with infrequent visits, reducing visit frequency might lead to higher perinatal mortality rates [3]. The effectiveness of reduced visits models thus remains uncertain, particularly in low-income countries where pregnant women already exhibit limited visits at appointments [2]. Early ANC visits are paramount, and implementing flexible pathways allowing for additional visits from the time of booking could enhance care for individuals initiating care later in pregnancy. Women with fewer visits express lower satisfaction with the care received compared to those adhering to the standard visit count [2,3]. Telemedicine presents novel alternatives for certain appointments [5,6].

In 2015, the WHO reported about 830 daily maternal deaths worldwide from pregnancy and childbirth complications, with only five (5) of such occurrences in high-income countries. This underscores the vast disparity, with most maternal deaths concentrated in low-income countries [6,7]. A Spanish study (1997 – 2008) on early and low-birth weight deliveries among local and immigrant women linked disparities to ANC attendance. Among 21,708 births, immigrants had higher rates of very preterm births (before 32 weeks of gestation) and very low birth weight (< 1500 g), emphasising the importance of universal ANC access [8,9]. ANC involves monitoring prenatal health through regular check-ups, including medical history review, blood pressure (BP) monitoring, anthropometric measurements, pelvic exams, doppler foetal heart rate checks, and blood and urine tests. Effective communication with pregnant women throughout pregnancy is prioritised [10-12]. ANC services include iron and folate supplementation (IFS), nutritional guidance, helminthic infestation therapies, and presumptive Intermittent Preventive Therapy with sulfadoxine-pyrimethamine (IPTp-SP).

ANC services are offered gratis to all pregnant women to improve maternal health during pregnancy. Of particular relevance to this study, these services include iron and folate supplementation (IFS), nutritional guidance, presumptive treatment for helminthic infestations, intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP), tetanus immunisation, blood pressure monitoring, urine testing, syphilis screening, hepatitis B and HIV screening, and health education. In a recent study conducted in the Kwaebibirem municipal area of the Eastern Region, Ghana, a notably high prevalence of maternal anaemia (MA) was observed, with rates reaching 71.2%. This finding is particularly concerning given that ANC coverage in the region was reported at 60.7% over the period from 2021 to 2023 [13]. This coverage comprises a calculated fraction of statistically projected expected births, representing approximately 4% of the municipal population. Approximately 89.6% of pregnant women made at least four visits.

## MATERIALS AND METHODS

### Study Area

The study was conducted at Kade Government Hospital in the Eastern administrative region of Ghana. This area exemplifies the common tripartite health model found in Ghanaian districts, consisting of district hospitals, health centres, and Community-Based Health Planning and Services (CHPS), which are akin to community clinics. The district hospital constitutes the primary hub for clinical healthcare services, delivering comprehensive maternal care, including ANC, labour and delivery, postnatal care, and emergency obstetric services. Health centres, operating at an intermediate level, offer basic maternal care services, including ANC, uncomplicated labour/delivery, and postnatal care. CHPS compounds offer limited ANC services, referrals for high-risk pregnancies, health education, and immunisations to pregnant women. This structured approach ensures accessible and comprehensive care for pregnant women across different levels of healthcare facilities. Service availability may vary depending on location and resource availability.

### Study design

Although data were collected over a five-year period (2018 – 2023), each observation reflects a single point in time, typically at delivery. The study is described as analytical because it seeks to identify patterns and associations between mHgbc and ANC attendance, including differences across specific subgroups. Particularly notable is the comparison of cohorts of women based on the total number of ANC visits attended throughout pregnancy, irrespective of timing. These absolute visit counts were not aligned with current WHO recommendations, which define quality ANC based on timing and content across trimesters [14,15]. The district hospital records an average of 55.27 (SD ± 10.94) monthly ANC registrants and 449.18 (SD ± 43.56) monthly ANC attendants. We therefore assessed whether different total ANC visit counts during pregnancy were significantly associated with mHgbc at delivery.

### Study setting

This study was conducted at the maternity/labour suite of the Kade Government Hospital, the primary referral health facility serving the municipal area. Accredited by the National Health Insurance, the hospital has a bed capacity of eighty-five and serves as the sole referral facility in Kwaebibirem, facilitating approximately 60 - 80 monthly births. Centrally located in Kade's municipal capital, the

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hospital serves an estimated population of 127,434, including approximately 3,114 women of reproductive age, and provides district-level health services. These figures are based on the Ghana Statistical Service's projected 2% annual population growth rate for 2021 (Ghana 2021 Population and Housing Census, Volume 3).

**Study population and sampling**

The study analysed obstetric records from Kade Government Hospital spanning 2018 to 2023. The sampling frame included all eligible birth records within this period. Systematic sampling was employed, selecting every second entry from the birth registers to enhance statistical rigour and generalizability. The starting point was randomly determined using a dice roll, and the sampling interval (2) was based on this result, with every second record selected thereafter. This approach ensured comprehensive coverage of the entire period. Records lacking mHgbc data were excluded to ensure internal validity. Trained research assistants used a pretested data collection tool, similar to a standardised questionnaire, to extract relevant information. When a record was excluded due to missing mHgbc data, the subsequent record in the sequence became the new starting point, continuing with every second record according to the systematic sampling procedure. Excluded records were not deliberately replaced, as the sample size was sufficient to accommodate exclusions without compromising statistical power or representativeness. Although systematic sampling can introduce periodicity bias, it was deemed appropriate for this study due to its practicality, transparency, and ability to minimise selection bias, thereby providing an accurate representation of the population's diversity. Maternal Anaemia (MA) was defined by mHgbc, with a threshold of less than 11.0 g/dl, aligning with healthy, iron-supplemented women. During the third trimester, MA was operationally defined as mHgbc below 11.0 g/dl, consistent with typical ranges for that period of gestation.

Assumptions included the absence of hemoglobinopathies among parturient women. MA severity was categorised based on mHgbc: 10.9 - 10 g/dl as mild, 9.9 - 7 g/dl as moderate, and 6.9 or less g/dl as severe MA. Analysis did not extend to mHgbc of 4 g/dl or less beyond the severe MA range. Pre-delivery mHgbc, measured within four weeks prior to delivery, was utilised to classify MA to mitigate potential post-delivery fluctuations from blood loss. Hospital protocols further ensure mHgbc is measured close to delivery to guide obstetric management and reduce risks from MA. Although we assumed all recorded mHgbc values were recent and adequate for clinical decisions, we acknowledge that outliers of remote mHgbc measurements, while rare, cannot be entirely excluded. To streamline data abstraction, the birth register was divided into four segments. The first segment comprised personal details of the parturient women: age, residential classification (urban/peri-urban or rural), highest education level, gravidity, and parity. The second segment included ANC indicators such as mHgbc, ANC attendance status and frequency, gestational age at birth, IPTp-SP doses, maternal 'ABO' phenotypic blood groups, and health statuses for syphilis, hepatitis B, and HIV, alongside systolic and diastolic blood pressure (S- & DBP). We used the single predelivery BP available for each patient as the representative value and excluded postdelivery BPs. We calculated the mean SBP and DBP for trichotomised BP groups (< 120, 120 - 139, ≥ 140 mmHg for SBP and < 80, 80 - 89, ≥ 90 mmHg for DBP) as proxies for all predelivery BP values during pregnancy.

The third segment focused on neonatal health evaluation at birth, including the APGAR score, foetal heart rate, fetal respiration within 30 minutes, foetal presentation, and fetal dimensions. The fourth section of the birth register records post-delivery complications such as postpartum haemorrhage, antepartum haemorrhage, and obstructed labour. Urban/peri-urban and rural communities were categorised based on statistical service population thresholds; urban areas have at least 5,000 inhabitants, while peri-urban areas are adjacent to urban areas with similar social dynamics. Married and cohabiting parturient women were grouped together based on perceived similarities in their dynamics. We did not anticipate missing records from the birth register, as professional obstetric nurses are required to document every birth as part of the Civil Registration and Vital Statistics (CRVS) system. Non-ANC attendants were included in the study due to the significance of their mHgbc readings, regardless of their attendance status. Their mHgbc levels corresponded to mean mHgbc estimates analysed for specific strata.

**Sample size**

The sample size was determined using the openEPI statistical software, considering summary data. The estimated percentage frequency (p) of the outcome factor was based on a prior study of MA prevalence in the Kwaebibirem municipal area, which reported a high prevalence of 71.2% using a similar study design [13]. A total of 1901 observations, representing records of parturient women who delivered at the hospital's maternity/labour suite, were entered into Epi Info 3.5.1 for further data analysis at a 95% confidence level. This choice aimed to enhance internal validity, reinforcing the generalizability of our results to diverse settings. This sample size was considered large enough to improve statistical power, generalizability, precision, reliability, stability, facilitate subgroup analysis, and better control for confounding variables.

**Management and analysis of data**

The analysis initially examined baseline characteristics of parturient women by proportions across different ANC visit categories and the burden of mHgbc less than 11.0 g/dl. This included stratum-specific analyses of maternal and pregnancy characteristics, presenting absolute numbers and percentages per characteristic. One-way ANOVA assessed the effect of varying ANC visit levels on mHgbc, comparing means across three independent groups (0 - 3, 4

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- 8, and ≥ 9 ANC visits) after confirming the normality of mHgbc distribution using the Shapiro-Wilk test. The test yielded a p-value of 0.069, indicating insufficient evidence to reject the null hypothesis of normality, with a computed W statistic of 0.97, suggesting near unity and indicative of normality. Skewness (-0.44) indicated a slight leftward skew, and excess kurtosis (-0.26) suggested a mesokurtic distribution, with no significant outliers detected. Therefore, the Shapiro-Wilk test suggested that the sample data did not substantially deviate from normal distribution, supporting the use of one-way ANOVA.

The F-statistic, degrees of freedom, and associated p-value from the Chi-squared test were used to evaluate differences in mean mHgbc across trichotomised ANC visit categories. Results from both parametric (assuming normal distribution) and non-parametric Kruskal-Wallis tests were reported. A post hoc assessment using two-sample t-tests, adjusted with Bonferroni correction ($\alpha = 0.01$) to minimise Type I error risk, determined statistically significant differences between ANC visit categories as suggested by the F-statistic. Specifically, we assessed variations in mean mHgbc between 0 - 3 vs. 4 - 8 ANC visits and 4 - 8 vs. ≥ 9 ANC visits. Data were analysed using OpenEpi, Epi Info 3.5.3, the GraphPad Prism version 10.3.1 and a T-test calculator.

## RESULTS

ANC visits ranged from 0 to 16, while mHgbc ranged from 1.6 to 16.3 g/dL. Mostly (54.7%), parturient women had 4 - 8 ANC visits, with 23.25% having 0 - 3 visits and 22.1% having ≥ 9 visits. The prevalence of mHgbc, categorised as mild, moderate, and severe MA, decreased with more ANC visits. Increased ANC visits shifted the prevalence of MA toward the 11.0 g/dL threshold, considered the lower limit of normal mHgbc (Table 1). The overall mean mHgbc was 9.85 g/dL (± 1.63) with 0-3 ANC visits, 10.31 g/dL (± 1.30) with 4 - 8 ANC visits, and 10.75 g/dL (± 1.33) with ≥ 9 ANC visits. A linear increase in mean mHgbc with higher ANC visits was observed, except among women aged 40 years and above. Variations in mean mHgbc across ANC visit categories were assessed using one-way ANOVA, focusing on subgroup analyses. Significant differences were found across the 0 - 3, 4 - 8, and ≥ 9 ANC visit categories, indicating a consistent rise with increasing ANC visits. Exceptions included women with tertiary education, grand multiparae, no IPTp-SP exposure during pregnancy, blood group AB, those not screened or positive for syphilis, lack of hepatitis B screening, non-screened or HIV-positive status, and those with SBP ≥ 140 mmHg and DBP ≥ 90 mmHg (Table 2).

The significance of variations in mHgbc between 0 - 3 vs. 4 - 8 ANC visits and 4 - 8 vs ≥ 9 visits was further assessed with an unpaired two-sample t-test as a post hoc analysis. Only ascending trends in mean mHgbc with increasing numbers of ANC visits were analysed. Declines in mean mHgbc for ≥ 9 visits were excluded from the analysis. The results indicated a predominant, significant increase in mean mHgbc with an increasing number of ANC visits. No significant variation in mean mHgbc was found between 0 - 3 and 4 - 8 ANC visits among women aged 21 - 30, those with senior high school education, those in formal occupations, and multiparae. Additionally, no significant variation in mean mHgbc was found between both 0 - 3 vs. 4 - 8 and 4 - 8 vs. ≥ 9 visits in grand multiparae, those not exposed to IPTp-SP, those with blood group AB, syphilis-positive women, those not tested for hepatitis B or HIV during pregnancy, HIV-positive women, and women with

Table 1. Evaluation of the trends and distribution patterns of maternal haemoglobin concentrations <11.0 g/dl by number of ANC visits

| Characteristic | Maternal Hemoglobin concentration (in g/dl) – N (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0-3 ANC visits | | | 4-8 ANC visits | | | ≥9 ANC visits | | |
| | ≤6.0 | 7.0-9.9 | 10.0-10.9 | ≤6.0 | 7.0-9.9 | 10.0-10.9 | ≤6.0 | 7.0-9.9 | 10.0-10.9 |
| Age group | | | | | | | | | |
| ≤20 years | 8(8.2) | 69(70.4) | 21(21.4) | 2(1.3) | 85(54.8) | 68(43.9) | 0(0.0) | 11(45.8) | 13(54.2) |
| 21-30 years | 3(3.2) | 51(53.7) | 41(43.2) | 3(1.0) | 160(54.4) | 131(44.6) | 3(2.3) | 57(44.5) | 68(53.1) |
| 31-40 years | 3(8.3) | 24(66.7) | 9(25.0) | 1(0.5) | 95(49.0) | 98(50.5) | 1(1.6) | 24(39.3) | 36(59.0) |
| ≥41 years | 1(9.1) | 7(63.6) | 3(27.3) | 0(0.0) | 10(55.6) | 8(44.4) | 0(0.0) | 5(100) | 0(0.0) |
| Residence | | | | | | | | | |
| Urban | 8(7.6) | 60(57.1) | 37(35.2) | 2(0.7) | 156(53.1) | 136(46.3) | 4(3.1) | 51(39.2) | 75(57.7) |
| Rural | 7(5.3) | 89(66.9) | 37(27.8) | 4(1.1) | 187(52.5) | 65(46.3) | 0(0.0) | 46(53.5) | 4045.5 |
| Educational background | | | | | | | | | |
| ≤ Junior high school | 13(6.2) | 131(62.4) | 66(31.4) | 4(0.8) | 285(55.7) | 223(43.6) | 2(1.5) | 64(47.1) | 70951.5) |
| Senior high school | 2(7.4) | 18(66.7) | 2(25.9) | 2(1.6) | 60(48.8) | 61(49.6) | 293.4) | 27(46.6) | 29(50.0) |
| Tertiary | 0(0.0) | 3(75.0) | 1(25.0) | 0(0.0) | 4(20.0) | 16(80) | 0(0.0 | 7(29.2) | 17(70.8) |
| Occupation | | | | | | | | | |
| Formal | 0(0.0) | 10(66.7) | 5(33.3) | 1(2.0) | 24(49.0) | 24(49.0) | 0(0.0) | 8(30.8) | 18(69.2) |
| Non-formal | 9(5.2) | 108(62.1) | 57(32.8) | 3(0.6) | 286(52.8) | 253(46.7) | 4(2.2) | 80(44.4) | 96(53.3) |

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Table 1. Cont.

| Characteristic | Maternal Hemoglobin concentration (in g/dl) – N (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0-3 ANC visits | | | 4-8 ANC visits | | | ≥9 ANC visits | | |
| | ≤6.0 | 7.0-9.9 | 10.0-10.9 | ≤6.0 | 7.0-9.9 | 10.0-10.9 | ≤6.0 | 7.0-9.9 | 10.0-10.9 |
| Parity | | | | | | | | | |
| Para 1 | 9(6.1) | 101(68.2) | 38(25.7) | 5(1.4) | 191(53.1) | 164(45.6) | 1(0.8) | 55(43.3) | 71(55.9) |
| Para 2-4 | 6(8.0) | 37(49.3) | 32(42.7) | 0(0.0) | 127(53.4) | 111(46.6) | 3(3.7) | 38(46.9) | 40(49.4) |
| ≥ Para 5 | 0(0.0) | 14(73.7) | 5(26.3) | 1(1.6) | 32(51.6) | 29(46.8) | 0(0.0) | 5(45.5) | 6(54.5) |
| Term status | | | | | | | | | |
| Preterm (< 36 weeks) | 5(17.2) | 13(44.8) | 11(37.9) | 1(1.9) | 28(51.9) | 25(46.3) | 0(0.0) | 2(66.7) | 1(33.3) |
| Early term (37-38 weeks) | 3(4.3) | 44(62.9) | 23(32.9) | 2(1.2) | 89(53.9) | 74(44.8) | 1(1.9) | 25(46.3) | 28(51.9) |
| Full term (39-40 weeks) | 5(5.5) | 57(62.6) | 29(31.9) | 1(0.3) | 156954.2) | 131(45.5) | 2(1.9) | 42(48.9) | 64(59.3) |
| ≥ Late term (≥ 41 weeks) | 0(0.0) | 28(73.7) | 10(26.3) | 2(1.6) | 59(47.6) | 63(50.8) | 1(2.0) | 25(51.0) | 23(46.9) |
| IPTp-SP during pregnancy | | | | | | | | | |
| Yes | 2(2.6) | 48(61.5) | 28(35.9) | 1(0.3 | 172(49.6) | 174(50.1) | 3(2.2) | 58(42.3) | 76(55.5) |
| No | 2(11.1) | 11(61.1) | 5(27.8) | 1(6.3) | 8(50.0) | 7(43.8) | 0(0.0) | 2(66.7) | 1(33.3) |
| ABO Phenotypic blood group | | | | | | | | | |
| A | 6(14.6) | 27(65.9) | 8(19.5) | 0(0.0) | 65(51.6) | 61(48.4) | 1(2.1) | 24(50.0) | 23(47.9) |
| AB | 0(0.0) | 7(77.8) | 2(22.2) | 0(0.0) | 11(68.8) | 5(31.3) | 0(0.0) | 1(25.0) | 3975.0) |
| B | 3(7.5) | 22(55.0) | 15(37.5) | 1(0.9) | 54(48.2) | 57(50.9) | 0(0.0) | 17(42.5) | 23(57.5) |
| O | 5(4.5) | 63(57.3) | 42(38.2) | 4(1.1) | 192(54.9) | 154(44.0) | 2(1.8) | 50(45.0) | 59(53.2) |
| Syphilis status | | | | | | | | | |
| Positive | 0(0.0) | 6(85.7) | 1(14.3) | 0(0.0) | 8(61.5) | 5(38.5) | 0(0.0) | 0(0.0) | 2(100) |
| Negative | 14(6.4) | 113(61.0) | 71(32.6) | 6(1.0) | 328(52.1) | 295(46.9) | 4(1.9) | 93(44.1) | 1143(54.0) |
| Not done | 1(12.5) | 6(75.0) | 1(12.5) | 0(0.0) | 4(66.7) | 2933.3) | 0(0.0) | 4(100) | 0(0.0) |
| Hepatitis B status | | | | | | | | | |
| Positive | 0(0.0) | 10(83.3) | 2(16.7) | 1(4.3) | 12(52.2) | 10(43.5) | 0(0.0) | 2(25.0) | 6(75.0) |
| Negative | 14(6.5) | 135(60.5) | 71(32.9) | 5(0.8) | 326(52.5) | 290(46.7) | 4(2.0) | 91(44.6) | 109(53.4) |
| Not done | 1(16.7) | 3(50.0) | 2(33.3) | 0(0.0) | 3(50.0) | 3(50.0) | 0(0.0) | 2(66.7) | 1933.3) |
| HIV status | | | | | | | | | |
| Positive | 0(0.0) | 2(66.7) | 1(33.3) | 0(0.0) | 6(50.0) | 6(50.0) | 0(0.0 | 2(100) | 0(0.0) |
| Negative | 14(6.3) | 141(62.9) | 69(30.8) | 6(1.0) | 332(52.8) | 291(46.3) | 3(1.4) | 91(43.8) | 114(54.8) |
| Not done | 1(25.0) | 2(50.0) | 1(25.0) | 0(0.0) | 2(100) | 0(0.0) | 1(20.0) | 2(40.0) | 2(40.0) |
| Systolic blood pressure | | | | | | | | | |
| 115.21 mmHg (±10.85) | 12(6.7) | 114(64.0) | 52(29.2) | 5(1.0) | 269(53.4) | 230(45.6) | 3(1.8) | 78(46.2) | 88(52.1) |
| 131.80 mmHg (±5.13) | 1(3.8) | 15(57.7) | 10(38.5) | 0(0.0) | 27(48.2) | 29(51.8) | 0(0.0) | 8(38.1) | 13(61.9) |
| 152.47 mmHg (±15.71) | 0(0.0) | 12(6.7) | 6(33.3) | 0(0.0) | 31(51.7) | 29(48.3) | 1(5.6) | 6(33.3) | 11(61.1) |
| Diastolic blood pressure | | | | | | | | | |
| 68.18 mmHg (±7.24) | 11(7.5) | 100(64.5) | 44(28.4) | 4(0.9) | 232(53.7) | 196(45.4) | 2(1.4) | 71(48.3) | 74(50.3) |
| 82.91 mmHg (±3.23) | 2(4.3) | 30(65.2) | 14(30.4) | 1(0.8) | 69(55.6) | 54 (43.5) | 1(2.6) | 14(35.5) | 24(61.5) |
| 98.07 mmHg (±11.34) | 0(0.0) | 10(50.0) | 10(50.0) | 0(0.0) | 26(41.9) | 36(58.1) | 1(4.5) | 7(31.8) | 14(63.6) |

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Table 2. Evaluation of patterns of mean maternal hemoglobin concentration analyzed by the number of ANC visits

| Characteristic | Mean (±SD) maternal hemoglobin concentration | | | ANOVA | Mann-Whitney/Wilcoxon Two-Sample Test (Kruskal-Wallis test for two groups) |
|---|---|---|---|---|---|
| | 0-3 ANC visits | 4-8 ANC visits | ≥9 ANC visits | F-statistic (p-value) | Chi square (p-value) |
| Age group | | | | | |
| ≤20 years | 9.34 (1.78) | 10.17 (1.23) | 10.60 (0.93) | 17.82 (0.00001) | 33.65 (0.00001) |
| 21-30 years | 10.24 (1.40) | 10.35 (1.39) | 10.69 (1.42) | 5.70 (0.0035) | 14.24 (0.0008) |
| 31-40 years | 9.98 (1.67) | 10.35 (1.23) | 10.98 (1.26) | 13.12 (0.00001) | 26.20 (0.00001) |
| ≥41 years | 9.49 (1.52) | 10.64 (1.15) | 9.75 (0.68) | 4.63 (0.01) | 7.19 (0.027) |
| Residence | | | | | |
| Urban | 9.78 (1.54) | 10.37 (1.34) | 10.76 (1.39) | 21.68 (0.00001) | 43.71 (0.00001) |
| Rural | 9.91 (1.70) | 10.31 (1.27) | 10.72 (1.23) | 14.44 (0.00001) | 25.63 (0.00001) |
| Educational background | | | | | |
| ≤Junior high | 9.79 (1.63) | 10.32 (1.31) | 10.69 (1.24) | 28.20 (0.00001) | 52.23 (0.00001) |
| Senior high | 9.92 (1.71) | 10.18 (1.30) | 10.54 (1.60) | 3.08 (0.047) | 8.35 (0.015 |
| Tertiary | 10.52 (1.55) | 10.90 (1.11) | 11.27 (1.08) | 2.20 (0.11) | 2 (0.18) |
| Occupation | | | | | |
| Formal | 10.23 (1.64) | 10.37 (1.41) | 11.12 (1.06) | 6.11 (0.0028) | 12.60 (0.0018) |
| Non-formal | 9.93 (1.53) | 10.34 (1.26) | 10.70 (1.37) | 22.28 (0.00001) | 44.38 (0.00001) |
| Parity | | | | | |
| Para 1 | 9.65 (1.68) | 10.31 (1.40) | 10.72 (1.32) | 28.80 (0.00001) | 57.64 (0.00001) |
| Para 2-4 | 10.15 (1.63) | 10.37 (1.16) | 10.78 (1.37) | 8.32 (0.0003) | 16.74 (0.0002) |
| ≥Para 5 | 9.90 (1.15) | 10.21 (1.28) | 10.46 (1.02) | 1.92 (0.14) | 4.11 (0.12) |
| Term status | | | | | |
| Preterm | 9.62 (1.93) | 10.40 (1.57) | 11.03 (1.72) | 3.82 (0.024) | 4.90 (0.086) |
| Early term | 9.75 (1.64) | 10.25 (1.26) | 10.49 (1.32) | 6.85 (0.0012) | 12.00 (0.0025) |
| Full term | 10.01 (1.59) | 10.35 (1.22) | 10.82 (1.33) | 16.14 (0.00001) | 35.69 (0.00001) |
| ≥Late term | 9.88 (1.39) | 10.37 (1.40) | 10.75 (1.31) | 6.53 (0.0017) | 15.63 (0.0004) |
| IPTp-SP during pregnancy | | | | | |
| Yes | 10.06 (1.50) | 10.46 (1.29) | 10.83 (1.36) | 13.57 (0.00001) | 32.38 (0.00001) |
| No | 9.68 (1.73) | 9.91 (1.65) | 10.30 (1.69) | 0.34 (0.70) | 0.91 (0.63) |
| ABO Phenotypic blood group | | | | | |
| A | 9.85 (1.92) | 10.30 (1.19) | 10.48 (1.19) | 3.76 (0.024) | 6.38 (0.041) |
| AB | 9.51 (1.53) | 10.46 (1.54) | 10.90 (1.31) | 2.78 (0.07) | 4.83 (0.08) |
| B | 9.76 (1.75) | 10.32 (1.29) | 10.81 (1.13) | 9.38 (0.0001) | 13.59 (0.0011) |
| O | 9.86 (1.60) | 10.34 (1.31) | 10.87 (1.31) | 24.72 (0.00001) | 44.61 (0.00001) |
| Syphilis status | | | | | |
| Positive | 9.67 (1.65) | 10.54 (1.51) | 11.30 (0.81) | 2.07 (0.14) | 4.59 (0.10) |
| Negative | 9.87 (1.66) | 10.32 (1.30) | 10.75 (1.34) | 33.47 (0.00001) | 65.13 (0.00001) |
| Not done | 8.80 (1.31) | 10.10 (1.32) | 9.96 (1.13) | 2.42 (0.11) | 3.04 (0.21) |
| Hepatitis B status | | | | | |
| Positive | 9.35 (1.04) | 10.45 (1.69) | 11.15 (0.97) | 6.04 (0.0039) | 13.33 (0.0013) |
| Negative | 9.85 (1.66) | 10.32 (1.29) | 10.72 (1.33) | 32.03 (0.00001) | 60.31 (0.00001) |
| Not done | 9.20 (1.49) | 10.17 (1.30) | 10.78 (1.07) | 2.26 (0.13) | 3.54 (0.17) |
| HIV status | | | | | |
| Positive | 10.04 (1.08) | 9.95 (1.64) | 10.67 (2.93) | 0.24 (0.78) | 0.23 (0.88) |
| Negative | 9.84 (1.65) | 10.33 (1.30) | 10.78 (1.23) | 40.32 (0.00001) | 73.15 (0.00001) |
| Not done | 9.16 (1.94) | 10.36 (1.55) | 8.70 (3.55) | 0.68 (0.52) | 1.58 (0.45) |
| Systolic blood pressure | | | | | |
| 115.21 mmHg (±10.85) | 9.77 (1.65) | 10.29 (1.29) | 10.66 (1.34) | 26.93 (0.00001) | 52.78 (0.00001) |
| 131.80 mmHg (±5.13) | 10.09 (1.59) | 10.57 (1.17) | 11.03 (1.16) | 5.65 (0.0042) | 8.66 (0.013) |
| 152.47 mmHg (±15.71) | 10.26 (1.64) | 10.46 (1.24) | 10.63 (1.39) | 0.57 (0.56) | 1.25 (0.53) |
| Diastolic blood pressure | | | | | |
| 68.18 mmHg (±7.24) | 9.75 (1.73) | 10.26 (1.26) | 10.63 (1.22) | 23.95 (0.00001) | 42.84 (0.00001) |
| 82.91 mmHg (±3.23) | 9.77 (1.32) | 10.34 (1.29) | 10.84 (1.56) | 10.22 (0.0001) | 25.27 (0.0000) |
| 98.07 mmHg (±11.34) | 10.63 (1.32) | 10.71 (1.32) | 10. 79 (1.44) | 0.13 (0.87) | 0.81 (0.81) |

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Table 3. Evaluation of mean maternal hemoglobin concentration variations by maternal and pregnancy characteristics using unpaired two-sample t-test

| Characteristic | 0 - 3 vs. 4 - 8 ANC visits | | | 4-8 vs. ≥ 9 ANC visits | | |
|---|---|---|---|---|---|---|
| | t-test | df | CI (p-value) | t-test | df | CI (p-value) |
| Age groups | | | | | | |
| ≤20 years | 4.95 | 323 | -1.15 to -0.50 (0.0001) | 2.11 | 245 | -0.82 to -0.03 (0.0350) |
| 21-30 years | 0.81 | 569 | -0.37 to 0.15 (0.41) | 2.93 | 649 | -0.56 to -0.11 (0.0035) |
| 31-40 years | 1.91 | 325 | -0.74 to 0.009 (0.056) | 4.35 | 396 | -0.84 to -0.31 (0.0001) |
| ≥41 years | 2.74 | 42 | -1.99 to -0.30 (0.0088) | - | - | - |
| Residence Area | | | | | | |
| Urban | 4.40 | 618 | -0.85 to -0.32 (0.0001) | 3.64 | 721 | -0.60 to -0.17 (0.0003) |
| Rural | 3.33 | 686 | -0.63 to -0.16 (0.0009) | 3.49 | 649 | -0.64 to -0.17 (0.0005) |
| Educational background | | | | | | |
| ≤Junior high | 5.35 | 1010 | -0.72 to -0.33 (0.0001) | 3.86 | 975 | -0.55 to -0.18 (0.0001) |
| Senior high | 1.08 | 200 | -0.73 to 0.21 (0.2799) | 1.93 | 249 | -0.72 to 0.0056 (0.053) |
| Tertiary | 0.78 | 43 | -1.35 to 0.59 (0.43) | 1.63 | 96 | -0.81 to 0.079 (0.10) |
| Occupation | | | | | | |
| Formal | 0.027 | 90 | -0.72 to 0.70 (0.97) | 3.30 | 124 | -1.19 to -0.30 (0.0013) |
| Non-formal | 4.18 | 1007 | -0.60 to -0.21 (0.0001) | 4.17 | 1083 | -0.52 to -0.19 (0.0001) |
| Parity | | | | | | |
| Para 1 | 5.27 | 706 | -0.90 to -0.41 (0.0001) | 3.72 | 737 | -0.62 to -0.19 (0.0002) |
| Para 2-4 | 1.55 | 447 | -0.49 to 0.058 (0.1210) | 3.42 | 490 | -0.64 to -0.17 (0.0007) |
| ≥Para 5 | 1.10 | 110 | -0.86 to 0.24 (0.2709) | 1.33 | 102 | -1.06 to 0.20 (0.1841) |
| Term status at birth | | | | | | |
| Preterm | 2.37 | 118 | -1.43 to -0.12 (0.019) | 1.07 | 86 | -1.79 to 0.53 (0.28) |
| Early term | 2.94 | 323 | -0.83 to -0.16 (0.0034) | 1.45 | 312 | -0.56 to 0.083 (0.14) |
| Full term | 2.55 | 538 | -0.60 to -0.07 (0.010) | 4.35 | 612 | -0.68 to -0.25 (0.0001) |
| ≥Late term | 2.18 | 224 | -0.93 to -0.048 (0.029) | 2.16 | 267 | -0.72 to -0.034 (0.031) |
| IPTp-SP | | | | | | |
| Yes | 2.81 | 623 | -0.67 to -0.12 (0.0050) | 3.73 | 783 | -0.56 to -0.17 (0.0002) |
| No | 0.45 | 43 | -1.25 to 0.79 (0.6533) | 0.50 | 24 | -1.98 to 1.20 (0.61) |
| Maternal ABO phenotypic blood groups | | | | | | |
| Group A | 2.12 | 229 | -0.86 to -0.031 (0.035) | 1.09 | 244 | -0.50 to 0.14 (0.27) |
| Group AB | 1.78 | 337 | -2.03 to 0.13 (0.083) | 0.85 | 37 | -1.47 to 0.59 (0.39) |
| Group B | 2.52 | 215 | -0.99 to -0.12 (0.012) | 2.78 | 232 | -0.83 to -0.14 (0.0058) |
| Group O | 3.69 | 643 | -0.73 to -0.22 (0.0002) | 4.96 | 713 | -0.73 to -0.32 (0.0001) |
| Syphilis | | | | | | |
| Positive | 1.39 | 27 | -2.14 to 0.40 (0.17) | 1.07 | 23 | -2.22 to 0.70 (0.29) |
| Negative | 4.81 | 1191 | -0.63 to -0.26 (0.0001) | 5.36 | 1247 | -0.58 to -0.27 (0.0001) |
| Hepatitis B | | | | | | |
| Positive | 2.19 | 47 | -2.10 to -0.090 (0.033) | 1.62 | 52 | -1.56 to 0.16 (0.11) |
| Negative | 5.03 | 1176 | -0.65 to -0.28 (0.0001) | 4.94 | 1245 | -0.55 to -0.24 (0.0001) |
| Not done | 1.33 | 13 | -2.53 to 0.59 (0.20) | 0.95 | 13 | -1.99 to 0.77 (0.35) |
| HIV | | | | | | |
| Positive | 0.11 | 17 | -1.58 to 1.76 (0.91) | 0.65 | 16 | -3.06 to 1.62 (0.52) |
| Negative | 5.29 | 1198 | -0.67 to -0.30 (0.0001) | 5.74 | 1272 | -0.60 to -0.29 (0.0001) |
| Not done | 1.14 | 9 | -3.57 to 1.17 (0.28) | 1.04 | 10 | -1.86 to 5.18 (0.31) |
| Systolic blood pressure | | | | | | |
| 115.21 mmHg (±10.85) | 4.97 | 934 | -0.72 to -0.31 (0.0001) | 4.04 | 985 | -0.54 to -0.19 (0.0001) |
| 131.80 mmHg (±5.13) | 1.91 | 127 | -0.97 to 0.01 (0.05) | 2.15 | 133 | -0.88 to -0.038 (0.032) |
| 152.47 mmHg (±15.71) | 0.70 | 123 | -0.76to 0.367 (0.48) | 0.65 | 127 | -0.68 to 0.34 (0.51) |
| Diastolic blood pressure | | | | | | |
| 68.18 mmHg (±7.24) | 4.50 | 794 | -0.73 to -0.28 (0.0001) | 2.43 | 837 | -0.66 to -0.071 (0.015) |
| 82.91 mmHg (±3.23) | 2.96 | 240 | -0.94 to -0.19 (0.0033) | 2.63 | 253 | -0.87 to -0.12 (0.0088) |
| 98.07 mmHg (±11.34) | 0.31 | 148 | -0.58 to 0.42 (0.75) | 0.32 | 151 | -0.56 to 0.40 (0.74) |

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SBP ≥ 140 mmHg and DBP ≥ 90 mmHg. Among preterm or early term deliveries and women with blood group A, variations were insignificant only for 4 - 8 vs ≥ 9 ANC visits (Table 3).

## DISCUSSION

ANC is a comprehensive framework designed to support pregnant women through critical interventions, including iron and folic acid supplementation (IFS), nutritional counselling, presumptive helminthic infestation therapy, and intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP). These services are provided from the time of registration through to childbirth, with a primary goal of elevating mHgbc to 11 g/dL or higher, either directly or indirectly. This study employed a stratified, subgroup-focused approach to investigate whether the relationship between ANC visits and mHgbc varies across different subpopulations of pregnant women. By identifying differences among subgroups, this research aimed to generate new hypotheses for future studies, potentially using alternative methodologies to examine the effectiveness of ANC visit frequency on mHgbc within distinct groups. Overall, the findings indicate a general trend of increased mHgbc with a higher number of ANC visits, suggesting a predictive role of ANC in enhancing mHgbc levels. However, some exceptions warrant further investigation into these subgroup-specific variations.

These findings, which are particularly pronounced in certain subgroups, align with existing literature. Ikeanyi et al. conducted a study to assess whether ANC attendance prevents MA at term among Nigerian women [16]. The investigators measured mHgbc levels at the initial booking and at term, comparing the proportion of anaemic individuals at booking with those at term. Using a retrospective cross-sectional comparative approach, 3,442 pregnant women were recruited at a South Nigerian mission hospital from 2009 to 2013. Approximately 33.0% had a hematocrit below 33% at booking, indicating a 32.2% prevalence of MA at this stage. By term or at childbirth, 21.4% of eligible subjects had their anaemia corrected, reflecting a prevention rate of 69.9%, with 9.2% still experiencing MA despite ANC attendance. The investigators concluded that high-quality ANC is a valuable preventive intervention to reduce the prevalence of MA, highlighting the need to ensure its widespread availability, accessibility, and affordability for all pregnant women. Our findings, however, further emphasise that subgroup analysis reveals varying outcomes or factors influencing the effectiveness of ANC [16].

Saapiire et al. conducted a cross-sectional study in Wa Municipality, Ghana, assessing the utilisation of antenatal care (ANC) services and their impact on maternal anaemia (MA) among pregnant women. Their findings are consistent with ours; despite 80.2% of women reporting sufficient ANC services, the overall adequacy of ANC was only 44.2%. After adjusting for confounders, women with inadequate ANC attendance were 2.3 times more likely to experience MA in the third trimester compared to those with adequate ANC attendance [17]. When comparing our study to that of Kofie et al., both studies suggest that increased ANC may reduce MA. Kofie et al. identify specific ANC practices, such as intensified iron and folic acid supplementation, that improve maternal haemoglobin levels. In contrast, our study finds that higher ANC frequency is associated with reduced MA prevalence, but does not specify which ANC services contribute to this reduction. Thus, while Kofie et al. detail effective practices, our study emphasises the general benefit of more frequent ANC visits [18].

Similarly, our findings align with Mishra et al. [19], who highlighted ANC's role in managing MA through iron and folic acid supplementation and educational interventions. However, they also identified poor adherence and limited awareness of MA symptoms as major barriers to its effectiveness. These factors may help explain anomalies in our data—such as among educated or employed women—where higher health literacy did not translate into significantly elevated mHgbc. This indicates that knowledge alone is insufficient without consistent adherence and supportive systems like structured follow-up or individualised counselling. Mishra et al.'s emphasis on personalised care may further clarify why certain subgroups in our study, such as formal workers, showed limited gains, possibly due to time constraints that reduced participation in counselling sessions and weakened the impact of ANC frequency. Massawe et al. [20] emphasised

The results of this study, consistent with existing literature, showed a trend of higher mHgbc with increased ANC visits, though some subgroups deviated from this pattern. Differences in mean mHgbc among these exceptional subgroups across the trichotomised ANC visit categories—and in post hoc comparisons between 0–3 vs 4–8 and 4–8 vs ≥9 ANC visits—were not statistically significant when tested using one-way ANOVA and unpaired t-tests. The unpaired t-test corroborated the findings from the ANOVA F-statistic and Kruskal-Wallis chi-squared test, confirming both significant and insignificant predictive roles of ANC visits on mean mHgbc. Due to data limitations, we did not explore the specific reasons for the exceptional trends in some subgroups. No significant variation in mean mHgbc between 0 - 3 and 4 - 8 ANC visits was observed among women aged 21 - 30, those with senior high school education, formal occupations, and multiparae. Similarly, no significant differences were found between 0 - 3 vs 4 - 8 and 4 - 8 vs ≥ 9 visits in grand multiparae, those not exposed to IPTp-SP, with blood group AB, syphilis-positive women, those untested for hepatitis B or HIV, HIV-positive women, and those with SBP of 153.45 mmHg (± 15.71) and DBP of 98.07 mmHg (± 11.34). Among preterm or early-term deliveries and women with blood group A, differences were insignificant only for 4 - 8 vs ≥ 9 visits.Further studies are needed to explore the few subgroups that showed no significant difference in mean mHgbc acr oss 0 - 3, 4 - 8,

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and ≥ 9 ANC visits, as this exceeds the scope of our study [21]. We recommend investigating these relationships using alternative models in future research. Although this study demonstrates positive correlations between ANC attendance and higher mean mHgbc, it remains unclear why this correlation does not consistently raise mean mHgb concentrations to levels above the optimal 10.99 g/dl. While the study shows associations between higher ANC visits and higher mHgbc, caution is needed when attributing causation due to the limitations of secondary data, which may not capture all factors influencing mHgbc during pregnancy. Future research should explore beyond routine interventions like IFS, IPTp-SP, and presumptive helminthic therapies, focusing on dietary counselling, increased screening for maternal anaemia, and other interventions to address low mHgbc. Evaluating factors that complement ANC services and prevent maternal anaemia is challenging, often requiring speculative hypotheses. This study cannot account for all unrecorded interventions that may have impacted mHgbc, as the birth register data were not originally collected for research. Interventions beyond standard ANC could have significantly influenced the increase in mean mHgbc among attendees.

Attributing our findings to specific interventions like routine IFS, presumptive helminthic therapies, or nutrition counselling is challenging due to the limitations of secondary data. Factors beyond the ANC package likely contribute to the observed rise in mean mHgbc with increasing ANC visits. The observed variations may reflect the influence of diverse clinical interventions that we could not control for, given their complexity and the use of secondary data. While cross-sectional studies limit causal inference, our methodology offers insights into how varying ANC visits may impact mHgbc. We emphasise the critical role of ANC, as any intervention contributing to the observed increase in mHgbc likely occurred within the ANC framework. However, we cannot confidently assert that ANC reduces the risk of MA despite its apparent association with increased mHgbc. Understanding and enhancing this relationship is crucial for achieving mHgbc levels consistent with normal iron-supplemented populations. Identifying specific ANC aspects that impact mHgbc improvement exceeds this study's scope. Prospective studies monitoring pregnant women throughout ANC are needed to better understand the factors influencing mHgbc.

### Conclusion

We observed a tendency for mHgbc to increase with a higher frequency of ANC visits, which aligns with previous research. However, exceptions were identified in subgroups such as women aged 21 - 30, preterm deliveries, non-exposure to IPTp-SP, mild and severe MA, positive HIV status, and those with high BP. While our findings offer insights into this association, we acknowledge limitations due to the use of secondary data not routinely collected for research. This limitation made it difficult to control for factors such as blood transfusions used to manage moderate to severe MA, which are not captured in birth registers. We recommend further prospective studies with larger sample sizes to prevent data reduction in subgroup analyses. These studies should aim to better understand the impact of specific ANC services on mHgbc, while controlling for clinical interventions outside traditional ANC services.

## DECLARATIONS

### Ethical consideration

Ethical approval was obtained from the Ghana Health Service Ethics Review Committee (GHS-ERC: 007/05/24).

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest

### Author contribution

The authors conceptualised and designed the study. The first author conducted data analysis with support from the second author. Both authors prepared the draft manuscript following data collection and analysis.

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### Availability of data

Data is available upon request to the corresponding author

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# Quality of life outcomes of head and neck cancer survivors and their family caregivers at the Korle Bu Teaching Hospital

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**Abstract**

***Background:*** A steady increase in the number of patients diagnosed with head and neck cancer (HNC) has necessitated the need for further studies on the quality-of-life (QOL) outcomes of these patients and their caregivers.

***Objective:*** The study evaluated the QOL of HNC survivors and their family caregivers in a sub-Saharan African tertiary health facility.

***Methods:*** This was a descriptive cross-sectional study at the Ear, Nose and Throat (ENT) Department and the National Radiotherapy, Oncology and Nuclear Medicine Centre at the Korle Bu Teaching Hospital. After consenting to be part of the study, the demographic characteristics of participants were recorded on a data collection form, and their QOL outcomes were evaluated using the World Health Organisation Quality of Life (WHO-QOL) questionnaires. An independent sample t-test was used to analyse the differences in mean score values in QOL. Logistic regression analysis was used to examine factors associated with the overall QOL of patients with HNC. Odds ratios and 95% confidence intervals were calculated. P-values less than 0.05 were considered statistically significant.

***Results:*** A total of 160 patients with HNC and 160 family caregivers participated in this study. The mean ages of the patients and caregivers were 45.1 (SD 15.9) years and 36.2 (SD 13.1) years, respectively. Both HNC patients and their caregivers had a good QOL overall. However, HNC patients had a better QOL compared with their family caregivers (72.12 (SD 19.30) vs. 62.70 (SD 16.6), p = 0.001) in each domain and the overall QOL, except satisfaction with health. A total of 74.4% (n = 119) of patients with HNC had a QOL outcome. Education and the type of treatment received were associated with a good quality of life.

***Conclusion:*** Both HNC patients and their caregivers have a good QOL. However, patients with HNC had a better QOL compared with their family caregivers.

**Keywords:** Head and neck cancers, psychological well-being, quality of life, family caregivers

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## INTRODUCTION

Head and neck cancer (HNC) includes a group of neoplasms affecting the paranasal sinuses, nasal and oral cavities, pharynx and larynx. It is among the ten most common cancers globally, with 540,000 new cases and 271,000 deaths annually worldwide [1]. Patients with HNC usually present with an advanced disease in middle adulthood at the time of diagnosis [2]. These patients may experience social and psychological issues that present with disfigurement, inability to return to work, resistance to eating in public, and stigma associated with having a disease that is increasingly transmitted through sexual practices [3,4,5]. Overall, these negative outcomes have a detrimental effect on their quality of life (QOL).

Cancer experience is not only a stressful event for patients but also for their caregivers, who are often the primary

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source of support and care for patients with HNC. A study has shown that these patients and their caregivers experience severe psychiatric symptoms, which are consistent with a diagnosis of post-traumatic stress disorder [6]. Caregivers experienced cancer-related distress equal to or even more severe than the HNC patients themselves [7]. Unpublished information at the ENT Unit at the Korle-Bu Teaching Hospital (KBTH) reveals a steady increase in the number of HNC cases. This increase may subsequently have a toll on the QOL of these patients and their caregivers. Hence, this study sought to explore the QOL outcomes of HNC survivors and their caregivers, provide insights into the magnitude of HNCs at the KBTH, and further determine the extent of the burden of care on family caregivers. The outcomes of this study will enable the implementation of appropriate interventions to enable caregivers and patients to cope with adverse quality of life.

## MATERIALS AND METHODS

This was a comparative cross-sectional study conducted at the Ear, Nose and Throat (ENT) Unit and the Oncology Centre at the KBTH from July 2022 to November 2022. On average, 210 patients are diagnosed with HNC yearly at the KBTH and ultimately undergo any of the treatment modalities, which include surgery, radiotherapy or a combination of surgery and radiotherapy. The study included adult HNC patients and their caregivers aged between 18 and 88 years who were receiving care at the ENT Unit and the Oncology Centre at the KBTH.

HNC patients and their family caregivers with psychological disorders, as well as those unaccompanied HNC participants, were excluded. The proportion of HNC patients who suffer some degree of depression (15% to 50%) at any given point across the disease trajectory from a previous study was used [8]. For this comparative cross-sectional study, the minimum sample size required for the study was derived from the formula [9];

$$N = (Z\alpha+Z\beta)(Z\alpha+Z\beta)*(p1(1-p1)+p2(1-p2)) / (p1-p2)(p1-p2),$$

Where N is the sample size required for both groups.

p1 is the prevalence of HNC patients who suffer some degree of depression [8].

p2 is the proportion of morbidity of depression in caregivers of HNC patients, which has been found to range from 9.0% to 57.0% [10].

$\alpha = 0.05$ the level of significance = 1.96, $\beta$ = the power of the test, i.e. 80 % power = 0.2.

Using p1 = 16%, p2 = 26%. From the above formula, a total of 248 persons from the two groups were required to be recruited into the study. After accounting for attrition (20%), the sample size was determined as (120/100) x 257 ≈ 308 participants. Therefore, a minimum of 154 HNC patients and 154 caregivers were required for the study. However, a total of 160 participants were recruited for each group in order to increase the power of the test.

A register of patients attending the HNC clinic was used as the sampling frame. A simple random sampling technique was used in the selection of participants. Identification numbers (IDs) of HNC patients who had been booked to be seen were entered in Microsoft Excel 2015 worksheets. A random number generator command (RAND function) in Excel 2015 was given for the randomisation of the IDs of participants. The first five (5) ID numbers that appeared on the spreadsheet for the list of random numbers were selected and invited to participate in the study. This was done weekly until the number of participants to be recruited was obtained. Recruitment was done with the help of the nurses at ENT, and two trained Research Assistants. Each patient was paired with a caregiver. The pairing was done at the preference of the patient and guided by the principal researcher (PR). In this regard, the PR guided patients with more than one caregiver in choosing a primary or close caregiver for the study.

Potential participants who met the criteria for inclusion were approached at the Outpatient Department of the study sites for consent after the purpose of the study had been explained to them. Those who consented were selected and given a questionnaire to complete at an agreed time and venue. Demographic characteristics of the participants recorded include gender, age, educational background, and employment status of HNC survivors and their caregivers. Age was categorised as follows: 18 - 40 years young adult, 40 - 59 years middle-aged adult, and ≥ 60 years old adults) [11]. The Medical history included the site of cancer diagnosis (oral cavity, oropharynx, hypopharynx, and larynx), type of treatment (surgery, radiotherapy, chemotherapy, and combination), and duration of treatment. The World Health Organisation Quality of Life (WHO-QOL) tool was used to assess the quality of life of HNC survivors and their caregivers. The tool was validated by the WHOQOL Group [12] and achieved a Cronbach alpha for the four domains: physical health 0.8, psychological health 0.76, social relationship 0.66 and environmental well-being 0.80 for reliability analysis.

The (WHO-QOL) is a 26-item Likert-type scale, of which 24 items are divided into four domains assessing physical health, psychological health, social relationships, and environmental well-being, and the remaining two questions examine self-perceived QOL and satisfaction with health. Each domain is represented by several questions formulated for a Likert response scale, with intensity (nothing - extremely), capacity (nothing - completely), frequency (never - always) and assessment scales (very dissatisfied - very satisfied; very bad - very good), all of them consisting of five levels (one to five). The domain scores are scaled positively; higher scores denote a higher quality of life. Three items were compulsorily reversed before scoring: items 3, 4 and 26. The transformed score for each domain was derived from the summation of raw scores. The overall

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scores for the QOL outcome were calculated by averaging the sum of all the other domain elements. The total score varied from 0 to 100%, with a mean score of 60% representing the cut-off point for a good quality of life outcome [13].

**Data Analysis**

Data obtained was entered into a Microsoft Access database and transferred into IBM SPSS version 25 for analysis. Descriptive data were presented as means and standard deviations, and categorical data were presented as counts and percentages. The quality of life of patients with HNC and their caregivers was measured using the World Health Organisation QOL questionnaire in the domain of physical health, psychological health, social relationships, and environmental well-being. Scores in these domains were presented as percentages. Raw scores were converted to transformed scores using SPSS syntax, which directly converted the raw score into transformed domain scores for each domain on a scale from 0 to 100 to enable comparisons between domains with unequal numbers of items. An independent sample t-test was used to analyse the significant difference in mean score values of the health-related quality of life scores for patients with HNC and their family caregivers. Logistic regression analysis was conducted to analyse the association between socio-demographic data and clinical factors and the overall quality of life of the patients with HNC. Odds ratios and 95% confidence interval were calculated. P-values less than 0.05 were considered statistically significant.

Table 1. Demographic characteristics of head and neck cancer patients and family caregivers

| Characteristic | HNC patients (N=160) N (%) | Family caregivers (N=160) N (%) |
|---|---|---|
| Age group : | | |
| 18-40 | 67(41.9) | 108(67.5) |
| 40-59 | 59(36.9) | 43(26.9) |
| ≥ 60 | 34(21.3) | 9(5.6) |
| Sex : | | |
| Male | 116(72.5) | 73(45.6) |
| Female | 44(27.5) | 87(54.4) |
| Religion | | |
| Christian | 139(86.9) | 141(89.2) |
| Islam | 21(13.1) | 19(10.8) |
| Education : | | |
| Primary School | 29 (58.0) | 6(3.8) |
| Junior High School | 41(25.6) | 46(28.7) |
| Senior High School | 39 (24.4) | 36(22.5) |
| Tertiary | 61 (38.1) | 72(45.0) |
| Employment status : | | |
| Employed | 128(80.0) | 125(78.1) |
| Unemployed | 32(20.0) | 35(21.9) |

Mean age patients = 45.1±15.9; min = 18.0; max = 88.0. Mean age caregivers = 36.2±13.1; min = 18.0; max = 80.0

## RESULTS

A total of 160 patients with HNC and 160 family caregivers participated in this study. The mean age of the patients was 45.1 ± 15.9 years, with minimum and maximum ages of 18 years and 88 years. The mean age of the caregivers was 36.2 ± 13.1 years, with minimum and maximum ages of 18 years and 80 years, respectively. Most (67.5 %, n = 108) family caregivers were aged 18 - 40 years, and the majority of patients and caregivers were male (72.5%) and female (54.4%), respectively. Christians constituted the majority among both patients and caregivers, with 86.9% (n = 139) and 89.2% (n = 141), respectively. The primary level of education among patients was comparatively higher than among caregivers (58% vs 3.8%). A large proportion of both patients (80.0%, n = 128) and caregivers (78.1%, n = 125) were employed, and more than half of the caregivers (n = 93, 58.1%) were children of the patients (Table 1).

**Clinical characteristics of patients with HNC**

For participants who had records for the duration of treatment, the mean duration of treatment for the patients with HNC was 9.0 ± 3.8 months, with the minimum and maximum duration of treatment being 1 month and 108 months, respectively. The majority (81.2%, n = 95) had a duration of treatment less than 12 months. Among the patients with HNC, the cancer location was as follows: larynx (25.6%, n = 41), oropharynx (11.4%, n = 18),

Table 2. Clinical characteristics of head and neck cancer patients

| Characteristics | Number (N) | Percentage (%) |
|---|---|---|
| Duration of treatment (months) | | |
| < 12 | 95 | 81.2 |
| 12 - 36 | 17 | 14.5 |
| 36 - 60 | 4 | 3.4 |
| >= 60 | 1 | 0.9 |
| Site of cancer : | | |
| Oral cavity | 7 | 4.4 |
| Oropharynx | 18 | 11.4 |
| Hypopharynx | 17 | 10.6 |
| Larynx | 41 | 25.6 |
| Duration of diagnosis | | |
| < 1 years | 74 | 46.3 |
| 1 - 3 years | 63 | 39.4 |
| 3 - 5 years | 14 | 8.8 |
| > 5 years | 9 | 5.6 |
| Type of treatment : | | |
| Surgery | 41 | 25.6 |
| Radiotherapy | 21 | 13.1 |
| Chemotherapy | 49 | 30.6 |
| Combination | 49 | 30.6 |

Mean duration of treatment = 9.0 ± 3.8 months Minimum duration of treatment = 1 month, maximum = 108 months.Note that records available for duration of treatment and site of cancer were analysed out of the 160 patients.

hypopharynx (10.6%, n = 17) and oral cavity (4.4%, n = 7) were also reported as cancer sites. About half of the patients (46.3%, n = 74) were diagnosed less than 12 months prior to the study. Approximately 30.6% (n = 49) of the patients were treated with chemotherapy in combination with either radiotherapy or surgery (Table 2).

Table 3. Health-related quality of life scores for head and neck cancer patients and family caregivers

| QoL Domain | Mean values | | Difference | P-value |
|---|---|---|---|---|
| | HNC patients Mean±SD | Caregivers Mean±SD | | |
| Physical health | 76.4±17.7 | 64.7±14.2 | 11.8 | 0.001* |
| Psychological health | 66.4±21.6 | 61.6±17.7 | 4.7 | 0.037* |
| Social relationship | 69.7±21.4 | 62.9±19.4 | 6.7 | 0.005* |
| Environmental wellbeing | 78.1±18.3 | 65.3±14.6 | 12.7 | 0.001* |
| Self-perceived QoL | 76.4±23.8 | 67.7±23.5 | 8.7 | 0.001* |
| Satisfaction with health | 66.9±29.5 | 70.3±24.7 | -3.4 | 0.267 |
| Overall | 72.12± 19.30 | 62.70 ±16.6 | 9.4 | 0.001* |

Table 4. Association between demographic and clinical characteristics and overall HRQOL of for head and neck cancer patients

| Factor | OR | Confidence | Interval | P-value |
|---|---|---|---|---|
| Age | | Lower | Upper | |
| 18-40 | Reference | | | |
| 40-59 | 1.90 | 0.60 | 6.20 | 0.290 |
| >=60 | 0.40 | 0.10 | 1.90 | 0.250 |
| Male | Reference | | | |
| Female | 0.70 | 0.20 | 0.20 | 0.20 |
| Education | | | | |
| Primary | Reference | | | |
| JHS | 0.10 | 0.02 | 7.05 | 0.036* |
| SHS | 0.11 | 0.02 | 25.16 | 0.017* |
| Tertiary | 0.16 | 0.03 | 28.47 | 0.041* |
| Employment: | | | | |
| Employed | Reference | | | |
| Unemployed | 3.20 | 0.80 | 12.70 | 0.096 |
| When diagnosed: | | | | |
| <1 year | Reference | | | |
| 1-3 years | 1.44 | 0.29 | 7.05 | 0.655 |
| 3-5 years | 1.98 | 0.16 | 25.16 | 0.599 |
| >5 years | 3.36 | 0.40 | 28.47 | 0.267 |
| Type of treatment | | | | |
| Surgery | Reference | | | |
| Radiotherapy | 0.04 | 0.02 | 0.65 | 0.025* |
| Chemotherapy | 0.43 | 0.12 | 1.57 | 0.200 |
| Combination | 0.09 | 0.01 | 0.59 | 0.013* |
| Treatment duration | | | | |
| <12 months | Reference | | | |
| 12-36 months | 2.60 | 0.53 | 12.85 | 0.241 |
| 36-60 months | 0.00 | 0.00 | - | 0.999 |
| > 60 months | 0.00 | 0.00 | - | 1.000 |
| *Statistically significant association. | | | | |

**Health-related quality of life scores for patients with HNC and family caregivers**

In an independent t-test analysis, with an exception from the domain "satisfaction with health", there was a significant difference in mean score for QOL between the patients and the caregivers in all the other domains (physical health, psychological health, social relationship, environmental well-being, and self-perceived quality of life) with the HNC patient having a better QOL compared with their caregiver ($p < 0.05$) in each domain. The HNC patients had a better overall health-related quality of life (HRQOL) compared with the caregivers ($p > 0.05$). Although there was a significant difference between patients with HNC and family caregivers in terms of the overall QOL outcome ($p = 0.001$), both had a good overall HRQOL (Table 3).

**Association between demographic and clinical characteristics and overall HRQOL of head and neck cancer patients and family caregivers**

A total of 119 (74.4%) patients with HNC had a good quality of life outcome. From the logistic regression analysis, education and type of treatment received (radiotherapy and a combination of other therapies) were associated with good quality of life outcomes among HNC patients. (Table 4).

## DISCUSSION

This study sought to evaluate the quality of life (QOL) outcomes of HNC survivors and their caregivers in a sub-Saharan African tertiary health facility. In our study, most (72.5%, n = 116) of the HNC survivors were males aged 18-88 years, and more than half (54.4%, n = 87) of the caregivers were females. This is similar to the study by D'Souza et al. [14], which reported 54% of males within the age bracket of 40 to 64 years out of the 89 HNC survivors assessed. Similarly, Terrell et al. [15] reported a male preponderance (78%) within the age group 27 - 88 years out of 570 patients with HNC studied. This variation of HNC prevalence in sex could be explained by the fact that men are more likely to be engaged in significant risk factors for HNCs, such as tobacco smoking and alcohol consumption [16].

Again, Lo et al. [17] demonstrated that the treatment impact on all dimensions of QOL generally affected younger patients more as compared to older patients. Our result of female preponderance in family caregiving is also supported by Guerrriere et al. [18], who found in their study on family caregivers of HNC survivors that 70% of caregivers were females with a mean age of 59 years. Another study done among 200 cancer fighters and their caregivers in New Delhi revealed that most caregivers were females (55%) with a mean age of 40 years. Globally, the task of family caregiving is predominantly seen as a female occupation involving the provision of informal care for family members with chronic health complications and disabilities [19,20]. Even in situations where each gender

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tends to share similar roles domestically, the task of family caregiving remains a feminine-dominated venture [21,22]. About 70 - 80% of caregivers were female and spent more than 50% of their time in caregiving compared to males [23,24]. In most societies and cultures, women are expected to adopt the role of a family caregiver by staying at home to perform house chores and care for kids, making them less likely to be employed away from home, while men are expected to work away from home [25,26]. Women's role in family caregiving is, therefore, directly premised on the sense of obligation to their families [27].

More than 70% of the patients with HNC in this study had a good QOL outcome. This result could be explained by the significant sacrifices and role of family caregivers in caring for their HNC patients and providing them with the needed social and psychological support for improving their health status, even at the expense of the caregivers. Our results also demonstrate that although HNC patients and their caregivers may have a good QOL, patients with HNC have a better QOL than their family caregivers. Both may experience some significant level of challenges associated with the cancer condition. This is consistent with a previous study by Hodges and Humphris [7], who indicated that caregivers experienced cancer-related distress equal to or even more severe than that of the patients. Furthermore, Verdonck-de Leeuw et al. [28] found clinical levels of psychological distress in one-fifth of caregivers and one-quarter of HNC patients. Similarly, Vickery et al. [29] showed that caregivers have more psychological disorders compared to patients with HNC. Caregivers have shown poor mental health (e.g., high levels of depression, anxiety symptoms, low QOL) compared to the general population or in comparison with HNC patients [7].

Our finding - that patients with HNC report better QOL than their caregivers is consistent with that of Richardson et al. [31], who also reported a better QOL among patients with HNC compared with their caregivers. This finding highlights the significant burden caregivers endure. Roing et al. [32] in their study explained this difference in QOL outcome between patients with HNC and their caregivers by indicating that lifestyle changes such as disrupted work-life balance and social isolation imposed on caregivers as a result of providing care negatively affect their QOL and significantly increase their stress level. Rigoni et al. [33] also indicated that caregivers had a compromised QOL, just as patients with HNC. The burden of caregiving primarily manifests as overwhelming responsibilities and substantial disruptions to daily routines. Our findings may suggest that caregivers of patients with HNC in Ghana may experience a burden similar to that reported in other contexts, contributing valuable insights to the literature on QOL among HNC survivors and their caregivers.

Quality-of-life (QOL) outcome measures play a key role in analysing the perception of the effects of the disease on the daily activities of patients and caregivers. Quality-of-life (QOL) outcomes in patients are determined not only by the activity of the disease and its associated treatment but also by other factors that may influence the QOL outcome among patients. From our logistic regression analysis, education and the type of treatment received were associated with good QOL outcomes among HNC patients. Our finding that education is associated with good QOL outcome among patients with HNC [34] could be explained by the fact that HNC patients with low educational backgrounds may tend to be involved in unhealthy behaviours and lifestyles that may further deteriorate respective disease conditions. Additionally, such persons may have fewer resources to cope with the HNC disease, leading to reduced QOL.

A higher level of education may enable patients to understand the course of the disease and increase their desire to seek additional educational programs and interventions which are directed towards improving health outcomes. Additionally, our results indicate that the type of treatment for HNC had a significant impact on QOL. Parkar and Shah [34] also explained that the type of treatment received was associated with good QOL outcomes among patients with HNC. Patients undergoing treatments that balance cancer control with preservation of function and appearance may tend to report better QoL outcomes [35]. For example, treatments such as chemoradiotherapy and minimally invasive surgical techniques may help maintain speech, swallowing, and appearance, which are critical to social functioning and self-esteem [35]. Similarly, Kara et al. [36] reported that HNC survivors exhibit different QOL-related symptoms depending on combined treatment modalities and time post-treatment; hence, there is a need to understand the QOL differences based on treatment modalities when developing treatment plans for patients with HNC. According to Parkar and Shah [34], other factors associated with QOL may include age, female sex, duration of treatment, advanced tumour, and site of the tumour.

The limitation of the study can be attributed to its comparative cross-sectional nature, which does not establish a cause-and-effect relationship. Again, the study did not factor in the possibilities of other comorbidities of HNC survivors and their caregivers, which may account for or influence their QOL. Future studies should highlight the effects of comorbidities on HNC survivors and their caregivers. Furthermore, the data obtained from the questionnaire could not determine the difference between the well-being of the two groups (HNC survivors and their caregivers) in the long term. Future researchers may consider a prospective studies to evaluate the long-term QOL of HNC survivors and their family caregivers.

The present study suggests that the treatment, management and intervention protocol for head and neck cancer patients should not be limited to only survival but also to ensure their quality of life and that of the caregivers throughout the intervention and recovery process. These findings are helpful in designing a comprehensive care program in Ghana to address QOL issues for HNC survivors and their

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caregivers. Quality of life (QOL) encompasses an individual's subjective perception of well-being and coping ability. Hence, there is a need for active support on the challenges of the caregiving burden. It is imperative to create a comprehensive cancer care program for patients and their caregivers at the time of diagnosis for sustainable health conditions and to improve their QOL.

### Conclusion

This study has demonstrated that both HNC patients and their caregivers have a good quality of life. However, patients with HNC had a better QOL compared with their family caregivers. Screening for psychological or emotional issues and early referral to (psychological) support in the first line, if needed, may, therefore, ensure caregivers are able to be the important source of support for patients and, thus, avert the creation of "another or second patient". Moreover, knowledge of the risk factors or causes can be used to identify caregivers who may benefit from additional counselling and psychological support, such as caring for patients who are non-spousal or non-biologically related, as well as with comorbidity or severe tumour stage.

## DECLARATIONS

### Ethical consideration

Ethical approval for the study was obtained from the Institutional Review Board of the Korle Bu Teaching Hospital in Ghana with approval number KBTH-IRB/000173/2022. Permission to conduct the study was obtained from the study sites, and informed consent was obtained from all study participants before the commencement of the study.

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest

### Author contribution

SOB and KKB conceptualised and designed the study. SOB and BA performed data curation and analysis. Methodology development and investigation were carried out by SOB and BA. SOB managed project administration and resource provision. Software support was provided by BA. Supervision was provided by KKB, EDK, and JY. The manuscript was drafted by SOB and BA and reviewed for intellectual content by KKB, EDK, JY, and MAD. All authors read and approved the final version of the manuscript.

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### Availability of data

Data is available upon request to the corresponding author

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# Programmed death-ligand 1 (PD-L1) expression in malignant and benign cervical and breast cancers

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**Abstract**

***Background:*** Programmed death-ligand 1 (PD-L1) expression has become a valuable biomarker for guiding immunotherapy selection in various cancers, including breast and cervical malignancies.

***Objective:*** This study aimed to investigate the immunohistochemical expression of PD-L1 in malignant and benign breast and cervical cancers.

***Methods:*** This retrospective study involved the analysis of 40 formalin-fixed paraffin-embedded tissue blocks, with 20 blocks from breast cancer patients and 20 from cervical cancer patients. Immunohistochemical analysis was performed via the avidin-biotin immunoperoxidase method to detect PD-L1 expression. The expression was assessed using a semi-quantitative method, grading the staining intensity and the percentage of stained cells per field. The stained sections were observed under a Leica microscope (Leica DM750, Switzerland) connected to a digital camera (Leica ICC50).

***Results:*** PD-L1 expression was greater in cervical cancer than in breast cancer. In breast cancer, benign cases mostly presented negative PD-L1 expression, with a mean percentage reactivity (MPR) of 14.8%, whereas malignant cases presented mild expression, with an MPR of 46.4%. In cervical cancer, benign cases were mainly negative, with an MPR of 18.4%, whereas malignant cases displayed mild to moderate PD-L1 expression, with an MPR of 71.3%.

***Conclusion:*** PD-L1 expression was more pronounced in cervical cancer than in breast cancer. The elevated levels of PD-L1 in cervical cancer suggest that this type of cancer may be more responsive to immunotherapeutic interventions targeting the PD-L1 pathway compared to breast cancer. Recognising these differences is crucial for tailoring treatment plans and implementing personalised medicine strategies for each specific cancer type.

**Keywords:** Cervical cancer, breast cancer, PD-L1, immunotherapy, HPV.

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## INTRODUCTION

Breast cancer mostly affects breast tissue in women and is less prevalent among men. It is the most common type of cancer among women worldwide and is characterised by the uncontrolled growth and spread of abnormal epithelial cells lining the ducts or lobules of the breast tissue [1]. Triple-negative breast cancer (TNBC) is a subgroup of breast cancer that tests negative for human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), and oestrogen receptor (ER) on the basis of immunohistochemistry (IHC) [2]. TNBC has distinct metastatic patterns, an aggressive nature, and a specific molecular profile but lacks targeted therapy. Worldwide, there are an estimated 170,000 cases of breast cancer, with TNBC accounting for 10–20% of invasive breast cancers [3]. Epidemiological data show that premenopausal women under 40 years of age make up 15–20% of all breast cancer cases, with TNBC primarily affecting these women [4]. Cervical cancer originates in the cervix [5] and remains a significant cause of morbidity and mortality worldwide among women. High-risk HPV infections (HPV 16 and 18) and an inflammatory tumour microenvironment are associated with cervical cancer and can be targeted by

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immunotherapy [6]. Approximately 95% of cervical cancers are caused by untreated persistent HPV infections of the cervix. With an estimated 570,000 new cases each year, cervical cancer is the fourth most common cancer in women worldwide, with 85% of cases occurring in developing countries [7]. Immunotherapy using immune checkpoint inhibitors (ICIs) has emerged as an effective therapeutic option. The immune checkpoint programmed death-receptor 1 (PD-1) negatively regulates T-cell immunological function. Programmed death-ligand 1 (PD-L1) on tumour cells interacts with PD-1, which is produced by T lymphocytes, to inhibit the growth and cytotoxic potential of T cells. Inhibiting the function of checkpoint inhibitors can enhance the immune response against cancer cells [8].

While the use of immunotherapy in breast cancer treatment is increasing, the impact of immune checkpoint inhibitor response biomarkers on prognosis remains unclear. A study by Parvathareddy et al. [9] revealed a correlation between PD-L1 expression and poor clinical and pathological characteristics in patients with breast cancer, including younger age, higher grade, and TNBC subtype. PD-L1 expression in cervical cancer has also been linked to a poorer prognosis and a reduced response to immunotherapy [10]. Research suggests that high PD-L1 expression is associated with decreased overall survival rates in cancer patients and accelerated tumour growth [11]. PD-L1 has indeed been proven to be a relevant diagnostic biomarker for various indeed been proven to be relevant, but further clinical studies are needed on its expression in breast and cervical malignancies. This study aimed to determine the immunohistochemical expression of PD-L1 in breast and cervical cancer.

## MATERIALS AND METHODS

### Tissue sample selection

In this retrospective study, a total of 40 formalin-fixed paraffin-embedded tissue blocks comprising 20 blocks from cervical cancer patients (10 benign and 10 malignant) and 20 blocks from breast cancer patients (10 benign and 10 malignant) were retrieved from the Pathological Archives of University College Hospital (UCH) Ibadan, Oyo State, Nigeria. All analyses were carried out in the Molecular Laboratory at the University of Ibadan, Oyo State, Nigeria.

### Immunohistochemical analysis

The expression of the PD-L1 biomarker was demonstrated immunohistochemically using the avidin-biotin immunoperoxidase method. Sections on adhesive-coated glass slides were deparaffinised in xylene and rehydrated using different gradients of ethanol. The sections were pretreated in a pressure cooker for antigen retrieval, using antigen retrieval buffer at 95°C for 30 minutes, 90°C for 10 seconds and 10°C for 10 minutes. Endogenous peroxidase activity was blocked by immersion in a 3% hydrogen peroxidase solution for 5 minutes. Nonspecific binding was blocked by a blocking buffer (or nonimmune serum) for 15 minutes. Two hundred microliters of diluted primary antibody (BioGenex mouse monoclonal primary antibody) for PD-L1 were added to the slides, which were subsequently incubated at room temperature for 80 minutes. The slides were then incubated with biotinylated rabbit anti-mouse secondary immunoglobulins for 15 minutes at room temperature. They were subsequently incubated with the avidin-biotin peroxidase complex. 3,3'-Diaminobenzidine was used as a chromogen. The sections were counterstained with hematoxylin [12].

### Immunostaining assessment

The expression of PD-L1 was determined through a semi-quantitative method. The immunoreactivity of the biomarker was determined by assessing the staining intensity and percentage of stained cells per field. The staining intensity was graded as mild, moderate or severe. The percentages of positive cells were graded as follows:
0.1–10% stained = negative (-), grade 0.
10.1–39% stained = positive (+), grade 1.
40.0–79% stained = positive (++), grade 2.
80.0–100% stained = positive (+++), grade 3 [12].

### Photomicrography

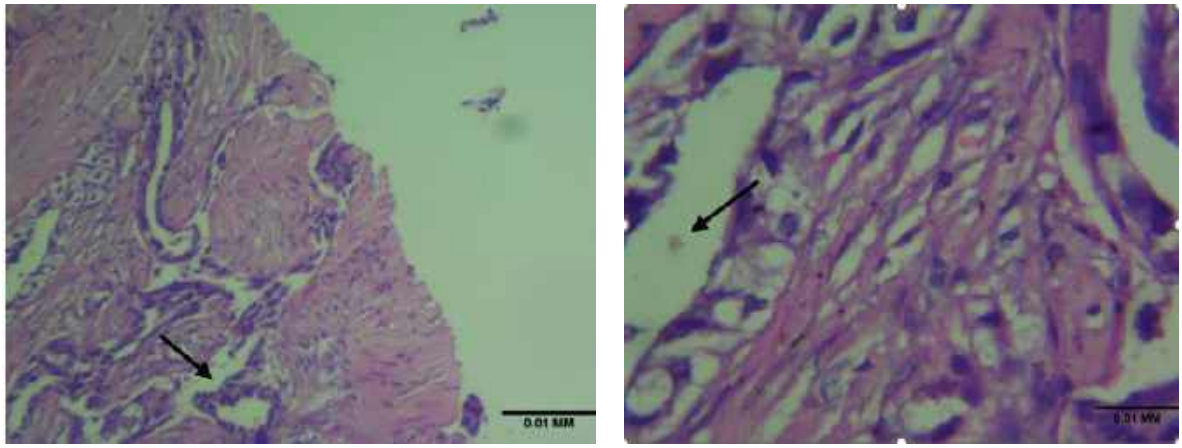
The stained sections were examined under a Leica research microscope (Leica DM750, Switzerland) interfaced with a digital camera (Leica ICC50). Digital photomicrographs of the stained sections for histomorphology and immunohistochemistry of the organs studied were taken at various magnifications and reported for morphological changes.

### Data analysis

The results are presented in figures, tables and pictures (micrographs). PD-L1 staining was evaluated using light microscopy at x100 and x400. The values are presented as simple frequencies and percentages. Statistical analysis was performed using Stata (Version 14.0, StataCorp, College Station, Texas).

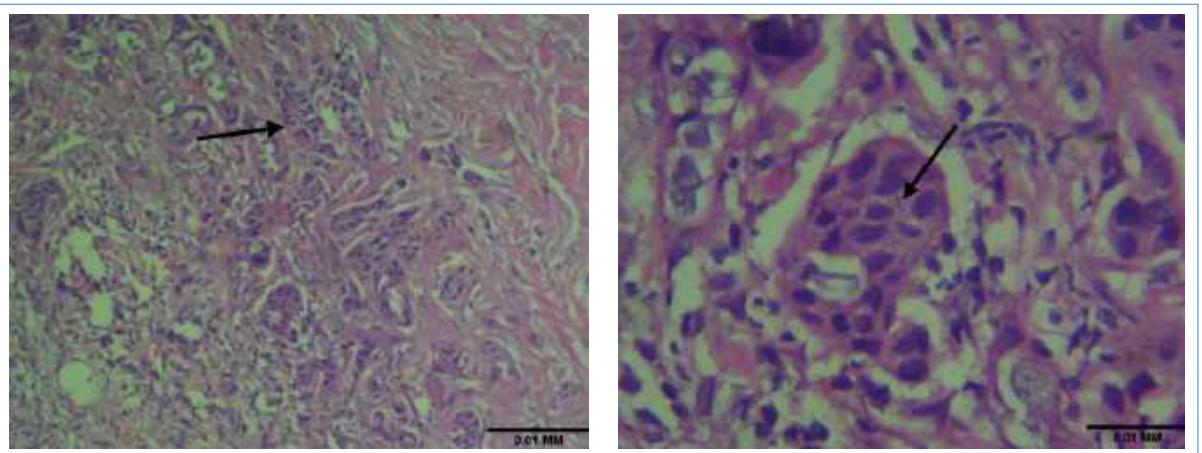
## RESULTS

Figure 1 is an H&E-stained micrograph of benign breast tissue sections at x100 and x400 magnification, showing the general tissue structure with purple nuclei and pink cytoplasm with well-defined structures. The tissue exhibited a uniform glandular pattern characteristic of normal breast tissue, with fibrous and fatty tissues supporting the lobules and ducts. The basement membrane separating the epithelium and stroma is present, along with connective tissues and fibroblasts. Figure 2 is an H&E-stained micrograph of malignant breast tissue sections at x100 and x400 magnification, showing stained nuclei, severe dysplasia, and hyperchromasia. The cells displayed a disorganised tissue structure and a high nuclear-cytoplasmic ratio. Figure 3 shows a micrograph of immunohistochemically stained PD-L1 in benign breast tissue sections at x100 and x400 magnification. The section



X100 X400

Figure 1. H&E-stained micrographs of a benign breast tissue section at ×100 and ×400 magnifications. The arrows indicate normal or hyperplastic epithelial cells lining the ducts and lobules.

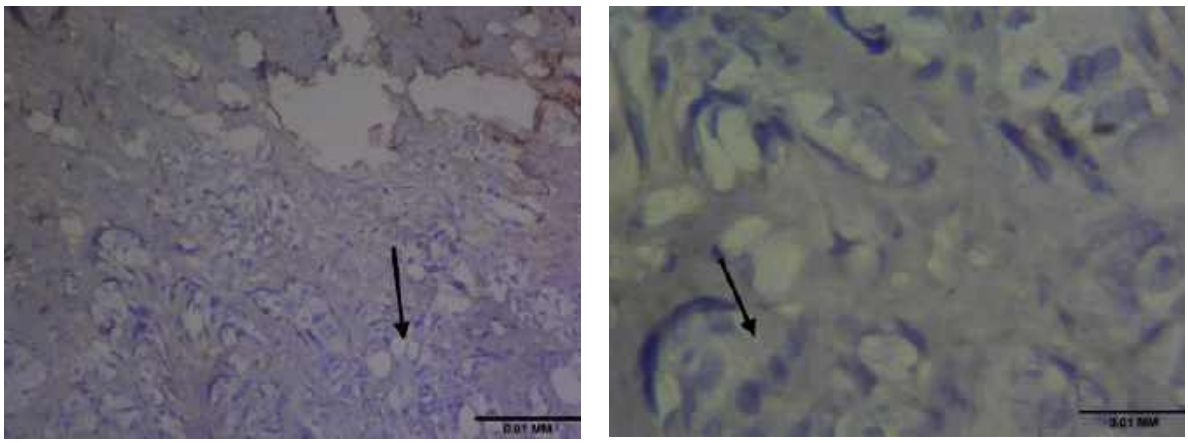


X100 X400

Figure 2. H&E-stained micrographs of malignant breast tissue sections at ×100 and ×400 magnifications. The arrows point to malignant epithelial cells showing features such as nuclear pleomorphism and disrupted tissue architecture.

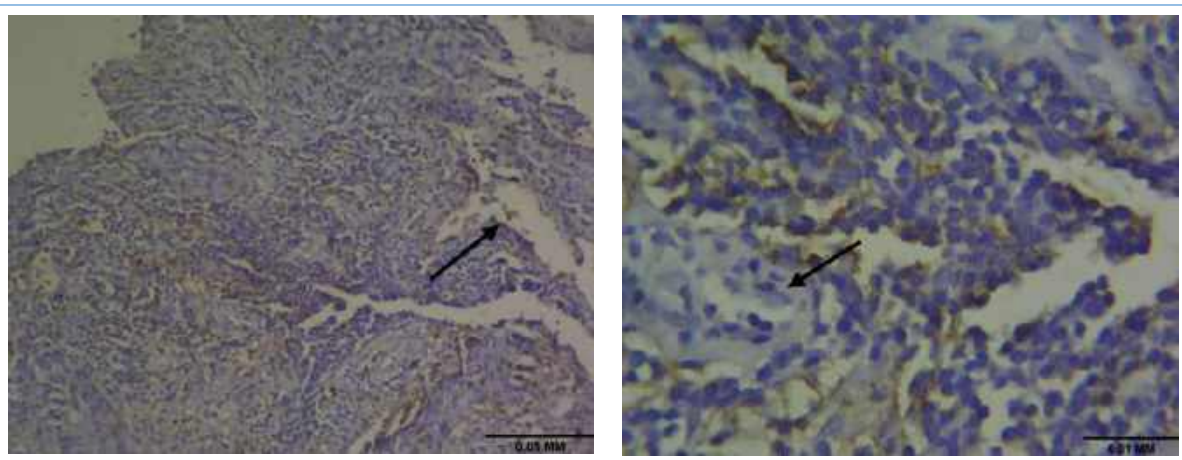
shows negative staining for PD-L1 in the majority of tumour cells, with only scattered cells exhibiting faint cytoplasmic staining (mild expression). Figure 4 shows a micrograph of immunohistochemically stained PD-L1 in malignant breast tissue sections at x100 and x400 magnifications. The section exhibits moderate staining intensity with mild dysplasia, which is indicative of hyperchromasia.

Figure 5 is an H&E-stained micrograph of benign cervical cancer tissue sections at x100 and x400 magnification, showing the general tissue structure with purple nuclei and pink cytoplasm, with well-defined structures. The basal layer, composed of small, cuboidal, or columnar cells, is observed at the bottom of the epithelium. The basement membrane separating the epithelium and stroma is present, as are the koilocytes. Figure 6 is an H&E-stained micrograph of malignant cervical cancer tissue sections at x100 and x400 magnification, showing severe dysplasia, hyperchromasia, and invasion of cells beyond the epithelium, indicating carcinoma in situ. Figure 7 shows a micrograph of immunohistochemically stained PD-L1 in benign cervical cancer tissue sections at x100 and x400 magnifications. The section shows mild staining intensity, suggesting the upregulation of PD-L1 expression in the tissue. Figure 8 shows a micrograph of immunohistochemically stained PD-L1 in malignant cervical tissue sections at x100 and x400 magnifications. The section displays moderate staining intensity with mild dysplasia and multiple tumours.



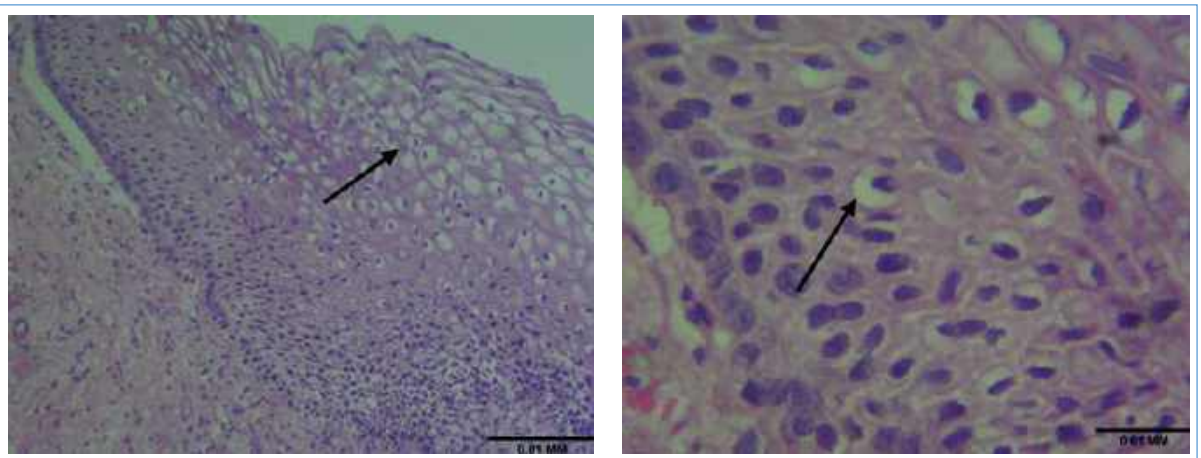
X100 X400

Figure 3. Immunohistochemically stained micrographs of a benign breast tissue section at ×100 and ×400 magnifications, showing PD-L1 expression. The arrows indicate weak or absent PD-L1 staining in the epithelial cells.



X100 X400

Figure 4. Immunohistochemically stained micrographs of malignant breast tissue sections at ×100 and ×400 magnifications. The arrows highlight malignant epithelial cells exhibiting positive PD-L1 expression.



X100 X400

Figure 5. H&E-stained micrographs of a benign cervical tissue section at ×100 and ×400 magnifications. The arrows highlight normal, non-dysplastic epithelial cells with uniform nuclei and organized tissue architecture.

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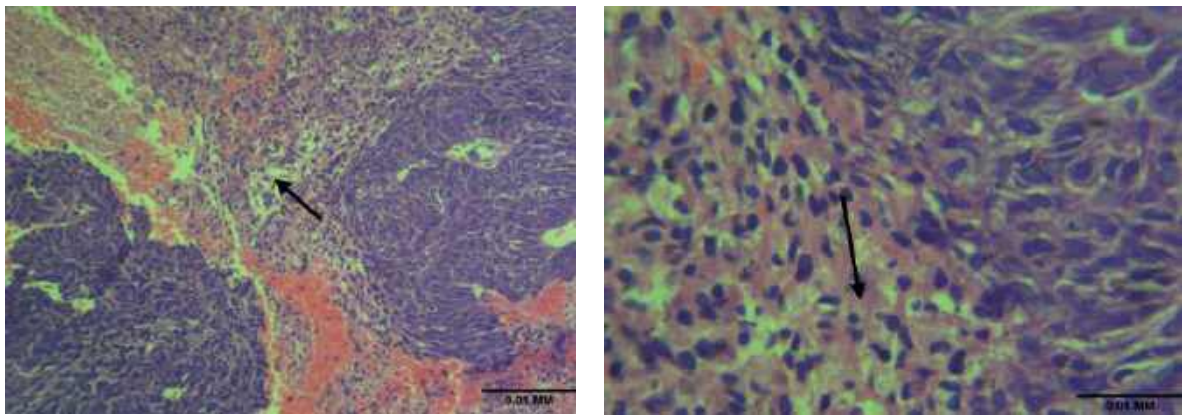
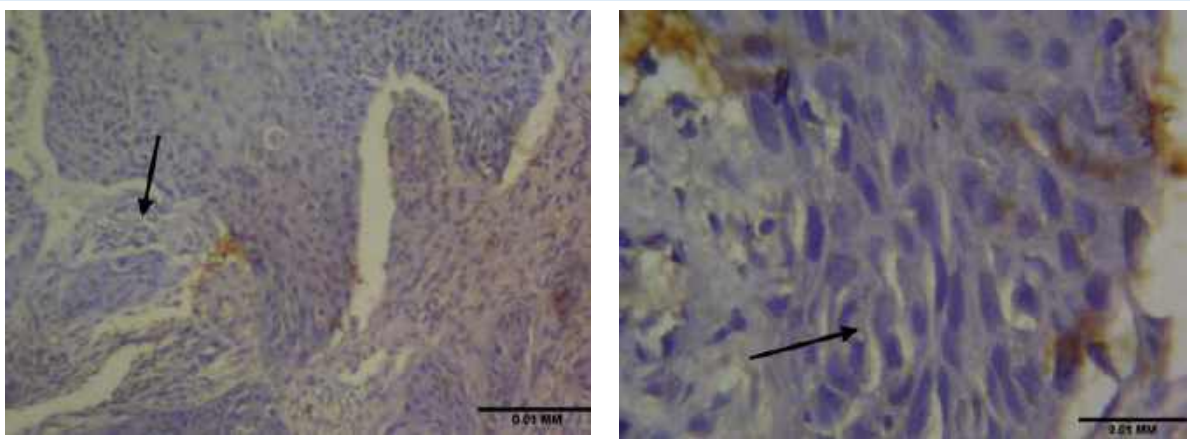


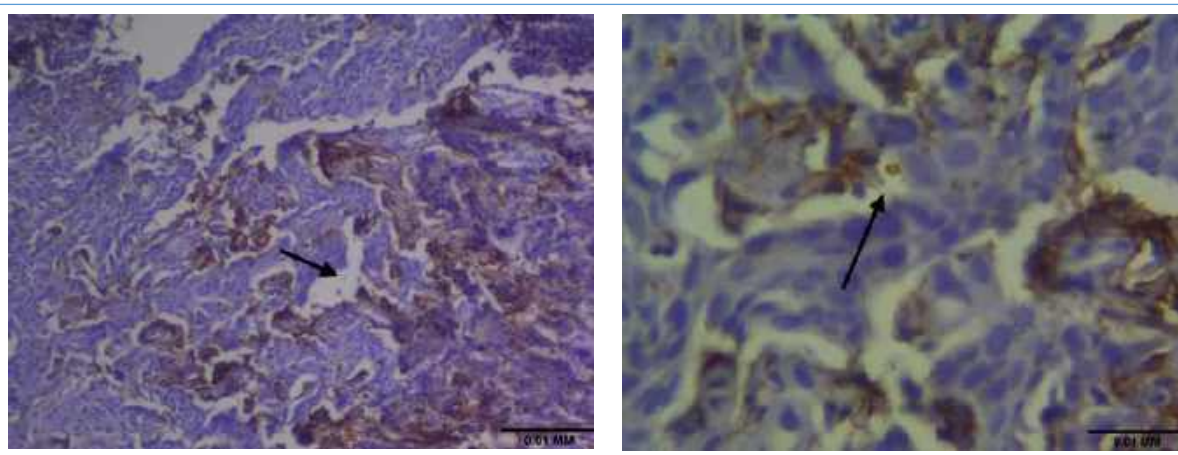
X100 X400

Figure 6. H&E-stained micrographs of malignant cervical tissue sections at ×100 and ×400 magnifications. The arrows highlight malignant epithelial cells characterized by nuclear pleomorphism, hyperchromasia, and disrupted tissue organization.



X100 X400

Figure 7. Micrograph of a benign cervical tissue section immunohistochemically stained with PD-L1 at ×100 and ×400 magnifications. The arrows highlight benign epithelial cells exhibiting weak or focal PD-L1 expression, indicating minimal immunoreactivity.



X100 X400

Figure 8. Micrographs of malignant cervical tissue sections subjected to immunohistochemical staining for PD-L1 at ×100 and ×400 magnifications. The arrows highlight malignant epithelial cells with strong, membranous PD-L1 expression, indicating positive immunoreactivity in cancerous regions.

Table 1. Semiquantitative expression of PD-L1 in breast lesions

| Case | No of samples | Neg (-) | Mild (+) | Moderate (++) | Marked (+++) | Mean Percentage Reactivity | p-value |
|---|---|---|---|---|---|---|---|
| Benign | 20 | 18 | 2 | - | - | 14.8% | 0.015* |
| Malignant | 20 | 4 | 9 | 7 | - | 46.4% | |

Table 2: Semiquantitative expression of PD-L1 in cervical cancer

| Case | No of samples | Neg (-) | Mild (+) | Moderate (++) | Marked (+++) | Mean Percentage Reactivity | p-value |
|---|---|---|---|---|---|---|---|
| Benign | 20 | 15 | 5 | - | - | 18.4% | 0.010* |
| Malignant | 20 | 3 | 2 | 13 | 2 | 71.3% | |

Table 1 shows the semi-quantitative expression of PD-L1 in breast cancer. The results indicate that benign breast cancer has mild (+) PD-L1 expression, whereas malignant breast cancer has mild (+) and moderate (++) PD-L1 expression. The mean percentage reactivity (MPR) of benign and malignant breast cancer was 14.8% and 46.4%, respectively. Table 2 shows the semi-quantitative expression of PD-L1 in cervical cancer. The results revealed that benign cervical cancer had only mild (+) PD-L1 expression, whereas malignant cervical cancer had mild (+), moderate (++) and marked (+++) PD-L1 expression. The mean percentage reactivity (MPR) of benign and malignant cervical cancer was 18.4% and 71.3%, respectively. The MPR was significantly higher in malignant cases compared to benign cases in breast and cervical cancers ($p < 0.05$).

## DISCUSSION

In this study, the mean positivity rate of PD-L1 expression was greater in patients with malignant cervical cancer (71.3%) than in those with benign cervical cancer (18.4%). In contrast to this finding, Schellens et al. [13] reported 50% PD-L1 expression in cervical cancer cells, Balar et al. [14] reported 17% and 35% positive PD-L1 expression in cervical adenocarcinoma and squamous cell carcinoma (SCC). Meng et al. [15] reported PD-L1 expression in 68 out of 97 cervical cancer cases (70.1%), and Chen et al. [16] reported PD-L1 expression in 61 out of 95 cases (64.2%). The variations in these results could be attributed to the use of different methods for determining PD-L1 expression (mRNA expression by IHC, tissue microarray, paraffin tissue blocks, and various monoclonal kits used in IHC staining) and variations in scoring systems [17]. Increased expression of PD-L1 on various solid tumours, such as those in cervical cancer, may enable the tumour to evade the immune system. While PD-L1 is rarely observed in normal cervical tissue, at least 50% of cervical cancer cases express PD-L1 [18]. Therefore, targeting PD-L1 in cervical cancer treatment may be crucial for identifying patients who will respond better to immunotherapies that target anti-PD-1/PD-L1.

The semi-qualitative analysis revealed that benign cervical cancer had only mild (+) PD-L1 expression, whereas malignant cervical cancer had mild (+), moderate (++), and marked (+++) PD-L1 expression. Consistent with this study, Saglam et al. [19] reported that PD-L1 expression is higher in inflammatory cells infiltrating tumours than in endometrial and ovarian adenocarcinomas. This may be due to increased PD-L1 expression in the tumour microenvironment through various mechanisms, leading to abnormal activation of the PD-L1/PD-L1 signalling pathway. This, in turn, results in T-cell death and inhibits T-cell proliferation and differentiation through multiple mechanisms, facilitating tumour immune evasion [20]. In addition to acting as a ligand for PD-1, PD-L1 can also function as a receptor for transmitting negative signals, preventing tumour cells from undergoing Fas-FasL-mediated apoptosis and protecting them from being lysed by cytotoxic T lymphocytes [19]. Increased PD-L1 expression in tumour cells is linked to lower disease-free and disease-specific survival rates in patients with squamous cell carcinoma of the cervix [18].

The results of this study revealed that PD-L1 expression was higher in malignant breast cancer patients (46.4%) than in benign patients (14.8%). Elevated PD-L1 expression in malignant breast cancer indicates its potential role in tumour immune evasion and disease progression. Previous research by Ghebeh et al. [21] revealed PD-L1 expression in 22 (50%) of 44 tumours evaluated, with 15 (34%) showing expression restricted to the tumour epithelium and 18 (41%) in tumour-infiltrating lymphocytes [21]. Another study investigating PD-L1 expression (defined as cell-

surface membrane staining > 5%) in breast cancer revealed higher levels in TNBC patients than in non-TNBC patients ($p < 0.001$) [22]. Soliman et al. [23] demonstrated through flow cytometry that PD-L1 expression was higher in basal-type breast cancer than in luminal-type breast cancer. Ghebeh et al. [24] also reported that PD-L1 expression is associated with tumour characteristics such as high grade, oestrogen receptor negativity, and increased T-regulatory (T-reg) expression. In a study by Morgan et al. [25], PD-L1 expression was found to be higher in tumour cells of medullary-type breast cancer than in those of TNBC. Criscitiello and Curigliano [26] reported no significant association between PD-L1 expression and the response to immunotherapy in breast cancer patients. PD-L1 expression has been observed in a significant proportion of breast cancer cases, ranging from 10–30%, with variability based on tumour stage and molecular subtype [27]. Compared with luminal subtypes, tumours with higher histological grades, including grade 3 tumours, triple-negative breast cancer, and other nonluminal subtypes, have higher PD-L1 expression [28]. Muenst et al. [29] reported positive staining (both membranous and cytoplasmic) for PD-L1 in 152 out of 650 (23.38%) breast cancer patients, with a significant correlation between PD-L1 positivity and several clinicopathological parameters (large tumour size, lymph node involvement, tumour grade, ER negativity, HER2-positive tumours, and high Ki67 index) [29]. Consensus on sampling, staining, and scoring procedures for detecting PD-L1 protein expression using IHC is needed to improve the reproducibility of studies and confirm interstudy results.

The results of this study revealed mild immunoreactivity in breast cancer, indicating low levels of PD-L1 expression. The subtle staining pattern suggests a slight upregulation of PD-L1 expression in the tissue, potentially reflecting an immune response. Mild IHC staining implies a poor response to anti-PD-1/PD-L1 immunotherapies, while the observed PD-L1 expression levels correlate with the aggressiveness of breast cancer [27]. Additionally, PD-L1 expression was greater in malignant cervical samples than in malignant breast samples, suggesting a potentially greater role of the PD-L1 pathway in cervical cancer progression. This finding is consistent with those of previous studies [26,30]. These differences in PD-L1 expression patterns may impact treatment strategies and the development of targeted therapies for each type of cancer. The association of PD-L1 expression with prognosis varies between cervical and breast cancers. The disparity in PD-L1 expression levels between the two types of cancer could indicate variations in immune responses and the tumour microenvironment.

### Conclusion

PD-L1 expression was more pronounced in cervical cancer than in breast cancer. The elevated levels of PD-L1 in cervical cancer suggest that this type of cancer may be more responsive to immunotherapeutic interventions targeting the PD-L1 pathway than breast cancer. Recognising these differences is crucial for tailoring treatment plans and implementing personalised medicine strategies for each specific cancer type.

## DECLARATIONS

### Ethical consideration

Ethical approval for this study was obtained from the Health Research Ethics Committee, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State, Nigeria. Informed consent was obtained from each participant in the study. All experiments in this study were performed in accordance with the Declaration of Helsinki.

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest

### Author contribution

VOE conceptualised the manuscript. The methodology was developed by CCE, and MAH and VOE conducted formal analyses and visualisations. Resources were contributed by all the authors. EAO wrote the original draft while all the authors reviewed and edited it. Supervision was provided by VOE. EAO was responsible for coordinating with the coauthors and submitting the article. All the authors read and approved the final manuscript.

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None

### Availability of data

Data is available upon request to the corresponding author

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# Prevalence of prediabetes and its risk factors among adults in selected communities in Accra

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**Abstract**

***Background:*** Diabetes mellitus is a global health issue, with cases projected to surge from 180,000,000 in 1980 to over 693,000,000 by 2045. Considering that prediabetes precedes type 2 diabetes, early diagnosis and timely intervention are essential to prevent or delay disease progression.

***Objective:*** This study assessed the determinants of prediabetes among adults in selected Accra communities.

***Methods:*** This study investigated prediabetes prevalence in five Accra communities - North Kaneshie, Madina, Teshie, Lapaz, and Legon. A cross-sectional study used multistage sampling to recruit 360 adults (≥ 18 years). Eligibility required Accra residency (≥ 1 year), 10 – 12-hour fasting, and informed consent. Sociodemographic variables, behavioural patterns, dietary intakes, anthropometric measures and clinical indicators were collected. Logistic regression was employed to estimate associations between all variables and prediabetes status.

***Results:*** Prediabetes and diabetes prevalence were 26.7% and 29.4%, respectively. Significant associations were found with prediabetes for female sex (OR: 2.03, 95% CI: 1.02 - 4.59, p = 0.031), age 40 - 59 years (OR: 2.97, 95% CI: 1.10-8.32, p = 0.039), and being single (OR: 2.60, 95% CI: 1.05-6.43, p = 0.038). Behavioral factors linked to prediabetes included salt intake (AOR: 6.25, 95% CI: 1.69-23.02, p=0.006), smoking (AOR: 10.14, 95% CI: 1.21-111.03, p = 0.002), caffeine intake (AOR: 2.51, 95% CI: 1.53 - 11.88, p = 0.012), and low physical activity (AOR: 3.53, 95% CI: 1.83 - 7.89, p < 0.001). Increased consumption of starchy foods (AOR: 3.63, 95% CI: 1.74 - 7.58, p = 0.007), animal-sourced foods (AOR: 2.54, 95% CI: 1.36 - 4.86, p = 0.015), fats and oils (AOR: 5.87, 95% CI: 2.76 - 12.51, p = 0.001), and legumes (AOR: 2.45, 95% CI: 1.23 - 6.11, p = 0.045) were significantly linked to prediabetes. BMI greater than 25kg/m2 (AOR: 4.55, 95% CI: 2.12 - 18.11, p < 0.001), MAP (AOR: 4.21, 95% CI: 1.50 - 11.81, p = 0.006), and stage 1 hypertension (AOR: 6.74, 95% CI: 1.50 - 30.29, p = 0.015) showed associations with prediabetes.

***Conclusion:*** Prediabetes prevalence was high, driven by sociodemographic, dietary, and behavioural factors. Lifestyle and physiological risks underscore the urgent need for targeted interventions in this population.

**Keywords:** Prediabetes, diabetes mellitus, body mass index (BMI), blood pressure, dietary predictors

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## INTRODUCTION

Diabetes mellitus (DM) is a highly prevalent global health disease, with cases soaring across regions and particularly in lower- and middle-income countries. The World Health Organisation (WHO) reported a dramatic increase from 180 million diabetes cases in 1980 to 422 million in 2014, and by 2019, diabetes and related kidney disease contributed to approximately 2 million deaths worldwide [1]. Approximately 693 million people could live with diabetes by 2045, with around half undiagnosed [2]. Diabetes is generally categorised into type 1, type 2, and gestational diabetes. Type 1 diabetes, previously known as "juvenile diabetes," results from insulin deficiency and requires lifelong administration, while type 2 diabetes is associated with insulin resistance and is often linked to obesity, family history, and lifestyle factors. Gestational diabetes, which affects pregnant women, increases the risk of diabetes later in life for both mother and child [3,4]. Recent global criteria define diabetes by a

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fasting plasma glucose threshold of > 7.0 mmol/L, with prediabetes marked by 6.1 - 6.9 mmol/L. Individuals with prediabetes have higher risks for type 2 diabetes, heart disease, and other complications, though lifestyle changes can significantly reduce this risk [5,6].

The rising global prevalence of prediabetes necessitates critical early intervention, with data indicating that impaired fasting glucose is common in both Asian and Caucasian populations [7]. US data from the CDC found that between 2009 and 2012, 37% of adults aged over 20 and 51% over 65 were living with prediabetes, equating to approximately 86 million Americans. The global prevalence of prediabetes was around 343 million (7.8%) in 2010, with the International Diabetes Federation estimating a rise to 471 million by 2035 [8]. In Africa, approximately 19.8 million people have diabetes, with approximately 75% of these cases undiagnosed, while type 2 diabetes accounts for about 90% of cases. This increase parallels a rise in obesity and cardiovascular risk factors in sub-Saharan Africa, where the prevalence of diabetes has increased from an estimated 7.1 million in the early 2000s to a projected 18.6 million by 2030 [9]. Ghana reflects similar trends, with prevalence estimates between 6.2% and 13.9%. Policymakers remain inadequately informed about diabetes prevalence and its public health impact, partly due to data gaps and regional variability.

Prediabetes, though often undiagnosed, poses serious public health implications as it often leads to type 2 diabetes, a condition associated with multiple health complications, including cardiovascular disease, neuropathy, and kidney disease [10]. Increasing urbanisation and sedentary lifestyles contribute significantly to prediabetes risk. Screening efforts remain limited in many developing nations, constraining the ability of healthcare systems to implement preventive measures. Research into prediabetes prevalence and associated risk factors in Accra, Ghana, offers valuable insights into the health effects of urbanisation, informing targeted prevention strategies and potentially alleviating future healthcare burdens. Despite the known progression of prediabetes to diabetes, a paucity of data exists on the risk factors for prediabetes in Ghana. The current study assessed prediabetes prevalence in Accra and identified key risk factors.

## MATERIALS AND METHODS

### Study design and sites

This cross-sectional study was conducted in Accra over six months (January to June 2024), assessing sociodemographic details, behavioural and lifestyle factors, dietary habits, and other prediabetes risk factors using a pre-tested questionnaire. The study involved both household and hospital outreaches. Five communities in Accra, North Kaneshie, Madina, Teshie, Lapaz, and Legon were selected for their demographic diversity, variations in healthcare access, and relevance to the study objectives. North Kaneshie and Lapaz, located in the Okaikoi South Sub-Metropolitan District, represented urban residential settings. Madina, part of the La Nkwantanang-Madina Municipal District, included Pentecost Hospital as a key healthcare centre. Teshie, situated in the Ledzokuku Municipal District, and Legon, home to the University of Ghana Hospital, served as both community and clinical recruitment sites. These diverse locations allowed for a comprehensive assessment of the target population.

### Sample size and sampling technique

The study targeted adults (18 years and above) residing in Accra. Using Cochran's formula with a 95% confidence level and a 2% margin of error, a sample size of 360 was calculated based on a 3.9% prevalence rate previously reported by Vuvor et al. [11]. A multistage sampling procedure was employed to ensure a diverse and representative sample while maintaining methodological rigour. The selection process combined a community-based and hospital-based approach to recruit participants from different settings within Accra. In the community-based sampling, study locations were selected using convenience sampling to reflect the city's diverse urban landscape, incorporating both residential and commercial areas. Within each chosen community, systematic sampling was applied to select streets, ensuring a structured and unbiased approach. A random starting point was determined, and every third house was approached for participation. To enhance fairness, data collection alternated between both sides of the street rather than arbitrary exclusion of any given side. At each household, informed consent was obtained, and participants were given a clear explanation of the study's objectives, potential risks, voluntary nature, and confidentiality. This procedure was repeated across multiple communities until the required sample size was obtained.

For the hospital-based sampling, simple random sampling was employed to ensure an unbiased selection of participants due for blood glucose checkups. Hospital records were used to compile a list of eligible patients, each assigned a number. A computer-generated random selection process was then applied to select participants systematically. This method was implemented across multiple hospitals, ensuring a mix of public and private healthcare facilities, thereby capturing a broad socioeconomic representation. By combining these two approaches, the study achieved a balanced and comprehensive sample, allowing for greater validity and generalizability of the findings across Accra's diverse population.

Inclusion criteria required participants to have lived in Accra for at least one year, be aged 18 or older, and fast overnight (10 - 12 hours) prior to testing. Pregnant or lactating women were excluded from the study to avoid potential confounding effects, as hormonal changes during pregnancy and lactation can significantly alter glucose metabolism and may not reflect typical prediabetes risk

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factors. Additionally, individuals with severe medical or mental conditions were excluded to ensure participants' safety and the reliability of the data. Participants were recruited from households and hospitals within the selected communities. After explaining the study objectives, verbal or written consent was obtained. Participants from households were advised to fast overnight, while hospital participants were already fasting, aligning with study requirements.

**Data collection and instruments**

The classification of prediabetes and diabetes was based on the World Health Organisation (WHO) criteria, ensuring consistency with globally recognised diagnostic standards. Blood glucose levels were measured, and individuals were categorised accordingly. A 7-day food frequency questionnaire (FFQ) was used to evaluate participants' habitual food intake for dietary assessment. This validated tool allowed for a comprehensive analysis of dietary patterns, capturing variations in food consumption over a week.

Blood pressure was assessed using an automated Omron digital sphygmomanometer. Measurements were taken twice on the left arm of each participant with a 5-minute rest interval between readings, and the average of the two values was used for analysis. Hypertension was defined according to the American Heart Association (AHA) guidelines. Participants were categorised as having normal blood pressure if systolic blood pressure was less than 120 mmHg and diastolic pressure was less than 80 mmHg. Stage 1 hypertension was defined as systolic blood pressure between 130 – 139 mmHg and diastolic pressure between 80–89 mmHg, while Stage 2 hypertension was defined as systolic pressure equal to or greater than 140 mmHg and diastolic pressure equal to or greater than 90 mmHg.

Physical activity levels were assessed using a modified version of the International Physical Activity Questionnaire (IPAQ) developed by Craig et al. (2003). Participants self-reported their activity levels over the past seven days, providing data on frequency, duration, and intensity. The IPAQ, a widely validated tool, allowed for the estimation of Metabolic Equivalent of Task (MET) scores, which facilitated the classification of participants' activity levels as low, moderate, or high. Anthropometric measurements, including height and weight, were recorded twice per participant for accuracy. Clinical assessments included blood glucose, measured using a glucometer, and blood pressure, measured twice on the left arm with a 5-minute interval using an Omron sphygmomanometer. Each data point was averaged for precision.

**Data Analysis**

Microsoft Excel was used for data entry and cleaning, and the IBM Statistical Package for Social Sciences (SPSS) version 26.0 software was used for all data analysis. The categorical sociodemographic variables of the participants were summarised into frequencies and percentages using descriptive statistics, and the continuous sociodemographic variables were analysed using mean and standard deviation. Binary logistic regression was used in predicting the risk factors of prediabetes by explaining the relationship between the dependent variable (prediabetes) and the independent variables (physical activity, age, religion, education level, monthly income, length of sleep, salt intake, BMI, dietary factors, marital status, smoking, stress management, blood pressure status and mean arterial pressure). Three confounding variables identified using bivariate analysis for the logistic regression model were marital status, sex and age. They were controlled and adjusted for in the model.

## RESULTS

Table 1 presents participant demographics, revealing an average age of 49 years (SD = 15) and a female majority (57.8%, n = 208). The sample was predominantly identified as Christian (82.5%, n = 297) and married (55%, n = 198). Regarding education, most participants had secondary-level education (43.3%), while income distribution indicated that 47.8% earned between 1001 and 2000 Ghana cedis (US $70.07 - $140) monthly. Blood glucose levels among participants, illustrated in Figure 1, show that 43.3% had blood sugar levels within the range of 3.9 - 6mmol/L, 29.4% had levels of 7mmol/L or above, and 26.7% were within the prediabetes range of 6.1-6.9mmol/L. Multivariate logistic regression analysis (Table 2) revealed that females (OR: 2.03, 95% CI: 1.02 - 4.59, p = 0.031), individuals aged 40 - 59 (OR: 2.97, 95% CI: 1.10 - 8.32, p = 0.039), and singles (OR: 2.60, 95% CI: 1.05 - 6.43, p = 0.038) had higher odds of prediabetes.

In examining behavioural factors (Table 3), salt and caffeine intake were strongly linked to prediabetes

Table 1. Background characteristics of participants

| Characteristic | n (%) |
|---|---|
| Sex | |
| Male | 152 (42.2) |
| Female | 208 (57.8) |
| *Age (years) | 49 ± 15 |
| Religion | |
| Christian | 297 (82.5) |
| Muslim | 58 (16.1) |
| Others | 5 (1.4) |
| Level of education | |
| Primary | 140 (38.9) |
| Secondary | 156 (43.3) |
| Tertiary | 64 (17.8) |
| Marital status | |
| Married | 198 (55.0) |
| Single | 162 (45.0) |
| Income (GHS) | |
| ≤ 1000 | 65 (18.1) |
| 1001-2000 | 172 (47.8) |
| ≥ 2001 | 123 (34.1) |

*Means data is represented in means and standard deviations

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Table 2. Sociodemographic predictors associated with prediabetes among participants

| Characteristic | OR (CI[1]) | p-value[2] |
|---|---|---|
| Sex | | |
| Male | 1 | |
| Female | 2.03 (1.02-4.59) | 0.031 |
| Age (years) | | |
| 18-39 | 1 | |
| 40-59 | 2.97 (1.10-8.32) | 0.039 |
| 60+ | 1.53 (0.60-3.94) | 0.377 |
| Level of education | | |
| Primary | 1.85 (0.96-3.55) | 0.066 |
| Secondary | 1.34 (0.47-1.89) | 0.535 |
| Tertiary | 1 | |
| Marital status | | |
| Married | 1 | |
| Single | 2.60 (1.05-6.43) | 0.038 |
| Income (GHS) | | |
| ≤ 1000 | 1.34 (0.52-1.99) | 0.972 |
| 1001-2000 | 1.08 (0.18-2.28) | 0.489 |
| ≥ 2001 | 1 | |

*OR = Odds ratio; CI = Confidence interval; GHS = Ghana Cedis 1 = Confidence interval at 95% 2 = p-value based on binary logistic regression; significance level $p < 0.05$

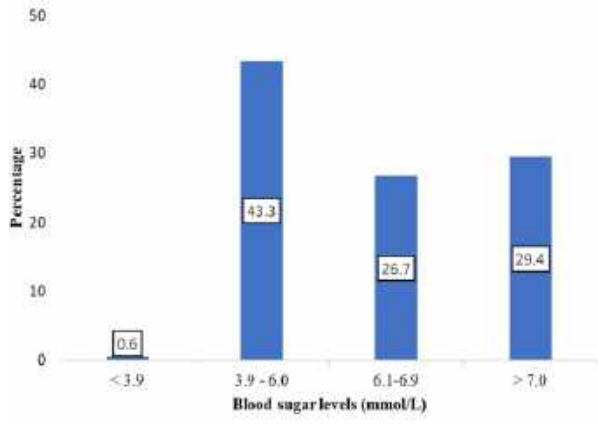


Figure 1. Blood glucose levels of participants

Table 3. Behavioural and lifestyle factors associated with prediabetes among participants

| Risk factor | Unadjusted | | Adjusted | |
|---|---|---|---|---|
| | OR (CI[1]) | p-value[2] | OR (CI[1]) | p-value[2] |
| Salt intake | | | | |
| Yes | 6.58 (1.87-23.22) | 0.003 | 6.25 (1.69-23.02) | 0.006 |
| No | 1 | | 1 | |
| Alcohol intake | | | | |
| Yes | 1.50 (0.47-4.91) | 0.144 | 1.54 (0.18-3.52) | 0.060 |
| No | 1 | | 1 | |
| Caffeine intake | | | | |
| Yes | 1.89 (1.19-6.78) | 0.039 | 2.51 (1.53-11.88) | 0.012 |
| No | 1 | | 1 | |
| Smoking | | | | |
| Yes | 8.90 (1.29-84.08) | 0.004 | 10.14 (1.21-111.03) | 0.002 |
| No | 1 | | 1 | |
| Snacking | | | | |
| Yes | 1 (0.53-1.90) | 0.992 | 1.24 (0.65-2.38) | 0.520 |
| No | 1 | | 1 | |
| Length of sleep | | | | |
| Healthy | 1 | | 1 | |
| Unhealthy | 2.53 (1.05-5.24) | 0.041 | 5.11 (1.54-9.43) | 0.005 |
| Meals in a day | | | | |
| ≤2 | 1 | | 1 | |
| ≥3 | 2.00 (1.11-3.04) | 0.021 | 2.54 (1.83-5.56) | 0.004 |

*OR = Odds ratio; CI = Confidence interval
Adjusted for age, sex and marital status.
1 = Confidence interval at 95%
2 = p-value based on binary logistic regression; significance level $p < 0.05$

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OR for salt: 6.25, 95% CI: 1.69 - 23.02, p = 0.006; for caffeine: 2.51, 95% CI: 1.53 - 11.88, p = 0.012). Smoking and poor sleep were also significant risk factors, with adjusted ORs of 10.14 (95% CI: 1.21 - 111.03, p = 0.002) and 5.11 (95% CI: 1.54 - 9.43, p = 0.005), respectively. High stress levels increased prediabetes risk eightfold (adjusted OR: 8.29, 95% CI: 3.30 - 20.80, p < 0.001) (Table 4). Dietary patterns (Table 4), particularly high starchy food and low fruit and vegetable intake, were associated with elevated odds of prediabetes (adjusted ORs for starch: 3.63,

Table 4. Physical activity levels, dietary choices and stress levels associated with prediabetes among study participants

| Risk factor | Unadjusted OR (CI[1]) | p-value[2] | Adjusted OR (CI[1]) | p-value[2] |
|---|---|---|---|---|
| Physical activity | | | | |
| Low | 3.20 (1.45-7.03) | <0.001 | 3.53 (1.83-7.89) | <0.001 |
| Moderate | 2.22 (1.03-4.76) | 0.005 | 1.53 (1.21-5.33) | 0.003 |
| High | 1 | | 1 | |
| Stress levels | | | | |
| Moderate | 1 | | 1 | |
| High | 6.36 (2.79-14.47) | 0.004 | 8.29 (3.30-20.80) | <0.001 |
| Starchy foods | | | | |
| ≤ 4 | 1 | | 1 | |
| ≥ 5 | 2.60 (1.43-6.82) | 0.004 | 3.63 (1.74-7.58) | 0.007 |
| Vegetables | | | | |
| ≤ 4 | 2.43 (1.03-5.72) | 0.043 | 2.22 (1.02-5.07) | 0.049 |
| ≥ 5 | 1 | | 1 | |
| Fruits | | | | |
| ≤ 4 | 1.23 (0.27-3.21) | 0.059 | 4.90 (2.57-9.37) | 0.031 |
| ≥ 5 | 1 | | 1 | |
| Animal sourced foods | | | | |
| ≤ 4 | 1 | | 1 | |
| ≥ 5 | 1.24 (1.01-2.93) | 0.032 | 2.54 (1.36-4.86) | 0.015 |
| Fats and oils | | | | |
| ≤ 4 | 1 | | 1 | |
| ≥ 5 | 3.43 (2.12-9.56) | 0.012 | 5.87 (2.76-12.51) | 0.001 |
| Legumes and nuts | | | | |
| ≤ 4 | 1 | | 1 | |
| ≥ 5 | 1.55 (0.62-3.88) | 0.241 | 2.45 (1.23-6.11) | 0.045 |
| Confectionaries | | | | |
| ≤ 4 | 1 | | 1 | |
| ≥ 5 | 2.10 (1.09-5.21) | 0.021 | 2.25 (1.19-5.23) | 0.019 |

*OR = Odds ratio; CI = Confidence interval
Adjusted for age, sex and marital status
1 = Confidence interval at 95%
2 = p-value based on binary logistic regression; significance level p < 0.05

Table 5. Association between BMI and blood pressure with prediabetes among participants

| Risk factor | Unadjusted OR (CI[1]) | p-value[2] | Adjusted OR (CI[1]) | p-value[2] |
|---|---|---|---|---|
| BMI (kg/m$^2$) | | | | |
| ≤ 25 | 1 | | 1 | |
| >25 | 3.45 (1.54-12.11) | 0.003 | 4.55 (2.12 - 18.11) | <0.001 |
| Blood Pressure | | | | |
| Normal | 1 | | 1 | |
| Elevated | 3.21 (0.43-18.83) | 0.132 | 4.51 (1.14 - 22.12) | 0.032 |
| Stage 1 hypertension | 4.55 (0.84-25.91) | 0.244 | 6.74 (1.50-30.29) | 0.015 |
| Stage 2 hypertension | 3.70 (1.33-10.31) | 0.045 | 2.77 (1.04-7.39) | 0.038 |
| Mean Arterial Pressure | | | | |
| Normal | 1 | | 1 | |
| High | 3.66 (1.26-10.64) | 0.017 | 4.21 (1.50-11.81) | 0.006 |

Adjusted for age, sex and marital status.
1 = Confidence interval at 95%
2 = p-value based on binary logistic regression; significance level p < 0.05

95% CI: 1.74 - 7.58, p = 0.007, fruit: 4.90, 95% CI: 2.57 - 9.37, p = 0.031). Elevated BMI (adjusted OR: 4.55, 95% CI: 2.12 - 18.11, p < 0.001) and hypertension stages 1 and 2, along with high mean arterial pressure, were strongly associated with prediabetes, even after adjustments (Table 5).

## DISCUSSION

The diagnostic thresholds for prediabetes in this study followed the World Health Organisation (WHO) criteria, defining impaired fasting glucose as 6.1 - 6.9 mmol/L, while hyperglycemia (diabetes) was defined as ≥ 7.0 mmol/L. The American Diabetes Association (ADA), in contrast, classifies prediabetes more broadly from 5.6 - 6.9 mmol/L [1]. Although this study employed WHO criteria for consistency with national practice, the broader ADA cut-off range could imply a higher estimate of prediabetes prevalence in similar populations. The prevalence of prediabetes in this study sample was 26.7%, surpassing previous rates reported in Ghana's Ho municipality (17.3%) and global estimates of 15.8% [7,11]. These findings highlight an emerging public health challenge, as individuals with prediabetes face a significantly increased risk of progressing to type 2 diabetes mellitus. The differences in prediabetes prevalence across regions likely reflect a complex interplay of sociodemographic, lifestyle, and environmental factors. Urbanisation in Accra contributes to risk factors such as processed diets, reduced physical activity, and higher exposure to environmental toxins, including air pollution and chemicals, which have been associated with metabolic disorders, including prediabetes [12]. Rural diets, such as those seen in Ho municipality, often feature complex carbohydrates and fibre, which may provide protective effects against prediabetes compared to Accra's urban diets, which are high in refined sugars and unhealthy fats.

Diabetes prevalence was also notably high in this sample at 29.4%, exceeding previous rates documented in Ghanaian studies, which reported rates of 3.9%, 5.4%, and 8.2%, respectively [13,14,15]. Many people living with diabetes remain unaware of their condition, with over 25% of cases going undiagnosed, according to these studies. The higher prevalence observed in this study could be attributed to the adoption of Westernised dietary habits, sedentary lifestyles, and reduced focus on preventive healthcare measures [16]. These results align with global trends projecting significant increases in diabetes and prediabetes cases, underscoring the urgent need for targeted interventions and public health education [3]. Comparative analysis with other African and international settings reveals regional variations in prediabetes prevalence. In Nigeria, estimates ranged from 10.4% (WHO criteria) to 13.2% (ADA criteria), while South Africa reported a notably higher prevalence of 67% [17]. In Ethiopia, prediabetes affected 15.7% of adults, and Egypt reported a prevalence of 21.7% [18,19]. The comparatively high prevalence of prediabetes in Accra suggests unique contextual factors, such as urbanisation, dietary patterns, and lifestyle changes, which require further investigation and tailored interventions [20].

Several key risk factors reported in previous investigations were similarly identified in this present study. Females were nearly twice as likely to develop prediabetes as males, consistent with evidence indicating that hormonal fluctuations and differential fat distribution contribute to increased susceptibility to prediabetes [21,22]. Middle-aged adults (40 - 59 years) demonstrated a significantly higher likelihood of prediabetes than younger adults, suggesting that metabolic changes and reduced physical activity during middle adulthood increase risk [23,24]. Marital status emerged as a significant factor, with single participants facing nearly triple the risk of prediabetes compared to married individuals, potentially due to the absence of social support networks associated with healthier behaviours [25].

Behavioural factors, including high salt intake, caffeine consumption, and physical inactivity, were strongly linked to prediabetes. High salt intake increased the odds sixfold, corroborating studies demonstrating its adverse effects on pancreatic beta-cell function and glucose intolerance [26,27]. Similarly, caffeine consumption was associated with elevated risk due to its stimulatory effects on stress hormones, which raise blood glucose levels [28]. Physical inactivity further increased risk, with low-activity participants nearly 3.5 times more likely to develop prediabetes, reinforcing established evidence linking reduced activity levels to poorly controlled blood glucose levels [29,30]. Sleep duration exhibited a U-shaped relationship with prediabetes risk, where both insufficient and excessive sleep negatively impacted glucose metabolism [31].

Dietary patterns significantly influenced prediabetes risk, as frequent consumption of starchy foods elevated risk nearly fourfold, consistent with evidence linking high-glycemic foods to impaired glucose tolerance [32]. Low intake of vegetables and fruits also doubled and quintupled risk, respectively, highlighting their protective role in regulating blood sugar levels [33,34]. High consumption of animal-sourced foods, fats, and oils further exacerbated risk, aligning with findings that diets high in saturated fats promote insulin resistance and chronic inflammation [35,36]. Confectionery intake similarly elevated risk due to high sugar content, while legume consumption showed unexpected associations, possibly influenced by preparation methods and sedentary behaviour.

Physiological factors, such as high BMI and elevated blood pressure, were strong predictors of prediabetes. Participants with a BMI over 25 kg/m² faced nearly fivefold higher risk, consistent with findings linking obesity to insulin resistance [37]. Elevated blood pressure and hypertension stages 1 and 2 significantly increased risk, with mean arterial pressure (MAP) further compounding susceptibility, thus supporting the bidirectional relationship between elevated blood

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pressure and impaired glucose metabolism [10,38]. These observances may stem from shared pathophysiological pathways such as endothelial dysfunction, arterial stiffness, and oxidative stress. The interplay between metabolic factors, systemic inflammation, and endothelial dysfunction highlights the critical need to address hypertension in prediabetes prevention.

### Study limitation

The inclusion of hospital participants may introduce selection bias, as these individuals could have underlying health concerns or be more health-conscious than the general population. This bias may overestimate the prevalence of prediabetes and diabetes in Accra. Additionally, reliance on self-reported dietary intake and physical activity data introduces the potential for bias, as participants might under-report unhealthy behaviours or over-report healthier ones. Future research should incorporate objective measures, such as dietary records or accelerometer data, to enhance data accuracy and reliability.

### Conclusion

This study identified a prediabetes prevalence of 26.7%, exceeding previous estimates in Ghana and highlighting an urgent public health challenge. Prediabetes and diabetes prevalence in this sample underscore the need for early detection and management to prevent progression to type 2 diabetes. Key risk factors included high BMI, elevated blood pressure, physical inactivity, high salt and caffeine intake, and a diet high in animal-sourced foods and fats. To address these findings, we suggest several policy actions: implementation of community-based screening programs for prediabetes to facilitate early detection, public health educational campaigns focused on promoting lifestyle modifications such as increased physical activity and dietary changes, and the integration of prediabetes screening and management into primary healthcare services to ensure accessibility and continuity of care.

The findings of this study have significant implications for health policy in Ghana. They strongly support the goals of Ghana's National Diabetes Strategy by providing evidence for the need to prioritise prediabetes prevention and management. Furthermore, the study contributes to the achievement of Sustainable Development Goal 3 (Good Health and Well-being), particularly target 3.4, which aims to reduce premature mortality from non-communicable diseases, including diabetes, by one-third by 2030.

## DECLARATIONS

### Ethical consideration

The study was approved by the Ethical Committee of the College of Basic and Applied Science, University of Ghana and the Ghana Health Service Ethical Review Board with identification numbers (ECBAS 021/23-24) and (GHS-ERC 031-12-23), respectively. Written informed consent was obtained from all study participants.

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest

### Author contribution

All authors contributed significantly to the study's conceptualisation, design, data collection, analysis, drafting and finalisation of the manuscript.

### Acknowledgement

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### Availability of data

Data is available upon request to the corresponding author

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# Extract of *Mallotus oppositifolius* ameliorates mercuric chloride-induced neurotoxicity

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**Abstract**

***Background:*** Mercuric chloride ($HgCl_2$) induces neurotoxicity in both animals and humans, with unclear treatment mechanisms and associated side effects. *Mallotus oppositifolius* leaf extract, known for its pharmacological properties like antidepressant and anti-inflammatory effects, thus suggests potential neuroprotection.

***Objective:*** The study aimed to assess the neuroprotective effect of Mallotus oppositifolius in a mercuric chloride-induced neurotoxicity mouse model.

***Methods:*** Male mice (20 - 25 g) from the Institute of Cancer Research (ICR) were randomly divided into six groups of eight (48 mice). Group 1 received the vehicle (without mercuric chloride) throughout the experimental period. Mice in groups 2, 3, 4, 5 and 6 were pre-treated with $HgCl_2$ orally for 7 days, after which groups 3, 4 and 5 were treated with the oral graded dose of *Mallotus oppositifolius* leaf extract (MOE 10, 30, 100 mg/kg) while group 6 was treated with the reference drug, piracetam (PCT 150 mg/kg, orally). The various groups were evaluated for neurotoxicity using the open field, catalepsy and novel object recognition (NOR) tests. Cresyl Violet staining was used to assess the neurohistological changes caused in the hippocampus of the brain.

***Results:*** $HgCl_2$-induced catalepsy and decreased posture correction time compared to the vehicle group. However, MOE and PCT significantly reversed this effect. In the novel object recognition (NOR) test, $HgCl_2$ reduced the recognition index and novel object time, while MOE and PCT increased both. Locomotor activity, assessed through line crossing, was significantly reduced with $HgCl_2$ but remained unaffected with MOE and piracetam. $HgCl_2$ also reduced time in the central compartment, while MOE and PCT reversed this effect. Neurohistological assessment revealed $HgCl_2$-induced reductions in neuronal count in cornu ammonis areas 1 and 3 (CA1 and CA3) and the dentate gyrus (DG) regions, with varied effects observed in MOE- and PCT-treated groups.

***Conclusion:*** This study demonstrates the neuroprotective effect of *Mallotus oppositifolius* against mercuric chloride-induced neurotoxicity in mice. The leaf extract may have potential in clinical conditions characterised by neurodegeneration.

**Keywords:** Mallotus oppositifolius; Mercuric chloride; Neurotoxicity; Hippocampus

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## INTRODUCTION

Neurotoxicity due to neurotoxicants disrupt normal nervous system activities, causing reversible or irreversible damage [1]. Neurotoxicants may be medications (e.g. ethambutol, isoniazid, vincristine); domestic products used in antidandruff shampoos (pyridinethione); fragrance raw materials (2,6-dinitro-3-methoxy-4-tert-butyltoluene), pyrolysis products in broiled, baked, or fried food (acrylamide), beverages (ethanol), pest-control agents (aldrin), and environmental pollutants (mercury) [1]. In high doses, some physiologically essential heavy metals such as copper, cobalt, iron, nickel, magnesium, molybdenum, chromium,

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selenium, manganese and zinc may cause neurotoxicity [2]. During neurotoxicity, glutamate activates the N-Methyl-D-aspartic acid (NMDA) receptors, resulting in the excessive release of calcium ions (Ca2+) [3]. This increases the stress on the mitochondria, resulting in excessive oxidative phosphorylation and production of reactive oxygen species (ROS) via the activation of nitric oxide synthase, ultimately leading to cell death [4]. In addition, the extracellular signal-regulated kinase (ERK) pathway is disrupted, which normally functions as memory control in the brain. The disruption, therefore, leads to memory dysfunction [5].

In the last two decades, more than a thousand published articles on mercury neurotoxicity have highlighted its relevance in public health discourse [6,7]. In Ghana, mercury contamination is primarily linked to artisanal and small-scale gold mining (legal and illegal), i.e. "galamsey", in which it is used in the gold purification process [8] and ends up in water bodies and in fish. Studies support fish consumption as one of the main means of mercury toxicity [8,9]. The classic symptoms associated with exposure to mercuric toxicity are a combination of renal, gastrointestinal and CNS symptoms, eventually leading to death [10]. Management of mercury toxicity includes GI decontamination, washing of exposed skin, and the use of activated charcoal [10]. Other studies suggest that selenium (i.e. sodium selenite) can elicit neuroprotective effects against mercuric chloride neurotoxicity or brain damage in chicken [11]. These options are, however, fraught with several limitations, prompting the need for alternative options.

In this regard, medicinal plants such as *Mallotus oppositifolius* with neuroprotective potentials may be useful [12,13]. *Mallotus oppositifolius* (Geiseler) Müll.Arg. (Euphorbiaceae) is an important and versatile medicinal herb prevalent across various African countries. Known for its diverse pharmacological properties, this plant thrives in multiple habitats, including semi-deciduous forests, wet and dry evergreen forests, grasslands, swamps, and savannahs with forest patches [14]. It is widely distributed in countries such as Ethiopia, Nigeria, Ghana, Cameroon, Madagascar, Senegal, Angola, Malawi, Zambia, Zimbabwe, Mozambique, Uganda, Kenya, and more [14]. Remarkably, *Mallotus oppositifolius* blooms and bears fruit throughout the year. The *Mallotus oppositifolius* leaf extract has demonstrated antidepressant, anticonvulsant and antiaggressive effects in murine models [13,15,16]. Various phytochemicals such as terpenoids, cardenolides, benzopyrans, flavonoids, (+)-α-tocopherol (vitamin E), stigmasterol, bergenin, methyl gallate and vitamin C with possible beneficial neuroactive effects have been identified in the plant.

We recently reported the presence of methyl laurate, ethyl palmitate, ethyl stearate, benzoic acid derivatives and phenolic compounds in the plant [15]. These constituents were associated with reduced nuclear factor κ-B, tumour necrosis factor-α, interleukin-6 levels and inhibition of α-synuclein in rats [17-19]. The reported pharmacological properties suggest that *Mallotus oppositifolius* may have a neuroprotective effect. Thus, this present work investigated the effect of *Mallotus oppositifolius* leaf extract (MOE) on the neurotoxicity caused by mercuric chloride in mice.

## MATERIALS AND METHODS

### Plant collection and extraction

Leaves from the *M. oppositifolius* (Geiseler) Müll. Arg (Family: Euphorbiaceae) plant was collected at the Centre for Plant Medicine Research (CPMR) in Mampong-Akuapem, Ghana (5°55′05.6″N, 0°08′04.9″W), and authenticated on-site (Voucher Specimen Number: CPMR 4977). Collection methods ensured the plant's well-being remained intact. After a 7-day period of air-drying, the leaves underwent pulverisation with a hammer mill to achieve a fine powder. Emulating traditional practices, cold maceration with absolute methanol was employed for 3 days, hinting at the likelihood of active constituents in a polar medium. The ratio of drug extract to solvent was maintained at 600 g of powdered leaves per 6000 ml of methanol. The resulting extract was concentrated at 60°C under pressure using a rotary evaporator, yielding a syrupy mass. This syrupy material was subsequently dehydrated into a dark brown semisolid mass using a water bath and stored in a desiccator for future use. This product was designated as *M. oppositifolius* leaf extract (MOE).

### Chemicals

Piracetam, ketamine and xylazine were obtained from Sigma Aldrich Inc., St. Louis, MO, USA, and mercuric chloride ($HgCl_2$) was from Merck KGaA, Darmstadt, Germany.

### Preparation of drugs

All the drugs were prepared just enough for daily use only. About 33.32 mg of the MOE was weighed daily into a container and diluted to 10 mL with distilled water to prepare 100 mg/kg/mL of MOE solution. Serial dilution was done to obtain the 10 mg/kg/mL and 30 mg/kg/mL solution of the MOE. Piracetam was prepared by dissolving the weighed amount in distilled water.

### Animals

Male ICR mice were obtained from the Department of Pharmacology, KNUST, Kumasi, Ghana and housed under standard laboratory conditions. Six groups of eight mice were kept in stainless steel cages measuring 34 × 47 × 18 $cm^3$ and lined with soft wood shavings for bedding. The mice were fed a regular commercial pellet diet (GAFCO, Tema) and given water ad libitum. The laboratory temperature was maintained between 24°C and 25°C, with an average humidity level of 77%. A daylight cycle between 7 am and 2 pm was maintained. All experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals and approved by the Ethical and Protocol Review Committee, College of Health Sciences, University of Ghana, Korle-Bu.

**Experimental design**

Group 1 (negative control) received normal saline orally administered using the oral gavage for 7 days, followed by distilled water for 3 days. Groups 2 to 6 received mercuric chloride (5 mg/kg) orally for 7 days. Following this, group 2 (disease control) received distilled water, groups 3, 4 and 5 received graded doses of MOE (10, 30, 100 mg/kg) and group 6 was given piracetam (150 mg/kg) for 3 days.

**Catalepsy test**

Neurotoxicity-associated motor incoordination and Parkinson-like effects were evaluated using the catalepsy test. Briefly, mice were placed on an elevated horizontal bar, and the time taken for them to descend was recorded. The duration spent on the rod served as an index for assessing motor coordination.

**Open field test**

The effect of treatments on the locomotor activity and anxiety behaviour of mice was evaluated using the open-field test [16]. Mice were placed in an open field box with an enclosed floor and walls, measuring 60 × 60 × 25 $cm^3$, with an open top. The centre region of the box floor was defined offline as a 20 × 20 $cm^2$ area, but it was not marked. Each box was placed on the floor of the experiment room and was dimly illuminated. Each mouse was gently placed in the centre of the box and allowed to walk freely. Locomotor activity was scored as the total distance travelled (marked by the number of lines crossed) and anxiety behaviour as the time spent in the centre during the 6-minute period using video tracking software (Boris v 7.9.6 - 2019). Scoring was done by a blinded experimenter.

**Novel object recognition (NOR) test**

Neurotoxicity affects cognitive function; thus, the effect of mercuric chloride on exploratory learning and recognition memory was assessed using the NOR test. The procedure used was as described by [20]. Mice were randomly assigned to eight groups (n = 8) and administered drugs as outlined in the experimental design. The test involved 3 phases: habituation, familiarisation, and testing. In the habituation phase, the mice were placed in an open field (33 × 33 × 20 $cm^3$) for 5 minutes twice daily, with a 6-hour interval, for three consecutive days. The familiarisation phase was carried out 24 hours after the last day of habituation. Two identical objects (in terms of shape, colour, and size) were placed 20 cm apart in the open field. The mice were placed in the centre of the field for 10 minutes and allowed to freely explore the objects. Behavioural assessment of each mouse was done for 10 minutes. This phase lasted for three days. Exactly 24 hours after the familiarisation phase, the testing phase was performed, which lasted for 3 days. One hour before each test day, the mice were treated with MOE (10, 30, and 100 mg/kg p.o.), piracetam (150 mg/kg p.o.), or the vehicle (saline, 10 ml/kg p.o.). The test was conducted for 5 minutes, with one of the identical objects replaced by a new object. Environmental cues were hung in the study environment to facilitate the exploration of the novel object and enhance discrimination against the familiar one [21]. Behavioural assessments were done with JWatcher, version 1.0 (University of California, Los Angeles, USA, and Macquarie University, Sydney, Australia) by a blinded observer. The time spent with the novel object and recognition index (RI) were assessed. RI was calculated to demonstrate the level of discrimination against the familiar object, using the formula according to [22]:

$$RI = \frac{(\%\text{ exploration of familiar object during training} - \%\text{ of exploration of familiar object during test})}{\%\text{ exploration of familiar object during training}}$$

**Sacrificing of animals and harvesting of the brain**

After the study period of 10 days, mice were euthanised with 100 µL of a 10:1 mixture of ketamine (100 mg/ml) and xylazine (10 mg/ml) and brains harvested. The harvested brain samples were placed in a solution of 4% formaldehyde until it was analysed using the cresyl violet stain technique.

**Sectioning and cresyl violet staining**

Each brain sample was divided into three coronal sections and placed in histological cassettes (Rotilabor embedding cassettes; K114.1, Carl Roth GmbH, Germany). The sections were subsequently processed through a graded ethanol series: 70% ethanol for 1 hour, 95% ethanol for 1.5 hours, and 100% ethanol twice for 2 hours each. Following this, the tissues were immersed in molten paraffin wax for 3 hours, embedded in the wax, and stored in a refrigerator at 4°C until sectioning. The refrigerated tissue blocks were sectioned at 50 µm using a microtome (Leica RM 2235) and placed in water at 60°c. The floating sections were carefully picked up with a brush and mounted onto gelatin-coated slides. Excess moisture was blotted with tissue paper, and moderate downward pressure was applied with the heel of the palm to ensure the sections adhered firmly to the slides. The slides were then dried in the dark for 3 days. Following the drying process, the sections were dehydrated through a graded series of alcohol solutions, starting with 70% ethanol, followed by 95% ethanol, and finally 100% ethanol. The sections were then immersed in a cresyl violet acetate solution for 15 minutes, allowing the dye to bind to the Nissl substance within the neurons. After staining, the sections were briefly rinsed in distilled water to remove excess dye. The sections were treated with 95% ethanol to achieve the desired contrast, highlighting the neuronal cell bodies against a clear background. The sections were rapidly dehydrated in 100% ethanol and then cleared in xylene to enhance tissue transparency. To clear the sections, they were transferred to xylene and then mounted with DPX (dibutyl phthalate in xylene). Once the sections were mounted, a coverslip was placed over the tissue, and the slide was made ready for examination under the light microscope.

**Data analysis**

Data were analysed using one-way or two-way analysis of variance (ANOVA), followed by Tukey or Bonferroni post-hoc tests to determine the differences between the different treatment groups. The level of significance was set at $p < 0.05$.

## RESULTS

### Catalepsy test

The study measured the time mice spent on the horizontal rod. Compared to the vehicle naïve group (VEH), there was an increase in time spent on the rod in the $HgCl_2$-treated mice (Figure 1). Conversely, MOE (10 - 100 mg/kg), just as piracetam (PCT), produced a significant ($p < 0.001$) increase in time spent on the rod (Figure 1). The results from the MOE and PCT group were comparable to VEH group.

### Open field test

We show that $HgCl_2$ treatment caused a significant decrease in time spent in the central compartment of the open field and the number of line crossings when compared to the VEH group (Figure 2A and B). MOE, just as PCT, significantly ($p < 0.01$) increased the time spent at the centre of the open field when compared to the $HgCl_2$ group (Figure 3A). The time spent in the centre by mice given the highest dose of MOE (100 mg/kg) was comparable to the VEH group. Moreover, MOE produced a modest increase in the number of line crossing relative to the $HgCl_2$ group, with MOE 30 mg/kg and PCT causing a significant ($p < 0.01$) increase in the number of line crossing (Figure 2B).

### Novel object recognition test

From the time-course curve, mice spent the same time when the objects were similar. However, after changing one of the objects, $HgCl_2$ treatment significantly reduced the time spent with the novel object throughout the experimental period when compared to the vehicle naïve group ($p < 0.01$). MOE (30 and 100 mg/kg) and PCT (150 mg/kg) significantly increased the time spent with the novel object when compared to VEH and $HgCl_2$ ($p < 0.05$). MOE's effect began on the second day of treatment and was sustained till the end of the experiment (Figure 3A). Moreover, MOE and PCT reversed the $HgCl_2$-associated decrease in total time spent (calculated as AUC) exploring the new object (Figure 3B). $HgCl_2$ decreased the recognition index while MOE and PCT significantly ($p < 0.0001$) reversed the $HgCl_2$-induced decline in recognition index (Figure 3C). Interestingly, PCT and MOE (10 and 100 mg/kg) produced a greater recognition index than the VEH.

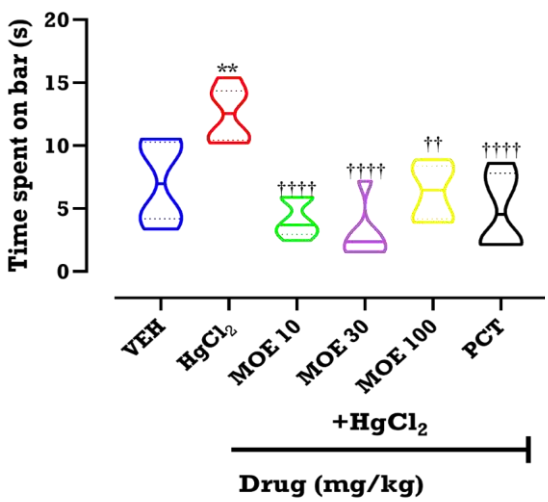


Figure 1. Effects of MOE and piracetam (PCT) on duration of the forelimb on the bar in the catalepsy est. Data are presented as group Means ± SEM (n=8). Significantly different from vehicle: **p < 0.01 (One-way ANOVA followed by Tukey's post hoc test). ††††p <0.0001, †††p < 0.001, ††p < 0.01, †p < 0.05; significantly different from untreated $HgCl_2$ group (One-way ANOVA followed by Tukey's post hoc test).

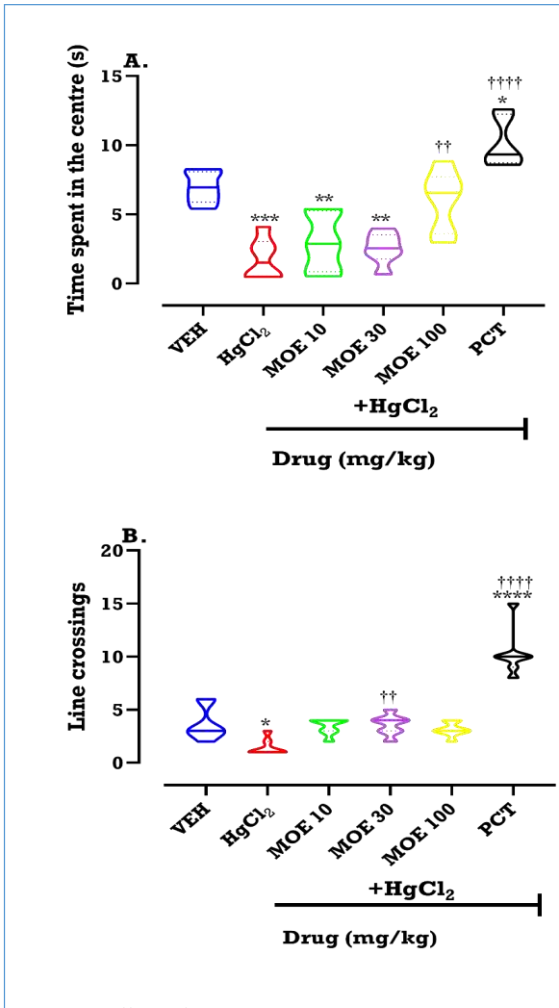


Figure 2. Effects of MOE and PCT on (A) Time spent at the centre and (B) Lines crossed in the OFT. Data are presented as group Means ± SEM (n=6). Significantly different from saline (VEH) group: *p < 0.05, **p < 0.01 and ***p < 0.001 and ****p < 0.0001; significantly different from untreated HgCl2 group: ††p < 0.01, †††p < 0.001 and ††††p <0.0001 (One-way ANOVA followed by Tukey's post hoc test).

**Cresyl violet staining of the hippocampus and neuronal count**

Figure 4 shows representative images of the hippocampus from mice treated with $HgCl_2$ or saline. While the $HgCl_2$ group showed loss of neurons in various parts of the hippocampus, the VEH and drug-treated groups showed preserved hippocampal neuronal architecture (Figure 4). From Figure 5, MOE (10 and 100 mg/kg) significantly ($p < 0.0001$) reversed the neuronal loss in the dentate gyrus (DG) caused by $HgCl_2$. The effect of MOE 30 mg/kg was not statistically significant, giving rise to a U-shaped effect. It is worth noting that MOE could not reverse the neuronal loss to the state of the vehicle naïve group (VEH). It can also be observed that the PCT could not reverse the $HgCl_2$-associated neuronal loss in the DG when compared to VEH.

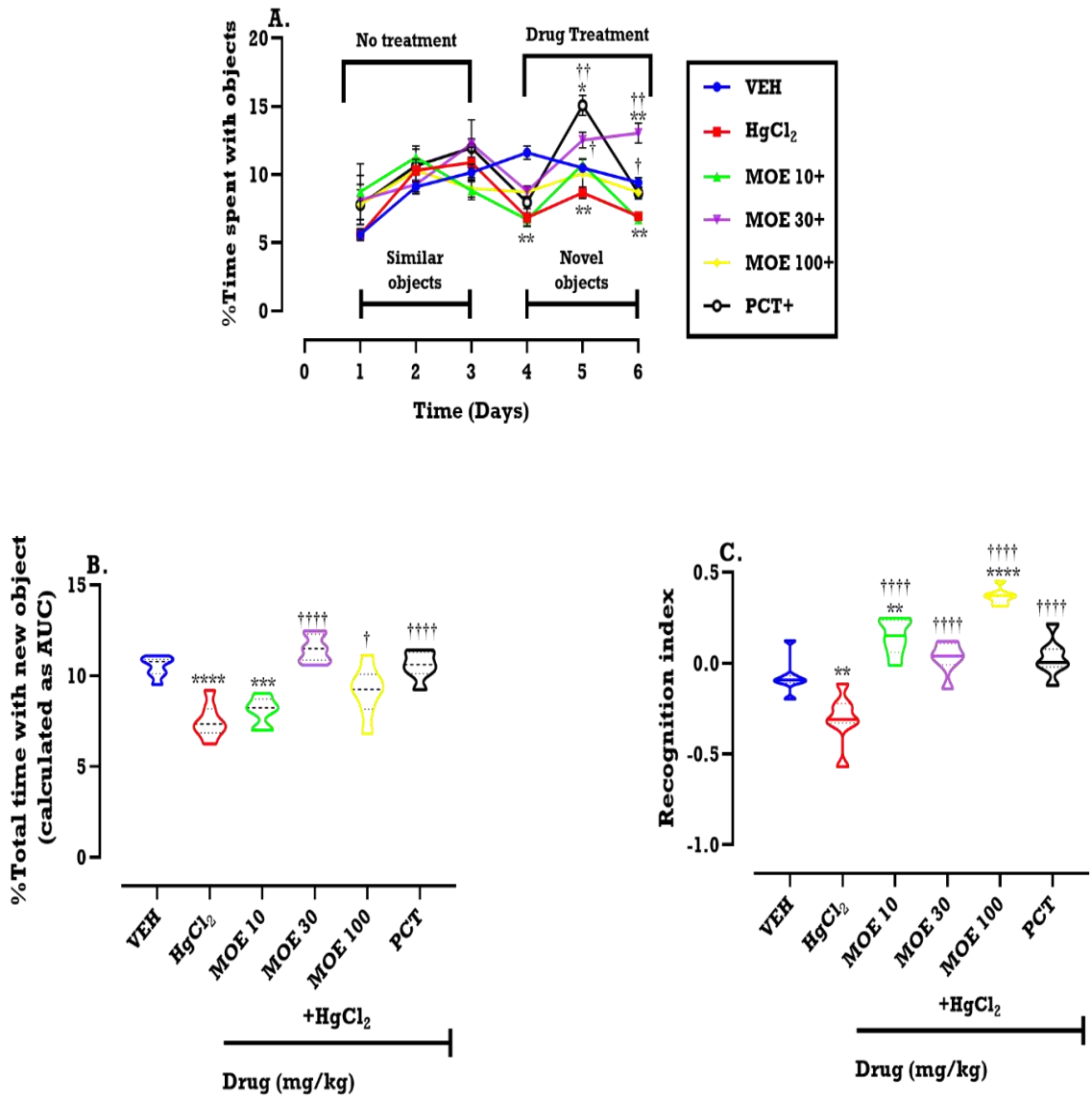


Figure 3. Effects of MOE (10, 30 and 100 mg/ kg) and PCT (150 mg/kg) treatment on the (A) Percentage time spent with the novel object (B) Total time with new object (C) Recognition index in the NOR test. Data are presented as mean ± SEM (n = 6) for the time course graph A and analyzed by Two-way ANOVA followed by Bonferroni's test. The total times spent with the new object are presented as the areas under the curve (AUC) (B) (One-way ANOVA followed by Tukey's multiple comparison test). Significantly different from the saline (VEH): *$p < 0.05$, **$p < 0.01$; significantly different from untreated $HgCl_2$: †$p < 0.05$, ††$p < 0.01$. The recognition index is presented (C) (One-way ANOVA followed by Tukey's multiple comparison test). Significantly different from the saline (VEH): **$p < 0.01$, ****$p < 0.0001$; significantly different from untreated $HgCl_2$: ††††$p < 0.0001$.

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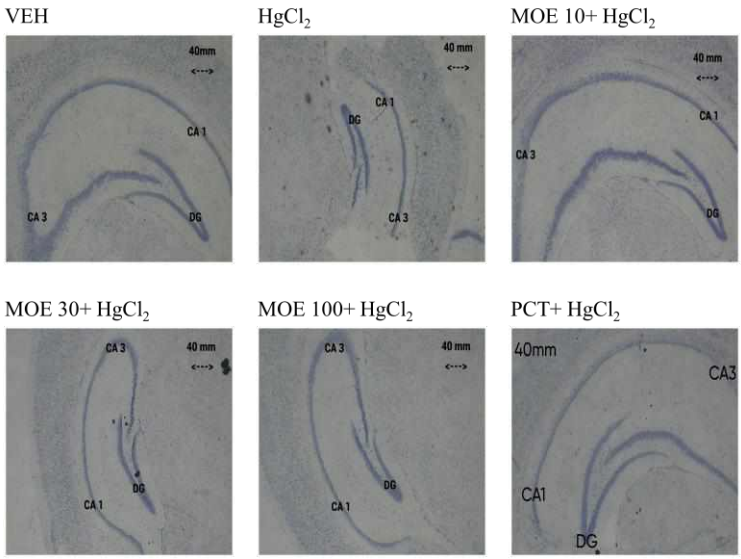


Figure 4. Representative images of Cresyl Violet stained Dentate Gyrus (DG), Cornu Ammonis (CA1), Cornu Ammonis (CA3) regions of the hippocampus of the brain of the mice for each experimental group. VEH = Vehicle-treated group; $HgCl_2$= $HgCl_2$ untreated group; MOE 10, 30, 100 = *M. oppositifolius* leaf extract-treated groups; PCT= Piracetam-treated group.

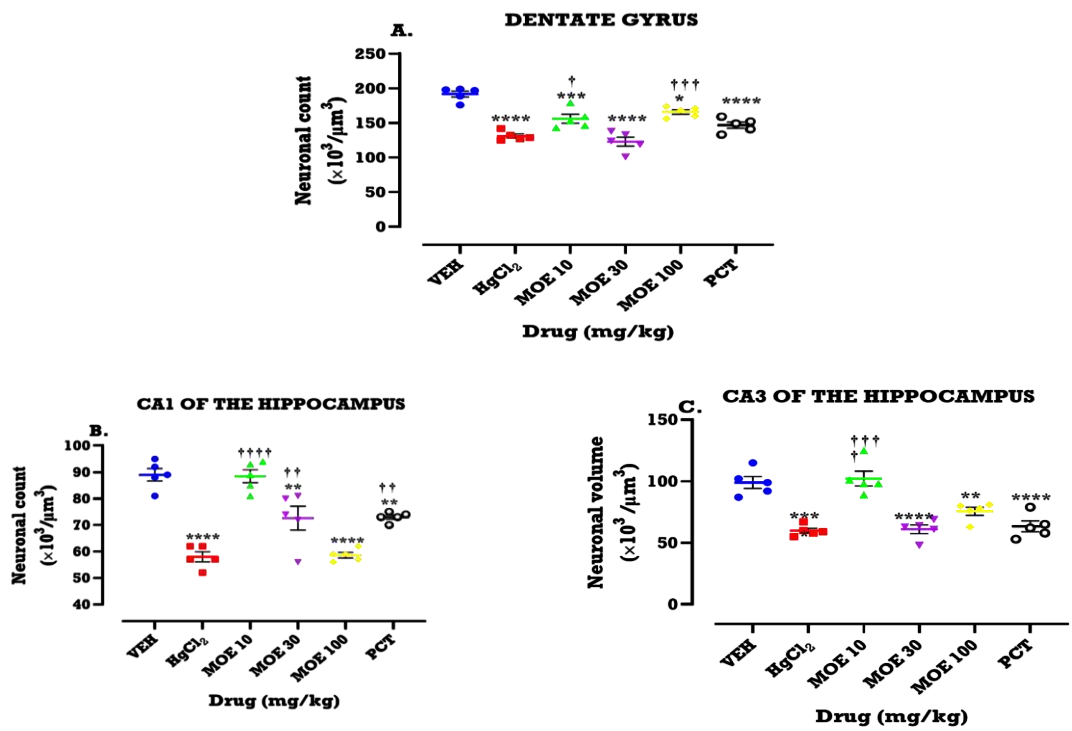


Figure 5. Quantification of neurons. Effect of MOE, $HgCl_2$ and PCT on neuronal count in the A. dentate gyrus (DG), B. CA1 and C. CA3 regions of the hippocampus of mice. The results are expressed as absolute values and expressed as mean ± SEM (n =5). Significantly different from saline (VEH) group: *p < 0.05, **p < 0.01 and ***p < 0.001 and ****p < 0.0001; significantly different from untreated $HgCl_2$ group: †p < 0.05, ††p < 0.01, †††p < 0.001 and ††††p <0.0001 (One-way ANOVA followed by Tukey's post hoc test).

From Figure 5, it was evident that $HgCl_2$ caused a significant ($p < 0.0001$) reduction in the neuron count of the Cornu Ammonis 1 (CA1) region of the hippocampus when compared to the vehicle naïve group (VEH). In contrast, MOE (10 and 30 mg/kg) significantly reversed the $HgCl_2$-associated neuronal loss in the CA-1 of the hippocampus. Surprisingly, MOE (100 mg/kg) could not reverse the $HgCl_2$-induced neuronal loss. It can also be observed that the PCT increased the neuronal count at the CA-1 relative to the untreated $HgCl_2$ group ($p < 0.01$). From the results in Figure 5, $HgCl_2$ caused a significant reduction in the neuronal count of the CA3 region of the hippocampus when compared to VEH. This effect was, however, reversed by MOE (10 mg/kg). MOE (30 and 100 mg/kg) failed to reverse the neuronal loss caused by $HgCl_2$. PCT treatment also failed to reverse the $HgCl_2$-induced neuronal loss in the CA3.

## DISCUSSION

The study provides evidence that MOE ameliorates the neurotoxic effects of mercuric chloride in mice. Here, we provide insight into the efficacy of the extract in mitigating mercury-related neurotoxicity, a significant concern in environmental and occupational health due to widespread exposure to it. Catalepsy, NOR, OF tests, and cresyl violet staining were used to assess the protective effect of the MOE. Catalepsy is a condition characterised by muscle rigidity and inability to correct an externally imposed posture. Catalepsy is associated with Parkinson's disease, catatonic schizophrenia, as well as brain damage involving the basal ganglia or cerebellum [23]. Ordinarily, when a healthy animal finds itself in an unfamiliar posture, it instinctively adjusts its position within a matter of seconds. However, a cataleptic animal remains in the imposed posture for an extended duration, often spanning several minutes. This has been used as a model for extrapyramidal symptoms. In addition, it is associated with dopamine D2 receptor antagonism and 5-HT1A receptor dysfunction [24]. Previous studies showed that mercury neurotoxicity is associated with disruption in neurotransmitter release and binding, especially dopamine and 5-HT. Considering the role of these neurotransmitters in catalepsy, it is not surprising that mercuric chloride produced a pronounced cataleptic effect in mice. Even more interesting is the fact that MOE attenuated the mercury-induced catalepsy. The MOE-associated effect may be related to its effect on 5-HT and catecholamines [13].

Coupled with catalepsy, mercury intoxication is associated with anxiety behaviour and impaired locomotor activity [25]. The open field test model was used to assess locomotor activity and exploratory behaviour (line crossing) as well as anxiety (time spent at the centre of the field) in mercury-exposed mice [26]. MOE significantly reversed the $HgCl_2$-induced locomotor impairment and anxiogenic effect [27], suggesting a possible anxiolytic effect. The putative anxiolytic effect of MOE is supported by its GABA and serotoninergic-enhancing effects previously reported [28,13]. Piracetam has been reported to influence the release, synthesis, and receptor binding of neurotransmitters such as acetylcholine, glutamate, and GABA. This may be responsible for its ability to attenuate the mercuric chloride-related effects in the open field test. The novel object recognition test was utilised to evaluate cognitive function and memory retention in the mice. The behavioural tests employed in this investigation aided in the assessment of exploratory work, recognition, and reference memories. Exploratory learning establishes a relationship between existing knowledge and new content or concepts, while working memory involves temporarily holding information and using it in cognitive tasks.

Reference memory is a form of long-term memory that utilises two aspects of episodic memory, which are content and place dimensions of activity [29,30]. Recognition memory comprises recollection and familiarity [31]. Impaired recognition memory is a common consequence of neurotoxicity. This test sought to determine whether the leaf extract could mitigate cognitive deficits caused by mercuric chloride exposure. Mercuric chloride induced cognitive deficits by impairing learning and memory in the novel object recognition (NOR) test. Both the acquisition of information and the retention of memory were disrupted by mercuric chloride, as evidenced by the reduction in the time spent with both the novel object and recognition index. As expected, piracetam, a nootropic agent, significantly increased both the time spent with the novel object and the recognition index. Similarly, the MOE reversed the deleterious effect of mercuric chloride on learning and memory. It is worth noting that the MOE- and piracetam-associated improvement in learning and memory was higher when compared to vehicle mice. The result suggests that MOE may have a nootropic effect. This result is supported by previous findings that showed that MOE rapidly reverses depressive symptoms without impairing spatial learning and memory [28]. A high percentage of time spent with the new object indicates improvement in exploratory learning and recognition memory [21,32]. In addition, the hippocampus, prefrontal cortex, cingulate cortex, neostriatum, entorhinal cortex, perirhinal cortex, and N-methyl-D-aspartate (NMDA) receptor function have been implicated in mice behaviour in the NOR test (D'Hooge & De Deyn, 2001; Vorhees & Williams, 2006). Indeed, a previous study has suggested that MOE inhibits the glycine co-stimulatory site of the NMDA receptor [28]. Moreover, MOE prevented loss of dendritic spine density and contributed to neurogenesis and/or neuroplasticity in the prefrontal cortex of mice [16]. It is plausible that the cognitive-enhancing effects of MOE may involve any of the above-mentioned structures or systems.

Furthermore, limitations in learning and memory typically affect quality of life, reduce creativity, slow academic performance, especially in children, and may increase the risk of developing attention-deficit hyperactivity disorder (ADHD), dyslexia, and Alzheimer's disease [33]. Since MOE improved exploratory learning, working, recognition,

and reference memory in mice, further studies exploring their efficacy in these conditions is required.

In order to prove that mercuric chloride caused neurotoxicity, the cresyl violet staining technique was used to assess the neuronal count in the hippocampus (CA1, CA3 and DG) [34]. The hippocampus is one of the brain structures affected during neurotoxicity, and considering its role in behaviour and cognitive processes, it was selected for the histological assessment. In this study, mercuric chloride significantly reduced the neuronal count in the CA1, CA3 and DG regions of the hippocampus. This may suggest mercuric chloride-associated increased neuronal death and/or inhibition of neurogenesis in these hippocampal regions. Both the MOE 10 and 30 mg/kg were able to reverse the toxic effects of mercuric chloride in all the regions assessed. The effect of MOE may be due to increased neurogenesis and/or suppression of mercuric chloride-induced neuronal apoptosis [14,35]. Further studies may be needed to elucidate the mechanism underlying the beneficial effects of MOE. Similarly, the standard drug, piracetam, was able to prevent the neuronal damage in the CA1 from the mercuric chloride. Our study proffers that MOE reverses the behavioural, cognitive and histological changes associated with mercury toxicity.

### Conclusion

We have shown for the first time that *Mallotus oppositifolius* leaf extract ameliorates mercuric chloride-induced increased catalepsy, anxiogenesis, impaired locomotion and learning and memory deficits. The behavioural effects of the leaf extract were associated with increased hippocampal neuronal count. The present study suggests that *Mallotus oppositifolius* may have neuroprotective potential against mercury chloride in mice.

## DECLARATIONS

### Ethical consideration

The animal study was reviewed and approved by the Ethical and Protocol Review Committee, College of Health Sciences, University of Ghana, Korle-Bu (CHS-Et/M.7 – P4.2/2022-2023).

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest.

### Author contribution

KKE conceptualised the study. BEO, KKE, and KKA designed the methodology and conducted the investigation. KKE and BEO collected and analysed the data. KKE and BEO drafted the original manuscript. KKE, BEO, PA, and KKA reviewed and edited the manuscript. All authors have accepted responsibility for the entire content of this submitted manuscript and approved the submission.

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### Availability of data

Data is available upon request to the corresponding author.

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# Optimised formulation of *Mallotus oppositifolius* extract reverses cognitive decline and beta-amyloid deposition in a murine Alzheimer's disease-like dementia model

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**Abstract**

***Background:*** *Mallotus oppositifolius* leaf extract (MOE) has potential neuroprotective effects, but no scientific investigation validates its use in mouse models of Alzheimer's disease (AD).

***Objective:*** The study evaluated the effects of an optimised formulation of MOE in aluminium chloride ($AlCl_3$)-induced AD-like dementia.

***Methods:*** Mice were randomly assigned to 6 groups (n = 10), and AD was induced in groups 2-6 using $AlCl_3$ (175 mg/kg), with group 1 representing the negative control. Optimised formulation of MOE (10, 30 and 100 mg) was administered orally to groups 3, 4 and 5, respectively, while group 2 represented the disease control. The Morris water maze (MWM) test was used to assess cognitive impairment, and the open-field test (OFT) for locomotor and anxiety behaviour. Biochemical and histological changes were also assessed.

***Results:*** $AlCl_3$ caused significant memory and learning disruption in the MWM test, but MOE formulation (10, 30, and 100 mg/kg) reversed these deficits. MOE formulation attenuated the reduction in both locomotion and time spent in the centre of the OFT in comparison to the $AlCl_3$-diseased untreated group. Brain superoxide dismutase (SOD) content was significantly increased while brain and serum malondialdehyde (MDA), as well as acetylcholinesterase (AChE), were reduced by the formulation treatment when compared to the $AlCl_3$-diseased untreated group. The administration of MOE formulation (30 and 100 mg/kg) resulted in a significant reduction in brain concentrations of IL-1β, IL-6, and TNF-α and a significant decrease in serum IL-6 and TNF-α concentrations when compared to the $AlCl_3$-diseased untreated group. Congo red-stained hippocampus CA1 showed that the formulation (30 and 100 mg/kg) significantly decreased amyloid deposition in comparison to the $AlCl_3$-diseased untreated group.

***Conclusion:*** This study reports that an optimised formulation of MOE improves learning and memory, attenuates anxiety, and reduces pro-inflammatory cytokines and oxidative stress associated with AD-like dementia. The formulation also ameliorates amyloid deposition.

**Keywords:** *Mallotus oppositifolius*, Alzheimer's disease, β-amyloid, neurodegenerative diseases

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## INTRODUCTION

Alzheimer's disease (AD) has become a global health menace among various neurodegenerative diseases (NDs) due to its debilitating nature [1,2]. The exact cause and associated factors that underlie individual variations regarding the disorder and related symptoms are still unknown [3]. The neurodegeneration associated with AD advances latently and persistently until symptoms such as challenges in memory retention and cognitive abilities that include orientation, problem-solving, and personality changes become evident. AD is distinguished by the

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presence of extracellular neurofibrillary tangles (NFTs) and intracellular amyloid accumulations [4]. Of these, beta-amyloid (Aβ) and hyperphosphorylated tau (p-tau) are major pathological markers found in AD brain tissues [5,6]. Additional features include mitochondrial dysfunctionality, synaptic destruction, neuroinflammation, dysregulation in neurotransmission, changes in hormonal levels, and dysregulation in the cell cycle [7]. Oxidative stress, a key element in the initiation and progression of AD, is also crucial for the development of Aβ and NFTs [6]. By 2018, dementia, a key AD symptom, had reached a pandemic level, affecting 50 million individuals globally with an estimated yearly economic cost of $1 trillion [8]. Ageing is projected to significantly contribute to a threefold increase in dementia cases by 2050 [8,9]. For most dementia patients, therapeutic options are limited, and there is no effective cure [2]. In this regard, evaluating the therapeutic effects of medicinal plants against dementia may be a viable option.

*Mallotus oppositifolius (M. oppositifolius)* extract has significant CNS depressant, analgesic, and anticonvulsant effects [10]. It improved spatial memory and learning tasks in mice [11] and reduced MDA levels in liver homogenate tissues of alloxan-induced diabetic rats, suggestive of anti-peroxidative potential [12]. Moreover, many phytochemicals such as diterpenoids, triterpenoids, cardenolides, benzopyrans, flavonoids, coumarinolignoids and phloroglucinol derivatives, (+)-α-tocopherol (vitamin E), lupeol, stigmasterol, phytol, bergenin, squalene, and methyl gallate, and vitamin C with possible beneficial neuroactive effects have been found in the plant [13]. Recently, we reported the presence of methyl laurate, ethyl palmitate, ethyl stearate, benzoic acid derivatives and phenolic compounds in *M. oppositifolius* [14]. Methyl laurate, the most abundant constituent, reduces LPS-induced nuclear factor κ-B levels, while ethyl palmitate, the most abundant fatty acid in the brain, caused a reduction in tumour necrosis factor-α and interleukin-6 in rats [15]. Ethyl stearate blocked α-synuclein in rats, suggesting a possible neuroprotective effect in Parkinson's disease [16]. These pharmacological properties make the plant a viable candidate in managing AD, although this has not been scientifically validated.

Despite these advantages, the effectiveness of plant-based therapies can be limited by poor solubility and instability in gastric and colonic juices, poor absorption, and reduced penetration across the blood-brain barrier [17,18,19]. To address this, the development of novel drug transport systems as carriers for plant extracts can facilitate efficient drug delivery to target sites at an optimal rate. In this regard, chitosan nanoparticles can be used as drug carriers because of their excellent biocompatibility and ease of creating sustained-release formulations [20]. Thus, our study used chitosan nanoparticles to incorporate *M. oppositifolius* leaf extract into a modified-release formulation and evaluated its effect in an AD-like model of dementia.

# MATERIALS AND METHODS

### Extraction of *M. oppositifolius* leaf extract

*M.* oppositifolius leaves were obtained from and authenticated at the Centre for Plant Medicine Research (CPMR), Mampong-Akuapem, Ghana. The extraction method followed a similar procedure according to Kukuia et al., 2022 [13]. The air-dried and pulverised leaves underwent cold maceration in 70% ethanol and 30% water for three days. The resultant extract was then concentrated under reduced pressure and at 60°C using a rotary evaporator. The extract was further dried at 45°C, yielding 31.5 g (1.05%) and stored in a desiccator for subsequent use.

### Preparation of optimised formulation of *M. oppositifolius*

Formulations of *M. oppositifolius* extract (MOE) were obtained from the Pharmaceutics Lab, School of Pharmacy, University of Ghana. The extraction of pectin from cocoa pod husk [21] and formulation of the oral modified release *Mallotus oppositifolius* multi-particulate matrix were done according to the method used by [22,23,24] with minor modifications. Table 1 shows the proportions used in the formulation of MOE extract in doses of 10, 30, and 100 mg, respectively.

Table 1. Proportions of MOE and excipients in formulation

| SN | MOE extract (mg) | Chitosan (mg) | Dicalcium phosphate (mg) | Pectin (mg) | Total weight (mg) |
|---|---|---|---|---|---|
| F1(10) | 10 | 50 | 240 | 50 | 350 |
| F1(30) | 30 | 50 | 220 | 50 | 350 |
| F1(100) | 100 | 50 | 150 | 50 | 350 |

### Chemicals

Aluminium chloride ($AlCl_3$) and chitosan were obtained from Central Drug House (India); ketamine hydrochloride from Swiss Parenterals Ltd (India); Sodium phosphate buffer from Thermo Fisher Scientific (USA).

### Experimental animals and housing

Institute of Cancer Research (ICR) mice (n = 60) were purchased from the Noguchi Memorial Institute for Medical Research, University of Ghana, and acclimatised for 7 days. Mice aged 24 weeks were grouped in sets of 10 and placed in six stainless cages, each measuring 47 cm × 34 cm × 18 cm (length, width, and height, respectively), containing softwood shavings. Temperature conditions of 25 - 28°C with a 12-hour light/12-hour dark cycle were maintained throughout the study. Mice had unrestricted access to both food and water during the study, except for periods when they were undergoing tests.

### Experimental design

A randomised sampling technique was used to group all animals (n = 60). Randomisation was performed by

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numbering (marking) the animals from 1 to 60. These numbers were entered into Microsoft Excel and randomised into six groups. Induction of AD followed a method similar to that employed by Chen et al. [25] with slight modifications. Group 1 was treated as the vehicle control group (VEH) and was given a regular diet and oral normal saline (0.9%) only. Group 2 was given 175 mg/kg of aluminium chloride by oral route for 25 days to induce AD, followed by administration of 0.9% (5 ml/kg) oral normal saline from the 26th day to the 35th day ($AlCl_3$ group). Groups 3, 4, and 5 received the same dose of $AlCl_3$ as those in group 2 for 25 days, followed by treatment with 10, 30, and 100 mg/kg of optimised MOE for each group, respectively, from the 26th day to the 35th day (+MOE group). Group 6 received the same dose of $AlCl_3$ as those in group 2 for 25 days, followed by administration of 3 mg/kg donepezil from the 26th day to the 35th day as a reference drug group (+DPZ group). While transgenic models offer advantages such as reproducibility, consistency, and genetic relevance to human subjects, the $AlCl_3$ model effectively mimics key features of AD, hence its application in this study.

**Morris water maze (MWM) test**

The MWM test was used to evaluate the animal's spatial memory and learning. Escape latency and probe memory trials were carried out as they are important for assessing cognitive function in rodent models of neurodegenerative diseases such as AD [26]. The MWM involved a circular pool (1.8 m diameter, 0.4 m height) divided into four quadrants, with a hidden escape platform (0.1 m diameter) in one quadrant. Mice were trained to find the platform within 60 seconds before inducing AD-like dementia. Post-induction, their ability to find the platform was tested to establish a baseline for learning impairment. Treatment with MOE or donepezil (DPZ) started 24 hours later and lasted 10 days. From days 6 to 10, the water level was raised to 0.01 m above the platform, and non-dairy milk was added to obscure it.

Escape latency was recorded to assess spatial learning and memory. During the training trials, each mouse was placed in the pool from different starting positions and allowed to swim for a maximum of 60 seconds to locate the hidden platform. If successful, the time taken to reach the platform was recorded as the escape latency; if unsuccessful, a maximum latency of 60 seconds was assigned, and the mouse was guided to the platform and allowed to remain there for 15 seconds to aid learning. Four trials per day were conducted over the 5-day testing period.

A probe trial was conducted 24 hours after the last test, measuring time spent in the target quadrant without the platform. For the probe trial, the platform was removed, and each mouse was allowed to swim freely for 60 seconds. The amount of time spent in the quadrant where the platform was previously located and the number of times the mouse crossed the former platform location were recorded as measures of spatial memory retention. All observations were made by a blinder.

**Open-field (OF) test**

The OF locomotion test was employed to examine motor function and to assess anxiety behaviour. The OF was made of a wooden box measuring 100 cm (length) × 100 cm (width) × 25 cm (height). The box was divided into lines of equal distance (20 cm apart). The centre square of the box measured 60 cm (length) × 60 cm (width). In the test, a behavioural tracker was used to assess animal behaviour for 5 minutes. At the beginning of the test, the mouse was positioned in the centre of the open field. Total distance travelled, which was measured by the number of lines crossing, time spent in the centre area, and the frequency of grooming, was evaluated.

**Biochemical analysis - Serum collection**

Mice were anesthetised with 100 mg/kg ketamine hydrochloride and sacrificed. Blood sample of 0.5 ml was collected from each mouse through cardiac puncture and allowed to clot for 20 minutes. After centrifugating the samples at 4000 rpm for 10 minutes, the serum was obtained and kept at $-2^0$ 0C for measurement of superoxide dismutase (SOD.), malondialdehyde (MDA), acetylcholinesterase (AChE), interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α).

**Brain tissue processing**

Using sterile instruments, the brain was quickly removed from each mouse's skull after anaesthesia and placed in a pre-chilled dish. The hippocampal, entorhinal, striatum, and cerebral cortex tissues obtained from 6 animals in each group were microdissected, weighed and transferred to microcentrifuge tubes. The brain tissue homogenates of 100 mg/ml were created by adding sodium phosphate buffer (pH of 7.4), using a homogeniser. After homogenisation, the samples were centrifuged at 3500 rpm for 20 minutes at a temperature of 4 °C. The resulting transparent supernatant was obtained and preserved at -20 °C for the measurement of SOD, MDA, AChE, IL-1β, IL-6, and TNF-α.

**Determination of biochemical markers**

Acetylcholinesterase (AChE) levels, which frequently increase around amyloid plaques and neurofibrillary tangles, are prevalent in AD pathology [28]. Brain and serum AChE, malondialdehyde (MDA), the antioxidant superoxide dismutase (SOD), inflammation-related markers, IL-1β, IL-6 and tumour necrosis factor-α were measured using the sandwich ELISA purchased from the Sunlong Biotech Co., Ltd, China.

**Histopathological Analysis**

The hippocampal brain tissues were carefully excised from the control and treatment groups (four mice per group), sliced into smaller pieces, and immersed in Bouin's fixative solution for 24 hours. After fixation, the tissues were subjected to paraffinisation and sectioned (5 µm thickness) with a microtome. The sections were stained with Congo red to identify amyloid protein deposits and examined

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under microscopy. Three (3) micrographs from each group were used for amyloid quantification.

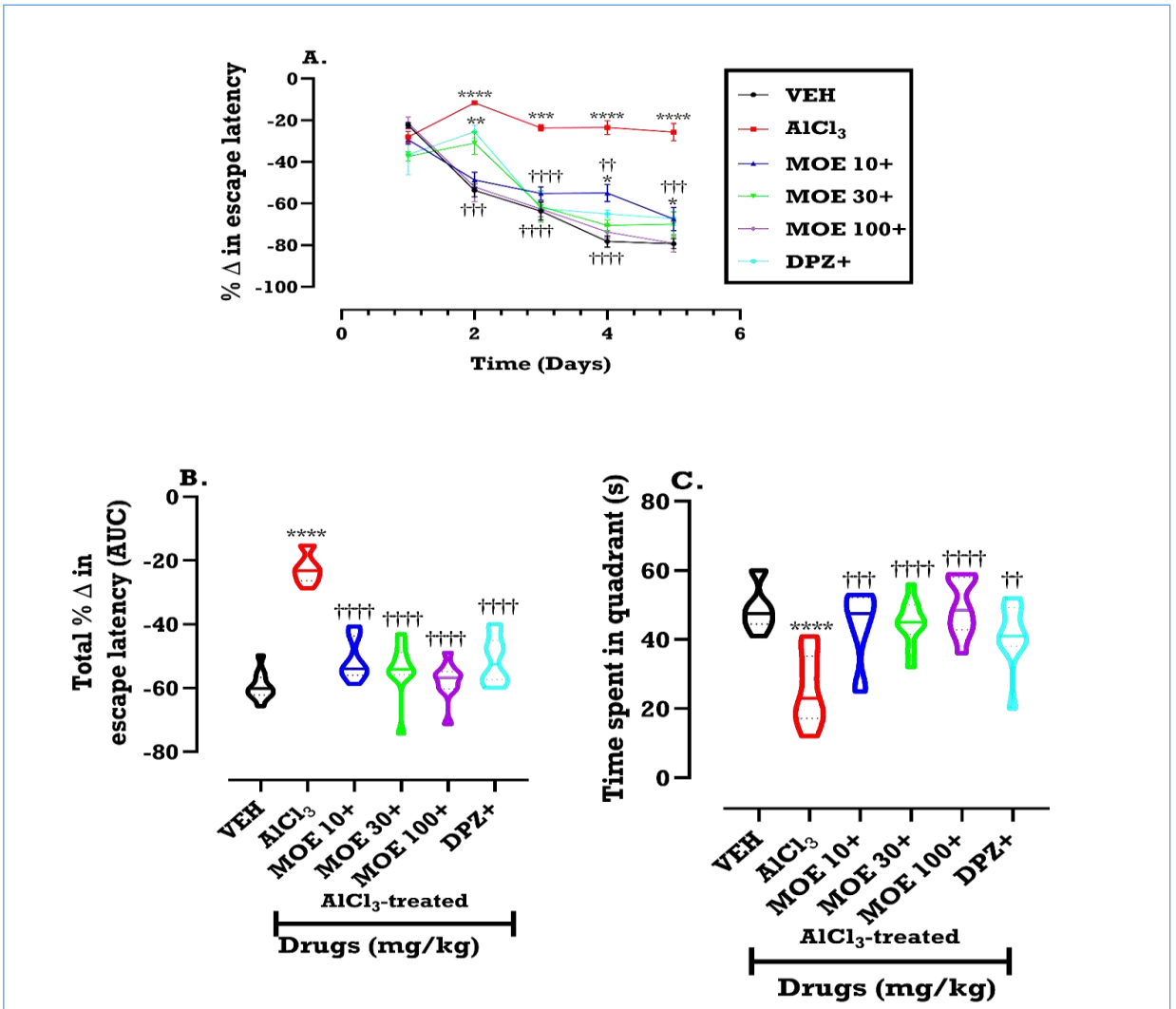
### Statistical analysis

GraphPad Prism for Windows version 10.0.2 (GraphPad Software, San Diego, CA, United States) was used for data and statistical analysis. All data were expressed as the mean ± standard error of the mean (SEM). The statistical analysis involved either one-way or two-way analysis of variance (ANOVA), followed by Tukey's post-hoc test. P value < 0.05 among means was considered statistically significant.

## RESULTS

### Effects of optimised leaf extract of *M. oppositifolius* formulation on $AlCl_3$-induced AD mice by MWM test

Results are shown as time course curves (Figure 1A) and violin plots (Figure 1B, C). In comparison to VEH, $AlCl_3$ treatment increased (F (4,38) = 6.579; p = 0.0003) the latency to locate the platform (escape latency) throughout the experimental period (Figure 1A). Similarly, $AlCl_3$ increased (F (5,58) = 45.65; p < 0.0001) the overall escape latency (depicted as the AUC, Figure 1B) while decreasing




Effects of optimised formulation from the leaf extract of *M. oppositifolius* on $AlCl_3$ induced AD-like dementia in the Morris water maze test (MWT): (A) Percentage change in escape latency; (B) total percentage change in escape latency, calculated as area under the curve (AUC), and (C) Probe memory trial. All data were presented as mean ± SEM (A) time course curve, (B) violin plot of its AUC, and (C) violin plot of its probe memory trail. (A): ****p < 0.0001, ***p < 0.001, **p < 0.01, *p < 0.05; compared to vehicle–control group: (two-way ANOVA followed by Tukey's post hoc test). (B), (C): Significantly different from vehicle-control group (n = 5): ****P < 0.0001: (One way ANOVA followed by Tukey's post hoc test). Significantly different from disease-control ($AlCl_3$) group (n = 5): ††††p < 0.0001, †††p < 0.001, ††p < 0.01: (One way ANOVA followed by Tukey's post-hoc test).

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significantly (F (5,54) = 10.56; p < 0.0001) the time spent in the target quadrant (probe trial, Figure 1C). Administration of MOE formulation improved escape time throughout the test days (Figure 1A), reduced total escape time (Figure 1B) and increased the time spent in the target quadrant when compared to the AlCl3 group (Figure 1C). The standard drug, donepezil (DPZ), also ameliorated the deficits induced by AlCl3 in the AD mice (Figure 1A, B, C). Interestingly, the improvement in learning and memory by MOE formulation and DPZ, as depicted by the MWM test, was similar to the vehicle group (VEH) with no AlCl3 AD induction.

Effects of optimised MOE formulation on AlCl3-induced AD mice by OF test.

The outcomes of the behavioural alterations evaluated in the OF test are illustrated in Figure 2. The AlCl3 AD mice showed a significant reduction (F (5,24) = 6.620; p = 0.0005) in the frequency of line crossing (Figure 2A) and time spent in the centre of the open field (F (5,24) = 4.867; p = 0.0033) (Figure 2B) when compared to the VEH group. However, there was no statistically significant difference (F (5,24) = 0.6312; p = 0.6778) observed in grooming frequency when compared to the VEH group (Figure 2C). In contrast, MOE formulation (10, 30, 100 mg/kg) or DPZ

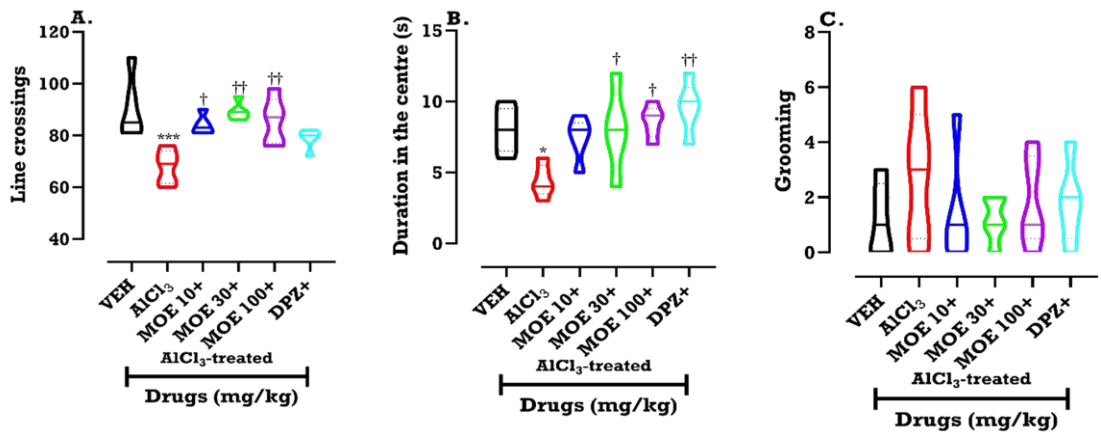


Figure 2. Effect of the optimized *M. oppositifolius* formulation on $AlCl_3$-induced AD-like dementia in the open field (OF) test: (A) frequency of line crossings, (B) time in center area and (C) grooming frequency. Data were presented as mean ± SEM. ***p < 0.001, *p < 0.05, compared to Vehicle-control group; ††p < 0.01, †p < 0.05, compared to disease-control ($AlCl_3$) group using one way ANOVA followed by Tukey's post-hoc test.

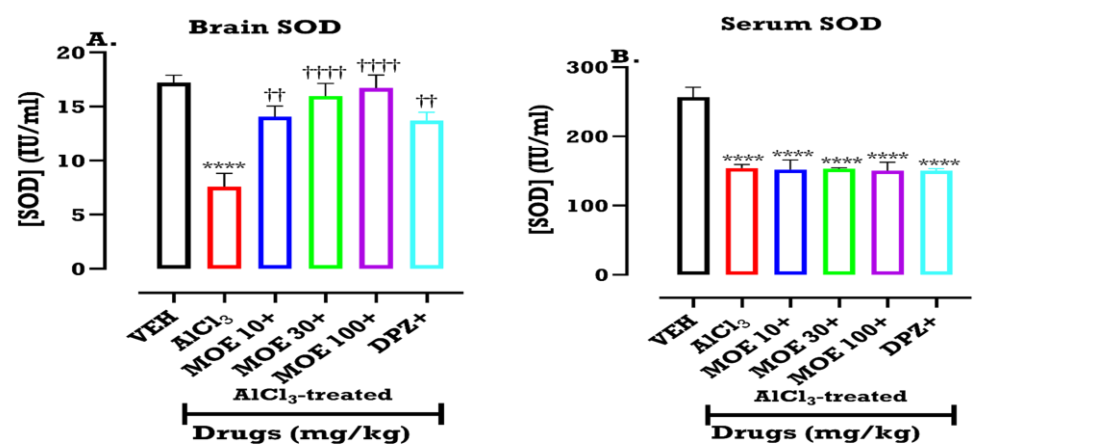


Figure 3. $AlCl_3$ induction and optimized formulation of MOE treatment effect on brain and serum SOD: (A) Brain SOD, (B) Serum SOD. Data were presented as mean ± SEM. ****p < 0.0001; significantly different form vehicle–control group: (One way ANOVA follow by Tukey's pot-hoc test). Significantly different from disease-control ($AlCl_3$) group: ††††p < 0.0001, ††p < 0.01: (One way ANOVA followed by Tukey's post-hoc test).

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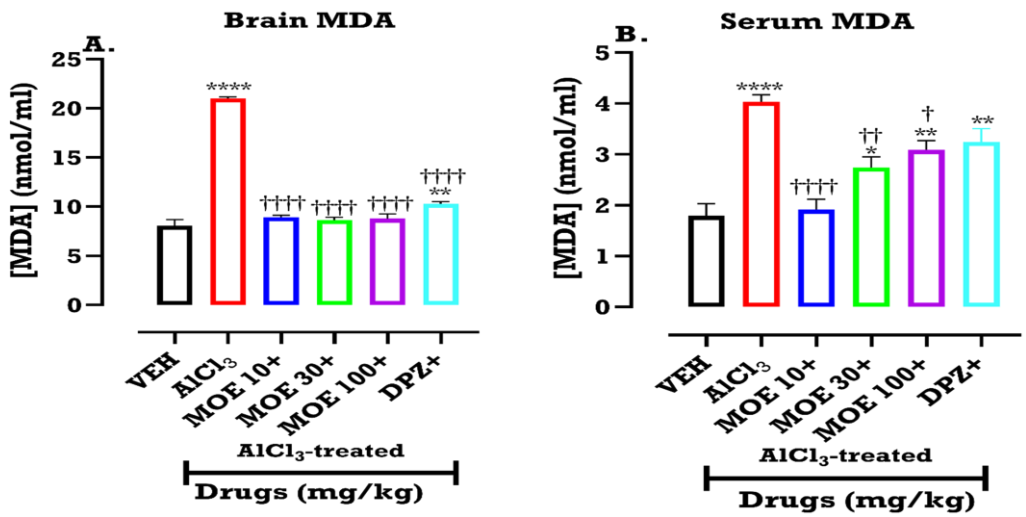


Figure 4. $AlCl_3$ induction and optimized formulation of MOE treatment effect on brain and serum MDA: (A) Brain MDA, (B) Serum MDA. Data were presented as mean ± SEM. ****p < 0.0001, **p < 0.01; significantly different form vehicle–control group: (One way ANOVA follow by Tukey's pot-hoc test). Significantly different from disease-control ($AlCl_3$) group: ††††p < 0.0001, ††p < 0.01, †p < 0.05: (One way ANOVA followed by Tukey's post-hoc test).

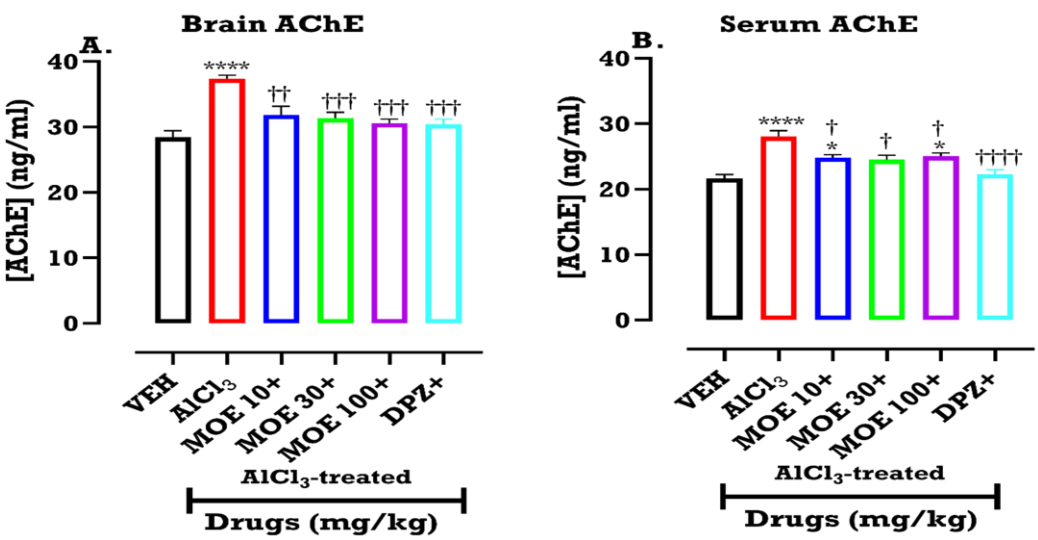


Figure 5. $AlCl_3$ induction and optimized formulation of MOE treatment effect on brain and serum AChE: (A) Brain AChE, (B) Serum AChE. Data were presented as mean ± SEM. ****p < 0.0001, *p < 0.05; significantly different form vehicle–control group: (One way ANOVA follow by Tukey's pot-hoc test). Significantly different from disease-control ($AlCl_3$) group: ††††p < 0.0001, ††p < 0.01, †p < 0.05: (One way ANOVA followed by Tukey's post-hoc test).

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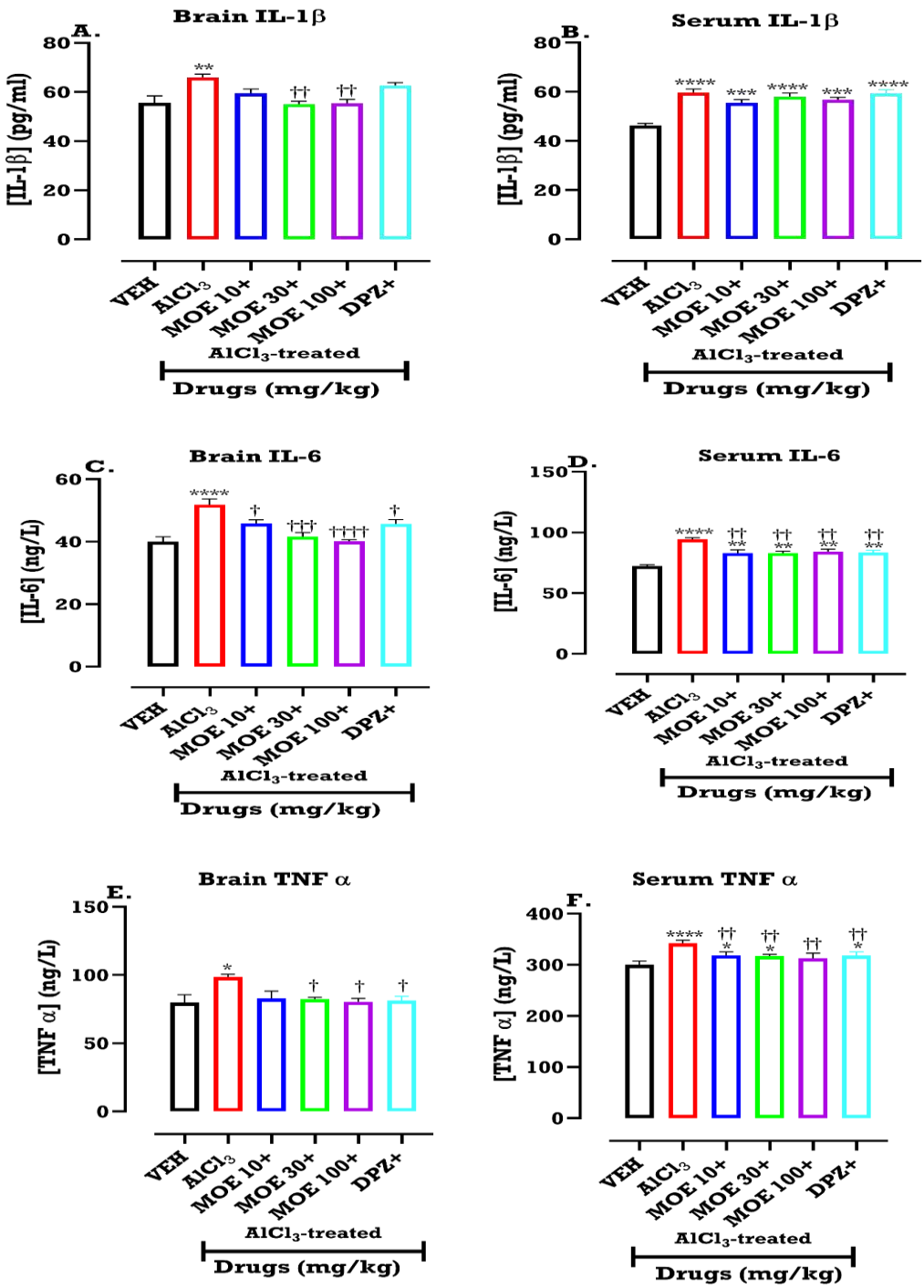


Figure 6. $AlCl_3$ induction and optimised formulation of MOE treatment effects on brain neurochemicals: (A) Brain IL-1β, (B) Serum IL-1β, (C) Brain IL-6, (D) Serum IL-6, (E) Brain TNF-α, (F) Serum TNF-α. Data were presented as mean ± SEM. ****p < 0.0001, ***p < 0.001, **p < 0.01, *p < 0.05; significantly different from vehicle–control group: (One way ANOVA followed by Tukey's post hoc test). Significantly different from disease-control ($AlCl_3$) group: ††††p < 0.0001, †††p < 0.001, ††p < 0.01, †p < 0.05: (One way ANOVA followed by Tukey's post-hoc test).

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administration to the AlCl3-induced AD mice significantly increased ($p < 0.05$) the frequency of line crossing (Figure 2A) and time spent in the centre square (Figure 2B), but not the grooming frequency when compared to the AlCl3 group (Figure 2C). The concentrations of the antioxidant SOD associated with AD pathology in the brain tissues and serum of mice are illustrated in Figure 3A and B, respectively. Brain and serum SOD were significantly decreased ($F (5, 30) = 11.86$; $p < 0.0001$); ($F (5,18) = 18.83$; $p < 0.0001$) in AlCl3-induced AD mice compared to the vehicle control group (Figure 3A and B, respectively). Conversely, MOE formulation (10, 30, and 100 mg/kg) and DZP (3 mg/kg) reversed ($p < 0.05$) the decrease in brain SOD concentration caused by $AlCl_3$ (Figure 3A). Unlike the brain SOD concentrations, MOE formulation and DPZ failed to reverse the $AlCl_3$-induced decrease in serum SOD (Figure 3B).

**Effect of MOE formulation on brain tissue and serum concentration of MDA in $AlCl_3$-induced AD mice.**

The oxidative stress marker, MDA, frequently observed in AD pathological findings was significantly elevated ($F (5, 30) = 182.4$; $p < 0.0001$); ($F (5, 18) = 16.59$; $p < 0.0001$) respectively by $AlCl_3$ in both the brain tissues and serum when compared to the vehicle control group (Figure 4A, B). In contrast, MOE formulation (10, 30, 100 mg/kg) just as DZP (3mg/kg) reversed ($p < 0.05$) the $AlCl_3$-associated increase in brain and serum MDA. Interestingly, MOE but not DZP reduced the brain MDA concentration to a level similar to vehicle control. In serum, however, both MOE formulation and DZP failed to reverse the MDA concentration to the vehicle control state (Figure 5B).

**Effect of MOE formulation on brain tissue and serum content of AChE in $AlCl_3$-induced AD mice**

AChE concentrations in brain tissue and serum were significantly elevated ($F (5, 30) = 11.29$; $p < 0.0001$); ($F (5, 18) = 12.45$; $p < 0.0001$) in the $AlCl_3$-induced AD mice compared to the vehicle control group (Figure 5A, B). Treatment with MOE formulation (10, 30, 100 mg/kg) and DZP (3 mg/kg) significantly reversed ($p < 0.05$) the $AlCl_3$-induced increase in both brain and serum AChE concentrations (Figure 5A, B). It is worth noting that the effect of MOE formulation on brain AChE was comparable to DPZ, the reference drug, and similar to the vehicle control group. However, the effect of MOE formulation on serum AChE was slightly lower compared to DPZ.

**Effect of MOE formulation on brain tissue and serum cytokines (IL-1β, IL-6 and TNF-α) in $AlCl_3$-induced AD mice.**

The concentrations of IL-1β, IL-6, and TNF-α in brain tissue were all significantly increased respectively ($F (5, 30) = 6.937$; $p = 0.0002$); ($F (5, 30) = 11.44$; $p < 0.0001$); ($F (5, 30) = 3.722$; $p = 0.0097$) in AD mice induced by $AlCl_3$ (Figure 6A, C, E). Treatment with 10 mg/kg MOE formulation significantly reduced the level of IL-6 (Figure 6C), but not IL-1β and TNF-α (Figure 6A, E). Both 30 and 100 mg/kg formulation of MOE treatment significantly decreased the IL-1β, IL-6 and TNF-α concentration. The reference drug, donepezil (3 mg/kg) treatment, significantly reduced the concentration of IL-6 and TNF-α (Figure 6C, E). Serum contents of the inflammation-related markers, IL-1β, IL-6, and TNF-α, in $AlCl_3$-induced AD mice were significantly elevated ($F (5, 18) = 15.73$; $p < 0.0001$); ($F (5,$

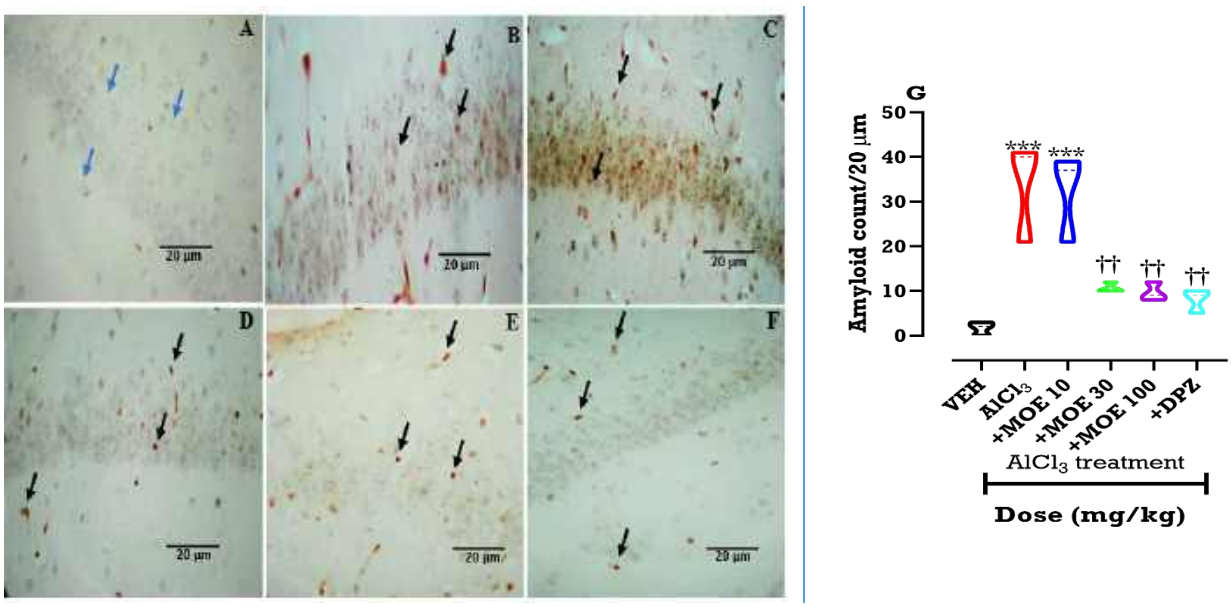


Figure 7. Effects of optimized *M. oppositifolius* formulation on Congo red staining of the hippocampus CA1 (400×) displayed as micrographs (left) and its amyloids quantification (right).

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18) = 16.62; p < 0.0001), (F (5, 18) = 14.96; p < 0.0001) when compared to vehicle control group respectively (Figure 6B, D, F). Treatment with all three doses (10, 30, 100 mg/kg) of *M. oppositifolius* significantly decreased (p < 0.05) the concentrations of IL-6 and TNF-α (Figure 6D, F), but not IL-1β (Figure 6B), when compared to the diseased group. Treatment with the standard drug donepezil (3mg/Kg) also significantly reduced (p < 0.05) the concentrations of IL-6 and TNF-α (Figure 6D, F), but not IL-1β when compared to the diseased group (Figure 6B).

**Effects of MOE formulation on Congo red-stained CA1 regions of the hippocampus**

The Congo red-stained CA1 regions of the hippocampus in the control and treated groups are shown in Figure 7. The hippocampus of the vehicle control group shows typical, with almost no amyloid deposition (blue arrow) (Figure 7A). The disease control ($AlCl_3$) group had the most amyloid aggregation, indicated as a black arrow (Figure 7B). There was no decrease in amyloid deposition in the MOE formulation (10 mg/kg) treatment group, as observed and quantified in the micrograph (Figure 7C). Both 30 and 100 mg/kg formulation of MOE treatment decreased amyloid deposition considerably (Figure 7D, E). The standard drug, donepezil, also greatly reduced the number of amyloids observed in the micrograph (Figure 5F). Data from amyloid quantification are presented as mean ± SEM. ***p < 0.001; significantly different from vehicle–control group: (One-way ANOVA followed by Tukey's post hoc test). Significantly different from disease-control ($AlCl_3$) group: ††p < 0.01: (One way ANOVA followed by Tukey's post-hoc test). (A) Vehicle control: showing normal histology (blue arrow), (B) Disease control ($AlCl_3$ group): showing β-amyloid deposition (black arrow), (C) *M. oppositifolius* (MOE 10 mg/kg group): showing β-amyloid deposition similar to disease control group (black arrow), (D) *M. oppositifolius* (MOE 30 mg/kg group): showing reduced β-amyloid deposition (black arrow), (E) *M. oppositifolius* (MOE 100 mg/kg group): showing reduced β-amyloid deposition (black arrow), (F) Donepezil (DZP 3 mg/kg group): showing reduced β-amyloid deposition (black arrow) in the hippocampus.

## DISCUSSION

This study evaluated an optimised formulation of *M. oppositifolius* leaf extract (MOE) in an $AlCl_3$-induced mouse model of Alzheimer's disease-like dementia. The study utilised chitosan and pectin to incorporate *M. oppositifolius* leaf extract into modified-release formulations in order to optimise its CNS effect. Modified-release drug delivery approaches are designed to meet specific clinical goals by adjusting drug release rates and sites while providing benefits that include better efficacy, fewer side effects, ease of use, and compliance among patients [29]. Herein, we report that MOE formulation reversed $AlCl_3$-associated cognitive deficits, neuro-inflammation, anxiogenic behaviour, impaired locomotion, and oxidative stress. In addition, MOE formulation reduced beta-amyloid deposition while preserving hippocampal neurons from degeneration. Dementia, which is characterised by learning and memory impairment, is one of the central features of AD [30,31,32]. This study used the Morris water maze (MWM) test to assess hippocampally dependent spatial learning and memory performance. Escape latency (i.e. the time required to locate the hidden platform) and probe trial (i.e. active exploration of the quadrant where the secret platform was previously positioned) were used to assess mouse spatial learning and memory retention. Here, we show that MOE formulation reversed the $AlCl_3$-associated decline in spatial learning by reducing the time it took for mice to find the platform.

In addition, MOE-treated mice performed better in the probe trial, suggesting that it was able to attenuate the $AlCl_3$-induced decline in memory retention. Consistent with our findings, previous studies with $AlCl_3$ have reported a marked decrease in spatial learning and probe trial memory performance in the MWM test [25,33]. The dentate gyrus (DG), CA3 and CA1 areas of the hippocampus are crucial in short-term and episodic learning and memory [34]. For instance, the ablation of granule cells in the DG caused deficits in spatial learning [35]. Also, inhibitory interneurons and excitatory pyramidal neurons in the CA1 region contribute to the regulation of spatial learning [36]. Since $AlCl_3$ causes neurodegeneration of several hippocampal regions with accompanying learning and memory deficits [25], MOE's ability to attenuate $AlCl_3$'s effect may suggest possible neurogenesis in the hippocampus. Though this assertion is yet to be proven, several lines of evidence have linked MOE's neuroactive effect to serotonin and brain-derived neuroprotective factor (BDNF), which are known to play pivotal roles in neurogenesis [37,13]. For instance, a study has proven that MOE improves depression-related aggressive behaviour in mice by increasing 5-HT levels and dendritic spine density in the prefrontal cortex [13]. Apart from this, various neurotransmitter imbalances, particularly acetylcholine (ACh), contribute to AD [38]. ACh is instrumental in learning and memory; thus, its hydrolysis by acetylcholinesterase (AChE) may cause learning and memory impairment. Indeed, ACh deficiency has been associated with AD-related dementia [39]. One of the mechanisms by which $AlCl_3$ causes memory impairment is via elevation in AChE activity, which leads to ACh deficiency [40]. In this study, MOE formulation reversed the $AlCl_3$-related increase in ACh, suggesting that the action of MOE formulation in improving learning and memory may be related to increased cholinergic neurotransmission.

Studies show a positive correlation between AD and anxiety behaviour as well as motor impairment [41,42]. In this study, mice exposed to $AlCl_3$ exhibited anxiety-like behaviour and reduced locomotor activity in the open field test. Consistent with previous reports where MOE improved anxiety behaviour and locomotor activity in the open field test, MOE formulation reversed the deficits

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induced by $AlCl_3$ [14,13]. The anxiolytic effect of MOE may be due to its GABA-enhancing effect previously reported by our lab [11]. Neuroinflammation, characterised by increased IL-1β, IL-6, and TNF-α, contributes to the onset and progression of AD [44]. These cytokines compromise neurogenesis and cause dysfunction in the neurotrophic system [45]. $AlCl_3$-induced AD promotes neuroinflammation through persistent activation of microglia, which releases IL-1β, IL-6, and TNF-α. The actions of these cytokines further contribute to beta-amyloid deposition, a primary feature of AD.

In our study, MOE formulation significantly reversed the $AlCl_3$-induced increase of IL-1β, IL-6, and TNF-α in the brain. In the serum, however, MOE formulation significantly reduced the IL-6 and TNF-α levels but not IL-1β. These findings suggest that MOE may reduce inflammation both peripherally and centrally. Indeed, previous studies reported that MOE exhibited an anti-inflammatory effect in carrageenan-induced paw oedema [46] and decreased activated microglia count in a lipopolysaccharide-induced neuroinflammation model [14]. Thus, the findings in this current study may suggest decreased microglial activation, as previously reported. The inception of AD is characterised by the build-up and clustering of beta-amyloid (Aβ) peptides, which may be occasioned by either an excess production or disruptions in the clearance mechanism [47]. Congo red staining techniques established that $AlCl_3$ induced the deposition of Aβ peptides in the hippocampus.

Conversely, MOE-treated mice displayed reduced neurodegeneration and exhibited minimal β-amyloid deposition, suggesting a protective effect against $AlCl_3$-induced neurotoxicity in mice [48,25]. Furthermore, the MOE-associated reduction in Aβ peptides in the hippocampus may further support the assertion that MOE reduces pathological activation of microglia in a manner that inhibits the release of pro-inflammatory cytokines and their involvement in amyloid formation and deposition [14]. A deficient antioxidant defence system in the brain leads to disequilibrium in initiating and eliminating reactive oxygen species, disruption of cellular pathways and lipid peroxidation. Similarly, oxidative stress is recognised as a significant etiological factor for the gradual deterioration of cognitive, memory, and motor functions [49]. Upon traversing the blood-brain barrier, aluminium promotes the generation of free radicals, which in turn impair mitochondrial function across various brain regions and cause neurodegeneration [50].

In the context of this study, MOE increased the antioxidant enzyme SOD in the brain tissue, while MDA, an indicator of lipid peroxidation, was significantly decreased in the serum and brain. The MDA result is consistent with a previous study that observed the anti-peroxidative effect of MOE in the liver [46]. In contrast, MOE failed to reverse the effect of $AlCl_3$ on serum SOD. The apparent discrepancy in serum SOD levels when compared to the study by [51] may be due to differences in solvent for extraction, impact of *in vivo* versus *in vitro* conditions, and differences in doses and species (mice versus rats) used.

### Study limitation

The study was conducted on an animal model (mice) of AD induced by $AlCl_3$. This model may not fully represent AD pathology in humans. This limits the direct applicability of the results to human patients. With just six groups (n = 10) of mice, the sample size may be limited for detecting smaller but possibly significant effects of the treatment. Moreover, the duration of the study may not capture long-term outcomes or delayed effects of the optimised MOE formulation. The study concentrated on specific biomarkers such as SOD, MDA, AChE, and pro-inflammatory cytokines. However, it did not assess other crucial AD markers, such as p-tau or glutathione levels, which could have provided a more complete picture of the treatment's effects.

### Future Research

The extract should be evaluated further by measuring other AD markers like Aβ, phosphorylated-tau, reduced glutathione (GSH), and catalase. Future research should also consider measuring other antioxidant markers such as glutathione S transferase, glutathione peroxidase and glutathione reductase associated with AlCl3-induced neurotoxicity. The neuroprotective effect of the extract should be further investigated in animal models that replicate human AD pathology using transgenic models. The optimised formulation used chitosan and pectin as carriers to enhance CNS delivery. While this method showed effectiveness in mice, further research is needed to evaluate whether these carriers would perform similarly in humans, especially regarding the permeability of the blood brain barrier (BBB)

### Conclusion

The research findings suggest that an optimised formulation of *M. oppositifolius* improves learning and memory impairment and reduces anxiety-like behaviour, oxidative stress, and neuroinflammation in $AlCl_3$ model of Alzheimer's disease. The formulation also reduced Aβ peptide deposition in the CA1 region of the hippocampus of mice.

## DECLARATIONS

### Ethical consideration

Ethical approval was obtained from the Ghana Health Service Ethics Review Committee (GHS-ERC: 007/05/24).

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest

**Author contribution**

KKEK and OAD conceptualised the research. JTP, KKEK, OAD, EKO, and KKAO conducted methodology and research investigations. JTP, KKEK, OAD, EKO, KKAO, PA, and DWA conducted data collection and analysis, manuscript writing, review, and editing. All authors read and approved the final manuscript.

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**Availability of data**

Data is available upon request to the corresponding author

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# Haematologic profile of children with laboratory diagnosed malaria: A prospective study

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**Abstract**

***Background:*** The high mortality rate of malaria is due, in part, to the associated extensive alterations in haematological indices in affected individuals.

***Objective:*** The study presents the haematological profile of malaria-infected children and determined the predictive values of haematological indices for severe malaria.

***Methods:*** Three hundred and twenty-three children with laboratory-diagnosed malaria, aged 1 - 12 years, were enrolled between March 10 and August 27, 2023, at Tamale Teaching Hospital. Three millilitres of venous blood were collected for malaria diagnosis through microscopy, and a full blood count was taken using an auto-haematology analyser. IBM SPSS version 26.0 was used for the data analysis.

***Results:*** Participants were mostly females (64.7%), aged 5 - 12 years (60.7%), and had high parasitaemia (>10000 malaria parasites). The prevalence of anaemia among the participants was 80.8%, and 44.6%, 18.3%, and 18.0% had mild, moderate, and severe anaemia, respectively. Approximately one-third of the malaria-infected children were thrombocytopaenic, and mild, moderate, and severe thrombocytopaenia occurred in 21.1%, 10.8%, and 3.4% of cases, respectively. Microcytic hypochromic anaemia was the most prevalent (54.5%) form of anaemia among the participants. Total leucocytes (AUC: 0.605, p = 0.021), absolute lymphocyte count (AUC: 0.600, p = 0.040), absolute monocyte count (AUC: 0.699, p < 0.001), absolute eosinophil (AUC: 0.649, p < 0.001), absolute basophil count (AUC: 0.774, p < 0.001) and platelet_large cell ratio (AUC: 0.693, p < 0.001) were fair predictors of severe malaria. Bicytopaenia and pancytopaenia were present in 37.2% and 7.1%, respectively.

***Conclusion:*** Childhood malaria presents with varying haematological abnormalities, notably severe anaemia, thrombocytopaenia and leucocyte disorders. Microcytic hypochromic anaemia is a common picture in children with malaria. Haematological indices may be useful in differentiating severe from uncomplicated malaria in children.

**Keywords:** Anaemia; Children; Cytopaenia; Full blood count; Malaria

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## INTRODUCTION

Malaria is caused by a protozoan belonging to the genus plasmodium, and transmitted via the bite of an infective female anopheles mosquito. Six plasmodium species: *P. falciparum*, *P. ovale curtisi*, *P. ovale wallikeri*, *P. vivax*, *P. malariae* and *P. knowlesi*, cause malaria in humans, with *P. falciparum* being the most infectious and lethal in Africa [1,2]. Two hundred and forty-nine million people were infected with malaria globally, and 608,000 people died from the disease in 2022, with 67% of its

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mortalities occurring among African children [3]. Malaria is hyper-endemic in Ghana, with *P. falciparum* accounting for approximately 90 – 98% of morbidity and mortality associated with the infection [2]. The endemicity of malaria in Ghana is facilitated by the presence of apt breeding environments, including high temperature, relatively heavy amounts of rainfall, especially from April to June, high humidity and poor surroundings characterised with several stagnant waters that promote the life cycle of the female anopheles mosquitoes which transmit malaria parasites from person to person [4]. In Northern Ghana, malaria remains the chief cause of patients' admission and death, with children mostly vulnerable [5].

Infants and young children infected with *P. falciparum* experience mild to severe complications, including fever, severe anaemia requiring blood transfusion, cerebral malaria, hypoglycaemia, and renal injury [6,7]. The direct interactions between malaria parasites and erythrocytes during the asexual phase of the parasite's life cycle cause haematological and biochemical alterations, which result in reduced blood cell counts and morphological abnormalities [8]. Anaemia remains the most predominant complication of malaria in children, as it occurs in approximately 76% of malaria-infected children in Ghana and other malaria-endemic areas [1,8]. Reduction in haemoglobin concentration in children with malaria has been reported in Ghana [2,9-14] and other tropical countries [15-18]. The reported anaemia associated with malaria occurs through various mechanisms, including splenic and bone marrow sequestration of red blood cells (RBCs), lysis of erythrocytes, suppression of erythropoiesis in bone marrow, complement-mediated, ineffective erythropoiesis, excessive inflammatory response and renal suppression of erythropoietin secretion [19,20]. Patients infected with *P. falciparum* malaria commonly experience thrombocytopaenia due to the associated extensive splenic sequestration and antibody-mediated destruction of platelets [2,4,8,21,22]. The massive involvement of immune cells, especially leucocytes, in the process of controlling parasites' growth and promoting their clearance results in alterations in leucocyte populations in peripheral blood. Leucocyte abnormalities reported in malaria-infected patients include leucopaenia, lymphopaenia, neutropaenia, leucocytosis, monocytosis and neutrophilia, depending on the phase of the infection [2,4,8]. Moreover, haematological indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV) have been used as inflammatory markers to predict severe malaria [23].

Even though Anabire et al. observed the occurrence of cytopaenias in patients with malaria within Tamale Metropolis [24], the findings were restricted to adults aged 18-77 years and may not represent the effects of malaria on haematological parameters in children in the area. Hence, this study assessed the haematological profile of malaria-infected children and determined the predictive values of haematological indices for severe malaria in Northern Ghana. The observable changes in haematological indices may provide additional information to strengthen the suspicion of malaria, promote meticulous search of malaria parasites, predict severe form of malaria, and direct effective treatment of malaria in children.

## MATERIALS AND METHODS

### Study setting and design

This descriptive cross-sectional study was conducted between March 10 and August 27, 2023, at the Tamale Teaching Hospital (TTH), Tamale, Ghana, and recruited children aged 1 - 12 years with laboratory-diagnosed malaria. Three hundred and twenty-three children with microscopy-confirmed malaria parasites in peripheral blood were selected as study participants. Children who were malnourished and had haemoglobinopathies such as sickle cell anaemia, Glucose-6-phosphate dehydrogenase (G6PD) deficiency or had other comorbidities, including helminthiasis, HIV, etc, were excluded from the study.

### Sampling and laboratory assays

Three millilitres of whole blood were collected from each treatment-naïve participant and dispensed into dipotassium ethylenediaminetetraacetic acid test tubes. The blood specimen and the anticoagulant were mixed thoroughly and immediately assayed for full blood count. Red blood cell, leucocyte and platelet parameters were estimated using a five-part fully automated haematology analyser (URIT-5250, China) [24]. Other parameters of the haematological profile, such as NLR and PLR, were calculated from the absolute neutrophil, lymphocyte and platelet counts. Thick and thin smear on the same slide were prepared after specimen collection with 6 µL and 2 µL of whole blood, respectively, from each participant. After the smears were air-dried, the thin smear was fixed in absolute methanol, and both smears were stained with a 10% Giemsa working solution. Each slide was examined microscopically (Olympus, Japan) by two independent Medical Laboratory Scientists, and the presence of plasmodium parasites and the parasite count per at least 200 leucocytes were determined using the WHO standard protocols (25). The parasite density was estimated as the ratio of parasites to WBCs per microliter of blood, as follows:

Parasites per µL of blood = (Parasite counted x absolute WBC)/(≥200 WBCs).

The definition of terms associated with blood cell parameters and malaria parasitaemia has been summarised in Table 1.

### Data analysis

IBM SPSS version 26.0 (Armonk, NY, USA) was used to analyse the data. Categorical data were presented in frequencies with corresponding percentages, and numerical data were presented as median (1st-3rd quartiles). Age- and sex-specific blood cell parameters of the participants were compared using the Mann-Whitney U test. The Kruskal-

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Table 1. Definition of terms associated with blood cell parameters and malaria parasitaemia

| Term | Description (in children) |
|---|---|
| Anaemia | Hb<11.0 g/dL (25)<br>Mild anaemia: Hb 9.0 – 10.9 g/dL<br>Moderate anaemia: Hb 5.0 – 8.9 g/dL<br>Severe anaemia: Hb <5.0 g/dL |
| Microcytosis | MCV <80 fL (25) |
| Hypochromasia | MCH <27 pg (25) |
| Leucopaenia | Leucocyte count <5.0×$10^3$/µL (4) |
| Leucocytosis | Leucocyte count >10.0×$10^3$/µL (4) |
| Neutropaenia | Absolute neutrophil count <2.0×$10^3$/µL (4) |
| Neutrophilia | Absolute neutrophil count >7.5×$10^3$/µL (4) |
| Lymphopaenia | Absolute lymphocyte count <1.0×$10^3$/µL (4) |
| Lymphocytosis | Absolute lymphocyte count >4.0×$10^3$/µL (4) |
| Monopaenia | Absolute monocyte count <0.2×$10^3$/µL (4) |
| Monocytosis | Absolute monocyte count >0.9×$10^3$/µL (4) |
| Eosinophilia | Absolute eosinophil count >0.5×$10^3$/µL (4) |
| Thrombocytopaenia | Platelet count <150×$10^3$/µL (4,25)<br>Mild thrombocytopaenia: platelet count 101-149 ×$10^3$/µL<br>Moderate thrombocytopaenia: platelet count 51-100 ×$10^3$/µL<br>Severe thrombocytopaenia: platelet count ≤50 ×$10^3$/µL |
| Severe malarial anaemia | Presence of plasmodium parasite in peripheral blood and Hb <5.0 g/dL (25) |
| Uncomplicated malaria | Presence of plasmodium parasite in peripheral blood and Hb ≥5.0 g/dL (25) |

Hb= Haemoglobin, MCV= Mean corpuscular volume, MCH= Mean corpuscular haemoglobin, g/dL= Gram per decilitre, fL= Femtolitre, pg= Picogram.

Wallis test was used to compare haematological parameters among participants in the various degrees of parasitaemia (< 1,000, 1,000 – 10,000, and > 10,000). The association between haematological parameters and *P. falciparum* density was determined using the Spearman correlation test. Receiver operating curve (ROC) analysis was used to determine the predictive abilities of haematological parameters for severe malaria. Statistical significance was set at $p < 0.05$.

## RESULTS

### Demographic, clinical and haematological characteristics of *P. falciparum*-infected children

The 323 *P. falciparum*-infected children visiting TTH included in this study were mostly females (64.7%, n = 209) and had a median age of 6.0 (2.0 - 10.0) years. The majority (60.7%, n = 196) of the participants were between 5 and 12 years of age, and the remaining were children under 5 years of age. The median temperature and parasite density of the 323 participants were 37.9 ℃ (36.9 ℃ - 38.5 ℃) and 4018.0 (549.0 – 22,447.0) parasites/µL, respectively. About one-third of the participants had > 10,000 malaria parasites in peripheral blood, and only 18.0% (n = 58) were diagnosed with severe malarial anaemia. Red cell parameters (RBC, Hb, and HCT) were low among the 323 P. falciparum-infected children, but the overall leucocyte and platelet counts were within the normal reference intervals. The overall median NLR and PLR of the participants were 2.4 (1.3 - 3.6) and 93.6 (52.1 - 133.5), respectively (Table 2).

Table 2. Demographic, clinical and haematological characteristics of P. falciparum infected children

| Variables | Results | |
|---|---|---|
| Categorical data | Frequency | Percentage (%) |
| Age group | | |
| <5 | 127 | 39.3 |
| 5-12 | 196 | 60.7 |
| Sex | | |
| Males | 114 | 35.3 |
| Females | 209 | 64.7 |
| Parasitaemia grading | | |
| <1000 | 102 | 31.6 |
| 1000-9999 | 106 | 32.8 |
| >10000 | 115 | 35.6 |
| Malaria severity | | |
| Severe malarial anaemia | 58 | 18.0 |
| Uncomplicated malaria | 265 | 82.0 |
| Continuous data | Median | 1st-3rd quartiles |
| Age (years) | 6.0 | 2.0-10.0 |
| Temperature (℃) | 37.9 | 36.9-38.5 |
| Parasite density (p/µL) | 4018.0 | 549.0-22447.0 |
| Erythrocytes (**$10^6$**/µL) | 3.3 | 2.7-3.7 |
| Haemoglobin (g/dL) | 9.5 | 7.8-10.7 |
| Haematocrit (%) | 25.8 | 21.3-30.1 |
| Mean cell volume (fL) | 78.3 | 71.7-82.5 |
| Mean cell haemoglobin (pg) | 28.5 | 25.1-31.2 |
| Mean cell haemoglobin concentration (g/dL) | 36.7 | 33.3-39.2 |
| Red cell distribution width-coefficient of variation (%) | 15.8 | 11.2-42.9 |
| Leucocytes (×**$10^3$**/µL) | 7.2 | 5.8-10.2 |
| Neutrophils (×**$10^3$**/µL) | 4.4 | 3.2-6.1 |
| Lymphocytes (×**$10^3$**/µL) | 1.9 | 1.2-3.2 |
| Monocytes (×**$10^3$**/µL) | 0.3 | 0.1-1.0 |
| Eosinophils (×**$10^3$**/µL) | 0.05 | 0.02-0.15 |
| Basophils (×**$10^3$**/µL) | 0.003 | 0.00-0.01 |
| Platelet (×**$10^3$**/µL) | 169.0 | 121.0-237.0 |
| Plateletcrit (%) | 0.3 | 0.2-1.4 |
| Mean platelet volume (fL) | 8.0 | 6.1-9.1 |
| Platelet distribution width (%) | 11.6 | 7.9-15.5 |
| Platelet large cell ratio (%) | 18.4 | 14.1-24.3 |
| Neutrophil-lymphocyte ratio | 2.4 | 1.3-3.6 |
| Platelet-lymphocyte ratio | 93.6 | 52.1-133.5 |

Categorical data are presented in frequencies with corresponding percentages. Continuous data are presented as median (1st-3rd quartiles). ℃= Degree Celsius, p/µL= Parasites per microlitre, g/dL= Gram per decilitre, fL= Femtolitre, pg= Picogram.

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**Sex and age-specific blood cell parameters of *P. falciparum*-infected children**

The median red cells, haemoglobin, haematocrit, platelets, neutrophils, eosinophils and platelet large cell ratio were similar between males and females. However, the mean cell volume ($p = 0.032$), mean cell haemoglobin ($p < 0.001$), mean cell haemoglobin concentration ($p < 0.001$), red cell distribution width ($p < 0.001$), plateletcrit ($p < 0.001$), mean platelet volume ($p < 0.001$) and platelet distribution width ($p < 0.001$) were significantly lower in males than females. Females had lower levels of leucocytes ($p < 0.001$), lymphocytes ($p < 0.001$), monocytes ($p < 0.001$), and basophils ($p < 0.001$) compared with their male counterparts. An approximate 2-unit difference in average leucocyte count was observed between both sexes. Both neutrophil to lymphocyte ratio ($p < 0.001$), and platelet lymphocyte ratio ($p < 0.001$) were relatively lower in males than females. With regards to age groups, *P. falciparum*-infected children less than 5 years of age had significantly reduced haemoglobin ($p = 0.002$), mean cell volume ($p = 0.014$), mean cell haemoglobin ($p < 0.001$), mean cell haemoglobin concentration ($p < 0.001$), red cell distribution width plateletcrit ($p < 0.001$), mean platelet volume ($p < 0.001$) and platelet distribution width ($p < 0.001$), plateletcrit ($p < 0.001$), mean platelet volume ($p < 0.001$) and platelet distribution width ($p < 0.001$), neutrophil to lymphocyte ratio ($p < 0.001$), and platelet lymphocyte ratio ($p < 0.001$), but higher leucocytes ($p < 0.001$), lymphocytes ($p < 0.001$), monocytes ($p < 0.001$), eosinophils ($p < 0.001$), and basophils ($p < 0.001$) than those within 5 - 12 years of age. About 0.5-unit difference of average haemoglobin and 1-unit of leucocytes were observed between the two age groups (Table 3).

**Correlation between haematological indices and *P. falciparum* parasite density**

This study observed negative correlation between malaria parasite density, and red cell count, haemoglobin, haematocrit, lymphocytes, eosinophils, platelet count, plateletcrit and platelet-to-lymphocyte ratio. However, there was weak positive correlation between red cell distribution width, mean platelet volume, platelet distribution width and platelet-large cell ratio, and parasite density of the participants (Table 5).

**Blood cell abnormalities of *P. falciparum*-infected children**

This study recorded that more than three-fourth of participants (80.8%, n = 261) with P. falciparum malaria were anaemic, while only 19.2% had normal haemoglobin concentrations. Mild anaemia was present in 44.6% (n = 144), 18.3% (n = 59) had moderate anaemia, and 18.0% (n = 58) had severe anaemia of the 323 malaria-infected children. Other red cell abnormalities detected among the participants were microcytosis (61.0%, n = 197), and

Table 3. Sex- and age-specific blood cell parameters of *P. falciparum*-infected children

| Haematological Parameters | *P. falciparum*-infected children | | | | | |
|---|---|---|---|---|---|---|
| | Sex | | | Age | | |
| | Males ($n$ = 114) | Females ($n$ = 209) | *P*-value | < 5 ($n$ = 127) | 5 - 12 ($n$ = 196) | *P*-value |
| RBC ($10^6$/µL) | 3.5 (1.7-3.8) | 3.3 (2.8-3.7) | 0.895 | 3.3 (1.8-3.7) | 3.3 (2.9-3.8) | 0.100 |
| Hb (g/dL) | 9.4 (4.9-10.7) | 9.6 (8.4-10.7) | 0.066 | 9.3 (4.8-10.7) | 9.8 (8.4-10.9) | 0.002 |
| HCT (%) | 26.4 (15.8-31.7) | 25.5 (21.8-28.9) | 0.907 | 25.1 (15.4-29.7) | 26.0 (21.9-30.7) | 0.141 |
| MCV (fL) | 76.9 (67.9-81.9) | 78.6 (73.3-82.9) | 0.032 | 77.5 (68.5-81.5) | 79.0 (73.4-83.0) | 0.014 |
| MCH (pg) | 25.7 (23.1-28.8) | 29.7 (27.0-31.9) | <0.001 | 26.4 (23.6-29.9) | 29.4 (26.4-31.9) | <0.001 |
| MCHC (g/dL) | 33.5 (31.6-36.6) | 38.1 (35.4-39.6) | <0.001 | 35.4 (32.1-37.9) | 37.6 (33.7-39.6) | <0.001 |
| RDW-CV (%) | 12.5 (9.7-16.8) | 38.8 (12.9-44.8) | <0.001 | 12.9 (10.1-17.8) | 38.9 (12.7-44.6) | <0.001 |
| WBC (×$10^3$/µL) | 8.7 (6.3-12.5) | 6.8 (5.6-8.8) | <0.001 | 9.6 (6.6-12.9) | 6.6 (5.4-8.3) | <0.001 |
| NEUT (×$10^3$/µL) | 4.5 (3.2-7.0) | 4.4 (3.4-5.9) | 0.696 | 4.6 (3.4-6.5) | 4.3 (3.2-5.9) | 0.058 |
| LYMPH (×$10^3$/µL) | 2.6 (1.6-4.6) | 1.7 (1.1-2.6) | <0.001 | 2.7 (1.6-4.9) | 1.7 (1.1-2.3) | <0.001 |
| MONO (×$10^3$/µL) | 0.7 (0.3-1.2) | 0.2 (0.1-0.6) | <0.001 | 0.8 (0.3-1.4) | 0.2 (0.1-0.6) | <0.001 |
| EOS (×$10^3$/µL) | 0.07 (0.02-0.20) | 0.05 (0.02-0.12) | 0.159 | 0.07 (0.02-0.20) | 0.05 (0.02-0.13) | 0.049 |
| BASO (×$10^3$/µL) | 0.01 (0.01-0.02) | 0.00 (0.00-0.01) | <0.001 | 0.01 (0.00-0.01) | 0.00 (0.00-0.01) | <0.001 |
| PLT (×$10^3$/µL) | 170.5 (128.0-250.3) | 169.0 (117.0-235.5) | 0.531 | 180.0 (124.0-268.0) | 165.0 (117.0-233.8) | 0.129 |
| PCT (%) | 0.2 (0.1-0.3) | 1.0 (0.2-1.5) | <0.001 | 0.2 (0.1-0.4) | 1.0 (0.2-1.5) | <0.001 |
| MPV (fL) | 6.7 (5.7-8.6) | 8.4 (6.9-9.2) | <0.001 | 6.6 (5.6-8.5) | 8.4 (6.9-9.2) | <0.001 |
| PDW (%) | 8.4 (7.5-11.4) | 15.2 (8.8-15.7) | <0.001 | 8.9 (6.7-15.1) | 15.2 (8.6-15.7) | <0.001 |
| P_LCR (%) | 19.9 (13.9-25.4) | 18.2 (14.1-23.4) | 0.152 | 17.6 (14.2-25.6) | 18.8 (13.9-24.3) | 0.976 |
| NLR | 1.9 (0.9-3.1) | 2.6 (1.7-3.9) | <0.001 | 1.8 (0.9-3.0) | 2.6 (1.7-4.0) | <0.001 |
| PLR | 71.6 (37.3-108.7) | 103.9 (73.2-141.6) | <0.001 | 68.2 (28.3-113.3) | 102.6 (74.9-143.8) | <0.001 |

n= Number of participants; RBC = Absolute red blood cell count, Hb = Haemoglobin concentration, µL= Microlitre, g/dL= Grams per deciliter; HCT = Haematocrit, MCV = Mean cell volume, MCH = Mean cell haemoglobin, MCHC = Mean cell haemoglobin concentration, RDW-CV = Red blood cell distribution width-coefficient of variation, WBC = White blood cell count; PLT= Platelet count; Neut.= Neutrophils; Lymph.= Lymphocytes; Mono = Monocytes; Eos.= Eosinophils; Baso.= Basophils; NLR= Neutrophil-lymphocyte ratio; PLR= Platelet-lymphocyte ratio; fL: Femtolitre; pg: Picogram. Data are presented as media (1st-3rd quartiles), and compared using Mann-Whitney U test. Statistical significance was set at $p < 0.05$.

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Table 4. Blood cell parameters based on the degree of parasitaemia

| Haematological Parameters | *P. falciparum*-infected children | | | |
|---|---|---|---|---|
| | < 1000 (n = 102) | 1000 - 10000 (n = 106) | 10000 (n = 115) | p-value |
| RBC ($10^6$/µL) | 3.5 (3.1-3.8) | 3.2 (2.9-3.8) | 3.0 (1.6-3.7) | <0.001 |
| Hb (g/dL) | 10.0 (9.0-10.9) | 9.5 (8.6-10.7) | 8.3 (4.7-10.3) | <0.001 |
| HCT (%) | 28.7 (24.7-32.4) | 25.1 (22.0-28.7) | 22.9 (15.1-27.4) | <0.001 |
| MCV (fL) | 78.7 (70.5-81.9) | 77.9 (73.5-82.7) | 78.1 (71.3-83.3) | 0.869 |
| MCH (pg) | 28.6 (24.6-30.7) | 30.1 (25.9-31.8) | 27.3 (24.9-30.4) | 0.003 |
| MCHC (g/dL) | 36.3 (33.5-38.4) | 38.3 (34.3-40.1) | 35.9 (32.1-38.6) | <0.001 |
| RDW-CV (%) | 11.2 (8.8-37.2) | 39.4 (13.2-44.9) | 15.7 (12.2-41.9) | <0.001 |
| WBC (×$10^3$/µL) | 7.5 (6.1-10.8) | 6.6 (5.6-8.5) | 7.6 (5.6-11.4) | 0.027 |
| NEUT (×$10^3$/µL) | 4.8 (3.3-6.1) | 4.3 (3.2-6.2) | 4.4 (3.2-6.3) | 0.846 |
| LYMPH | 2.3 (1.5-4.1) | 1.7 (1.2-2.7) | 1.8 (1.1-3.7) | 0.008 |
| MONO | 0.5 (0.2-1.1) | 0.2 (0.1-0.6) | 0.3 (0.1-1.5) | <0.001 |
| EOS | 0.09 (0.05-0.20) | 0.04 (0.02-0.12) | 0.03 (0.01-0.11) | <0.001 |
| BASO | 0.01 (0.00-0.01) | 0.00 (0.00-0.01) | 0.01 (0.00-0.02) | <0.001 |
| PLT (×$10^3$/µL) | 235.0 (172.8-321.0) | 170.0 (134.0-212.3) | 124.0 (95.0-169.0) | <0.001 |
| PCT (%) | 0.3 (0.2-1.0) | 1.3 (0.2-1.6) | 0.2 (0.1-1.0) | <0.001 |
| MPV (fL) | 6.2 (5.5-8.3) | 8.3 (7.4-9.0) | 8.4 (6.6-9.5) | <0.001 |
| PDW (%) | 7.6 (6.7-15.1) | 15.2 (10.1-15.6) | 11.5 (9.0-15.7) | <0.001 |
| P_LCR (%) | 17.9 (14.5-24.1) | 17.4 (11.8-21.2) | 22.1 (15.2-30.3) | <0.001 |
| NLR | 2.1 (1.2-3.1) | 2.6 (1.7-3.7) | 2.5 (1.1-3.9) | 0.034 |
| PLR | 97.3 (62.6-156.7) | 102.6 (73.6-132.2) | 74.8 (28.6-133.3) | <0.001 |

hypochromasia (72.4%, n = 234). Red cell distribution width was increased in 55.1%, but decreased in 26.9% of the participants. Regarding the forms of anaemia, microcytic hypochromic anaemia was the most prevalent (54.5%) observed among the malaria-infected children, followed by normocytic normochromic anaemia (21.7%) and normocytic hypochromic anaemia (17.3%). Only a few of the participants had macrocytic normocytic anaemia (6.0%, n = 20) and microcytic normochromic anaemia (5.9%, n = 19). More than half of the participants had normal leucocyte count (59.8%), while 14.9% and 25.4% showed leucopaenia and leucocytosis, respectively. Most participants (85.4%, n = 276) had normal neutrophil count, with neutropenia and neutrophilia recorded in 5.9% and 8.7%, respectively. Lymphopaenia and lymphocytosis were observed in 13.6% and 17.3%, respectively, among the participants, with 69.0% of them having normal values of lymphocytes. Also, 40.9% (n =132) of the participants had normal values of monocytes, while 35.3% (n =114) and 23.8% (n = 77) had monocytopaenia and monocytosis, respectively. Only 9.0% (n = 29) of the participants had eosinophilia, and none of them had basophilia. Furthermore, over one-third of the participants (35.3%, n = 114) were thrombocytopaenic, and the remaining (64.7%, n = 20) had normal platelet counts. The number of participants with mild, moderate and severe thrombocytopaenia recorded in the study was 68, 25, and 11, representing 21.1%, 10.8% and 3.4%, respectively. Platelet microcytosis was observed in approximately half of the participants, and 48.3% had high platelet distribution width, while one-third had low platelet-large cell ratio. Bicytopaenia and pancytopaenia were present in 37.2% (n = 120) and 7.1% (n = 23) of the participants, respectively (Table 6).

Table 5. Correlation between haematological indices and P. falciparum parasite density

| Haematological indices | *P. falciparum* parasite density (p/µL) | |
|---|---|---|
| | Correlation coefficient, r | p-value |
| RBC ($10^6$/µL) | -0.309** | <0.001 |
| Hb (g/dL) | -0.350** | <0.001 |
| HCT (%) | -0.395** | <0.001 |
| MCV (fL) | -0.013 | 0.810 |
| MCH (pg) | -0.073 | 0.191 |
| MCHC (g/dL) | -0.090 | 0.107 |
| RDW-CV (%) | 0.186** | 0.001 |
| WBC (×$10^3$/µL) | -0.016 | 0.780 |
| NEUT (×$10^3$/µL) | 0.023 | 0.678 |
| LYMPH | -0.112* | 0.045 |
| MONO | -0.068 | 0.225 |
| EOS | -0.256* | <0.001 |
| BASO | 0.060 | 0.284 |
| PLT (×$10^3$/µL) | -0.544** | <0.001 |
| PCT (%) | -0.143** | 0.010 |
| MPV (fL) | 0.306** | <0.001 |
| PDW (%) | 0.305** | <0.001 |
| P_LCR (%) | 0.173** | 0.002 |
| NLR | 0.095 | 0.087 |
| PLR | -0.208** | <0.001 |

**Correlation is significant at 0.01; *correlation is significant at 0.05. r= Correlation coefficient; RBC = Absolute red blood cell count, Hb = Haemoglobin concentration, µL= Microlitre, g/dL= Grams per deciliter; HCT = Haematocrit, MCV = Mean cell volume, MCH = Mean cell haemoglobin, MCHC = Mean cell haemoglobin concentration, RDW-CV = Red blood cell distribution width-coefficient of variation, WBC = White blood cell count; PLT= Platelet count; PCT= Plateletcrit, MPV= Mean platelet volume, Neut.= Neutrophils; Lymph.= Lymphocytes; Mono.= Monocytes; Eos.= Eosinophils; Baso.= Basophils; NLR= Neutrophil-lymphocyte ratio; PLR= Platelet-lymphocyte ratio; fL: Femtolitre; pg: Picogram. Data are presented as media (1st-3rd quartiles), and compared using Mann Whitney U test. Statistical significance was set at p<0.05.

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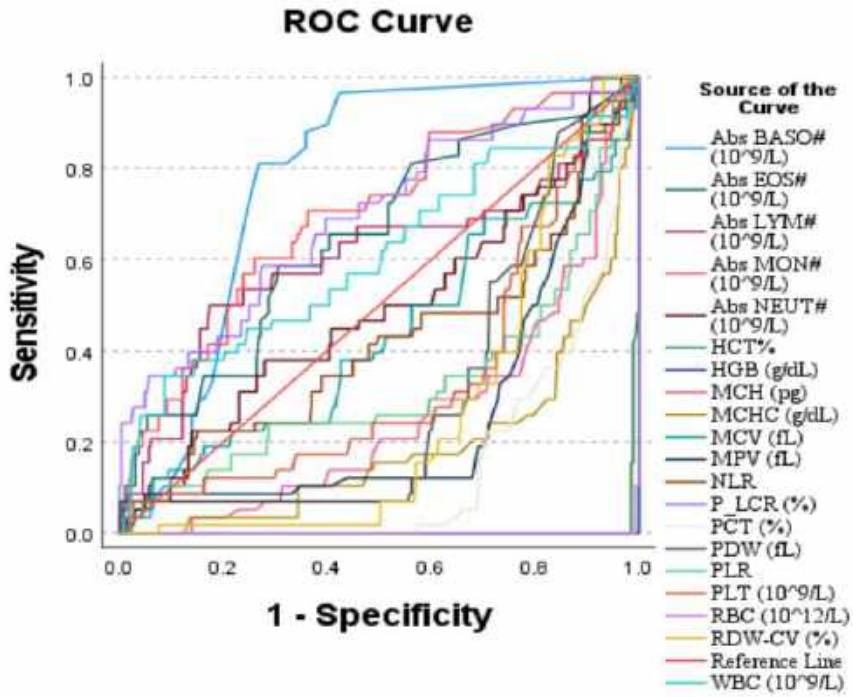


| Variables | Cut-off point | AUC | 95% CI | *P*-value | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|
| RBC ($10^6$/µL) | 2.065 | 0.001 | -0.001-0.002 | <0.001 | 0 | 100 |
| Hb (g/dL) | 4.950 | 0.000 | - | <0.001 | 0 | 100 |
| HCT (%) | 17.150 | 0.006 | 0.000-0.012 | <0.001 | | |
| MCV (fL) | 87.350 | 0.432 | 0.346-0.519 | 0.128 | 12.1 | 36 |
| MCH (pg) | 15.950 | 0.256 | 0.188-0.325 | <0.001 | 100 | 0.8 |
| MCHC (g/dL) | 27.20 | 0.191 | 0.127-0.346 | <0.001 | 100 | 1.5 |
| RDW-CV (%) | 8.150 | 0.262 | 0.206-0.318 | <0.001 | 100 | 6.8 |
| WBC (×$10^3$/µL) | 12.960 | 0.605 | 0.516-0.695 | 0.021 | 34.5 | 91.3 |
| NEUT (×$10^3$/µL) | 5.873 | 0.493 | 0.406-0.580 | 0.870 | 37.9 | 72.1 |
| LYMPH | 3.293 | 0.600 | 0.505-0.696 | 0.040 | 50 | 82.6 |
| MONO | 0.477 | 0.699 | 0.625-0.774 | <0.001 | 70.7 | 63.8 |
| EOS | 0.0975 | 0.649 | 0.570-0.729 | <0.001 | 58.6 | 68.7 |
| BASO | 0.0055 | 0.774 | 0.721-0.827 | <0.001 | 81.0 | 64.2 |
| PLT (×$10^3$/µL) | 377.0 | 0.335 | 0.257-0.413 | <0.001 | 6.9 | 97.4 |
| PCT (%) | 16.0 | 0.143 | 0.101-0.185 | <0.001 | 0 | 100 |
| MPV (fL) | 10.450 | 0.263 | 0.191-0.335 | <0.001 | 8.6 | 95.1 |
| PDW (%) | 27.0 | 0.308 | 0.239-0.377 | <0.001 | 6.9 | 100 |
| P_LCR (%) | 22.685 | 0.693 | 0.614-0.773 | <0.001 | 58.6 | 72.5 |
| NLR | 4.378 | 0.415 | 0.326-0.504 | 0.043 | 22.4 | 84.9 |
| PLR | 264.966 | 0.326 | 0.240-0.411 | <0.001 | 6.9 | 95.5 |

Figure 1. ROC analysis to predict the diagnostic values of blood cell indices for severe malaria.

RBC = Absolute red blood cell count, Hb = Haemoglobin concentration, µL= Microlitre, g/dL= Grams per deciliter; HCT = Haematocrit, MCV = Mean cell volume, MCH = Mean cell haemoglobin, MCHC = Mean cell haemoglobin concentration, RDW-CV = Red blood cell distribution width-coefficient of variation, WBC = White blood cell count; PLT= Platelet count; PCT= Plateletcrit, MPV= Mean platelet volume, Neut.= Neutrophils; Lymph.= Lymphocytes; Mono.= Monocytes; Eos.= Eosinophils; Baso.= Basophils; NLR= Neutrophil-lymphocyte ratio; PLR= Platelet-lymphocyte ratio; fL: Femtolitre; pg: Picogram. Statistical significance was set at $p < 0.05$.

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Table 6. Blood cell abnormalities of P. falciparum-infected children

| Variables | Comments | Reference interval | Frequency | Percentages |
|---|---|---|---|---|
| Haemoglobin (g/dL) | Normal | ≥11.0 | 62 | 19.2 |
| | Anaemia | <11.0 | 261 | 80.8 |
| MCV (fL) | Normal | 80.0-100.0 | 124 | 38.4 |
| | Microcytosis | <80.0 | 197 | 61.0 |
| | Macrocytosis | >100.0 | 2 | 0.6 |
| MCH (pg) | Normal | 27.0-31.0 | 89 | 27.6 |
| | Hypochromasia | <27.0 | 234 | 72.4 |
| RDW-CV (%) | Normal | 11.0-14.5 | 58 | 18.0 |
| | Low | <11.0 | 87 | 26.9 |
| | High | >14.5 | 178 | 55.1 |
| Leucocytes (×10$^3$/µL) | Normal | 5.0-10.0 | 193 | 59.8 |
| | Leucopaenia | <5.0 | 48 | 14.9 |
| | Leucocytosis | >10.0 | 82 | 25.4 |
| Neutrophils (×10$^3$/µL) | Normal | 2.0-7.5 | 276 | 85.4 |
| | Neutropaenia | <2.0 | 19 | 5.9 |
| | Neutrophilia | >7.5 | 28 | 8.7 |
| Lymphocytes (×10$^3$/µL) | Normal | 1.0-4.0 | 223 | 69.0 |
| | Lymphopaenia | <1.0 | 44 | 13.6 |
| | Lymphocytosis | >4.0 | 56 | 17.3 |
| Monocytes (×10$^3$/µL) | Normal | 0.2-0.9 | 132 | 40.9 |
| | Monocytopaenia | <0.2 | 114 | 35.3 |
| | Monocytosis | >0.9 | 77 | 23.8 |
| Eosinophils (×10$^3$/µL) | Normal | 0-0-0.5 | 294 | 91.0 |
| | Eosinophilia | >0.5 | 29 | 9.0 |
| Basophils (×10$^3$/µL) | Normal | 0.0-0.20 | 323 | 100 |
| | Basophilia | >0.20 | 0 | 0 |
| Platelet (×10$^3$/µL) | Normal | 150-450 | 209 | 64.7 |
| | Thrombocytopaenia | <150 | 114 | 35.3 |
| MPV (fL) | Normal | 8.0-12.5 | 161 | 49.8 |
| | Low | <8.0 | 161 | 49.8 |
| | High | >12.5 | 1 | 0.4 |
| PDW (%) | Normal | 10.0-17.9 | 49 | 15.2 |
| | Low | <10.0 | 118 | 36.5 |
| | High | >17.9 | 156 | 48.3 |
| P_LCR (%) | Normal | 15.0-35.0 | 196 | 60.7 |
| | Low | <15.0 | 103 | 31.9 |
| | High | >35.0 | 24 | 7.4 |
| Multiple abnormalities | Bicytopaenia | - | 120 | 37.2 |
| | Pancytopaenia | - | 23 | 7.1 |

Data are presented in frequencies and corresponding percentages. RBC = Absolute red blood cell count, Hb = Haemoglobin concentration, µL= Microlitre, g/dL= Grams per deciliter; HCT = Haematocrit, MCV = Mean cell volume, MCH = Mean cell haemoglobin, MCHC = Mean cell haemoglobin concentration, RDW-CV = Red blood cell distribution width-coefficient of variation, WBC = White blood cell count; PLT= Platelet count; PCT= Plateletcrit, MPV= Mean platelet volume, Neut.= Neutrophils; Lymph.= Lymphocytes; Mono.= Monocytes; Eos.= Eosinophils; Baso.= Basophils; NLR= Neutrophil-lymphocyte ratio; PLR= Platelet-lymphocyte ratio; fL: Femtolitre; pg: Picogram

Also, common haematological abnormalities detected among the fifty-eight children with severe malaria were microcytosis (13.0%, n = 42/323), hypochromasia (16.1%, n = 52/323), leucocytosis (7.1%, n = 23/323), lymphocytosis (6.2%, n = 20/323), monocytosis (7.4%, n = 24/323), and thrombocytopaenia (11.5%, n = 37/323). Thirty-eight and nine children with severe malaria had bicytopaenia and pancytopaenia, respectively. Regarding forms of anaemia among participants with severe malaria, 13.0% (n = 42/323) had microcytic-hypochromic anaemia, (1.9%, n = 6/323) had normocytic-normochromic anaemia, and 3.1% (n = 10/323) had normocytic-hypochromic anaemia. Again, the proportion of severe malaria-infected children with mild, moderate and severe thrombocytopaenia was 7.7% (n = 25/323), 2.8% (n = 9/323), and 0.9% (n = 3/323), respectively.

**ROC analysis to predict the diagnostic values of blood cell indices for severe malaria**

Full blood count parameters that fairly predicted severe malaria in children were total leucocytes (AUC: 0.605, p = 0.021), absolute lymphocyte count (AUC: 0.600, p = 0.040), absolute monocyte count (AUC: 0.699, p < 0.001), absolute eosinophil (AUC: 0.649, p < 0.001), absolute basophil count (AUC: 0.774, p < 0.001) and platelet_large cell ratio (AUC: 0.693, p < 0.001) (Figure 1).

## DISCUSSION

The high mortality rate of malaria in the tropics is associated with extensive alterations in haematological indices in affected individuals [4]. Malaria is associated with the occurrence of cytopaenia, where there is

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suppressed production or enhanced haemolysis of one or more blood cell lines, leading to reduced counts of the affected cell types in peripheral blood. Common cytopaenias such as anaemia, thrombocytopaenia, and leucopaenia have been reported in childhood malaria [8]. This study presents the haematological profile of malaria-infected children and determined the predictive values of haematological indices for severe malaria in Tamale. The observation of fever as a common symptom in malaria-infected children has been reported earlier, and it is related to the efflux of pyogenic inflammatory cytokines following malaria infection, which influence the thermoregulatory centre of the brain to increase axillary body temperature [26-28]. Generally, the malaria-infected participants included in this study were moderately anaemic, with most of the participants recording haemoglobin concentration less than 11.0 g/dL, revealing anaemia in 80.8% (n = 58) of the reviewed cases. Of the 323 P. falciparum-infected participants, 44.6%, 18.3% and 18.0% had mild, moderate and severe anaemia, respectively.

The high prevalence of anaemia among children with malaria identified in this study is similar to previous studies [29,30], but higher than findings from Offinso [31] and Ho in Ghana [2], Nigeria [18] and Indonesia [8]. Other studies in Ghana [9,10,32] and other malaria-endemic areas [15–17] observed reduced haemoglobin concentration among children with malaria compared to their counterparts without malaria. During the asexual phase of the malaria parasite's life cycle, P. falciparum-erythrocytes express P. falciparum erythrocyte membrane protein-1 surface protein, which promotes the adhesion of infected red cells to endothelial surfaces. This phenomenon facilitates the extreme sequestration of both infected and uninfected erythrocytes in organs, especially the spleen, bone marrow and brain, and enhance haemolysis, leading to the development of anaemia [33,34]. Other related mechanisms, such as associated complement activation, bone marrow suppression, and the contribution of inflammatory mediators and dyserythropoiesis, could account for the development of anaemia in malaria-infected patients [6,15,35].

The great effect of malaria on erythrocytes makes anaemia the most predominant haematological abnormality detected among P. falciparum-infected children in this study, and this observation is similar to the findings from previous studies [22,29–31], but contrary to another study where thrombocytopaenia was the most common cytopaenia in adults [24]. Moreover, the proportion of participants with severe anaemia observed in this study is lower than the 39.8% prevalence of severe anaemia reported in Navrongo War Memorial Hospital in the Kassena-Nankana District of Ghana [12]. The higher proportion of severe anaemia among malaria-infected children observed in the study by Oduro et al. [12] is because they included hospitalised patients and children with cerebral malaria, whilst the present study selected only laboratory-diagnosed non-hospitalised patients. Also, the 48.0% prevalence of anaemia reported in Tamale by Anabire et al. was lower than the prevalence observed in the present study, and the variations may be due to the differences in the study participants as adults were included in the previous study [24].

Microcytic hypochromic anaemia was the most prevalent morphological abnormality detected among the malaria-infected participants in this study, and this may be due to the associated loss of appetite and nausea resulting in iron deficiency [36]. A key component of haemoglobin, haem is formed from a complex of protoporphyrin IX and iron, and protoporphyrin IX-iron complex combines with genetically determined globin to form haemoglobin [37]. Thus, deficiency in iron leads to reduced red cell size (microcytosis) and reduced haemoglobinization (hypochromasia) [38]. Also, the significant observation of normocytic normochromic anaemia identified in this study may result from the associated haemolytic episodes in malaria [36].

Haemoglobin concentration was not different between male and female children infected with malaria in this study, and this agrees with a recent study that reported similar reference intervals of haemoglobin in both sexes among children in Tamale [39]. This observation is attributed to the fact that haemoglobin concentration begins to differ between males and females after puberty, where females start experiencing menstruation, and males exhibit enhanced androgen synthesis. More than half of the malaria-infected children included in this study had elevated red cell distribution width, and this may be due to the probable bone marrow's ability to release reticulocytes in peripheral circulation to compensate for the associated anaemia [40,41].

In this study, thrombocytopaenia was observed in 35.3% of the cases included in the review, with 21.1%, 10.8% and 3.4% experiencing mild, moderate and severe thrombocytopaenia, respectively. This finding is in consonance with findings from previous studies in children [2,21,22,29,31,42] and adults [4,24]. Malaria-triggered thrombocytopaenia may be linked to the hypersplenic sequestration of thrombocytes, associated antibody-mediated lyses of thrombocytes, impaired megakaryoblasts proliferation and differentiation, as well as consumptive thrombocytes coagulopathy, which results from enhanced inflammation during malaria [4,21,42,43]. In thrombocytopaenia, the bone marrow releases more megakaryocytes into circulation as compensation, causing platelet anisocytosis with subsequent elevation of platelet distribution width [40,44]. This observation was present in the current study.

The host's immunity plays a vital role in controlling the replication of plasmodium species and enhancing the parasites' clearance to obviate any complications. The clearance of the parasites from the body is facilitated by immune cells, principally leucocytes, through various mechanisms, including phagocytosis, and the release of

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inflammatory cytokines. The interactions between plasmodium parasites and immune cells may affect the numbers of leucocytes in the peripheral blood, which could result in either leucopaenia or leucocytosis, depending on the phase and severity of malaria, environmental factors, host's immunity, among other factors [4,8]. Generally, the malaria-infected participants included in this study had averagely normal leucocyte counts, and this has been reported by previous studies [4,8,24,45]. However, about one-fourth and 14.9% of the malaria-infected participants had leucocytosis and leucopaenia, respectively. The lymphopaenia experienced by the participants has been reported previously and may be linked with possible Fas-induced apoptosis with subsequent acute lysis of lymphocytes [4]. A significant proportion of malaria-infected children experienced abnormalities in neutrophil counts, and this is similar to the earlier observation by Jiero et al. [8].

This present study highlights the significant relationships between haematological indices and P. falciparum parasite density in infected children. Notably, we observed a negative correlation between parasite density and several critical blood parameters, including red cell count, haemoglobin, hematocrit, lymphocyte count, eosinophil count, platelet count, plateletcrit, and the platelet-to-lymphocyte ratio. Again, the haematological abnormalities, including microcytosis, hypochromasia, anaemia, leucocytosis, lymphocytosis, monocytosis, thrombocytopaenia, bicytopaenia, and pancytopaenia were greatly observed among the fifty-eight children with severe malaria. These findings indicate that increasing parasitemia is associated with deterioration in haematological parameters, particularly the development of anaemia and thrombocytopaenia [6–8]. The predictive ability of haematological indices as biomarkers for severe malaria was assessed in this study. Full blood count parameters that fairly predicted severe malaria in children included total leucocytes, absolute lymphocyte count, absolute monocyte count, absolute eosinophil, absolute basophil count and platelet_large cell ratio. Blood cell parameters have been reported as surrogate markers associated with severe malaria due to the direct interaction between plasmodium and blood cells, associated inflammatory response, direct bone marrow suppression, dysregulated iron metabolism, immune-mediated and hypersplenism [21–23].

The study recognises a few limitations. The study did not collect data on other clinical manifestations of malaria, except axillary temperature. This study did not recruit controls to allow for comparison of the findings. Again, this study recruited only children with laboratory-diagnosed malaria.

### Conclusion

Childhood malaria presents with varying haematological abnormalities, notably severe anaemia, thrombocytopaenia and leucocyte disorders. Microcytic hypochromic anaemia is a common picture in children with malaria. Blood cell parameters may be useful in differentiating severe from uncomplicated malaria in children. Blood cell indices should be assessed and keenly monitored in childhood malaria to prevent life-threatening complications.

## DECLARATIONS

### Ethical consideration

Written informed consent was obtained from the parents or guardians of each participant prior to their inclusion in the study. The Institutional Review Board of the University for Development Studies approved the protocols of this study (Ref. No. UDS/IRB/15/2023).

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest

### Author contribution

CN conceptualised the study, designed the methodology, conducted the investigation, performed formal analysis, validation, visualisation, and manuscript drafting and revision. EFC supervised the study and contributed to conceptualisation, methodology, validation, visualisation, and manuscript revision. FOB, MB, EAK, and IA handled formal analysis, methodology, and data curation. SKA, GA, RVD, CAD, SBB, SD, BNU, SA, PS, YQ, VUU, PO, EB, and SMK contributed to methodology, investigation, resources, and manuscript drafting and revision. All authors read and approved the final manuscript.

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### Availability of data

Data is available upon request to the corresponding author

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# A haematological and biochemical analysis of variability of whole blood across different blood donor groups in Yaoundé, Cameroon: A cross-sectional, descriptive study

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**Abstract**

***Background:*** Data on blood donor variability in sub-Saharan Africa is scarce, despite whole blood being the primary transfusion product. Donor-related haematological and biochemical differences may impact storage quality and transfusion outcomes.

***Objective:*** The study aimed to identify associations between blood donor characteristics and baseline haemato-biochemical parameters of blood units in the Yaoundé University Teaching Hospital (YUTH).

***Methods:*** A descriptive cross-sectional study was conducted on blood donors of the YUTH between May and August 2023. A structured questionnaire was used to collect socio-demographic, lifestyle and medical information. Blood samples were taken from donors and analysed for haematological and biochemical parameters. Pearson's chi-squared test was applied to determine donor characteristics that affect the baseline hemato-biochemistry of blood units. Statistical significance was set at 0.05.

***Results:*** One hundred and five donors were included; 74 (70.5%) were men, 79 (75.2%) were under 35 years old, and 49 (46%) were students. Hemolysis was higher in smokers (OR: 0.30, CI: 0.01 to 0.60, p-value: 0.001). Alcohol consumers had lower red blood cells (OR: 1.14, CI: 1.04 to 1.25, p-value: 0.02). Abnormally shaped red blood cells were more common in overweight donors (OR: 3.11, CI: 1.20 - 8.10, p-value: 0.02).

***Conclusion:*** Baseline haematobiochemical parameters of whole blood vary due to differences in donor lifestyle and medical background. Information from this study could contribute to blood management in SSA, especially in the elaboration of blood donor education programs and in the adjustment of medical selection criteria.

**Keywords:** Blood donor variability, hemato-biochemical parameters

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## INTRODUCTION

Whole blood (WB) is the most commonly used blood product in sub-Saharan Africa (SSA) [1]. Recently, there has been increasing interest in the disparaging storage efficacy of WB units stored under similar banking conditions [2]. Researchers have observed that inter-individual storage performance is highly variable, depending greatly on certain haematological and biochemical parameters of the blood unit [3]. While storage lesions comprising hematological, biochemical, and immunologic alterations progressively accumulate with increasing shelf-life [4–6], the donor variation effect, defined as inter-donor differences that result in markedly disparate blood product quality despite standardised storage

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conditions and durations [7], accounts for variability in storage performance observed at the point of transfusion [7–9]. In high-income settings, omics studies have identified donor characteristics such as sex, age, uric acid, complement receptor status, and body mass index (BMI) as determinants of blood quality [10-12]. However, in SSA, where the demand for blood is high [13], existing studies on donor variability are scarce. Inadequate resource allocation for transfusion medicine, coupled with competing healthcare priorities, has contributed to the relative neglect of blood-related research in the region [14]. This study, therefore, sought to investigate the variability of haematological and biochemical parameters across diverse blood donor demographics and lifestyles in an SSA context.

In Cameroon, donor selection practices primarily involve screening prospective donors for four communicable diseases (HIV 1 and 2, hepatitis B, hepatitis C and syphilis), with limited attention to medical background checks [14]. However, all potential blood donors are administered a questionnaire prior to donor selection. Responses obtained are used to exclude persons for whom blood donation holds a risk of harm through blood depletion or the subsequent blood recipient through pathogen transmission. Due to constraints in human and material resources, vital signs such as oxygen saturation (SpO2), respiratory frequency (RF), BMI, random blood glucose (RBS), and temperature are rarely assessed before blood donation [15]. Moreover, routine screening for endemic conditions such as malaria and sickle cell trait (SCT) is not mandatory. Currently, the understanding of donor characteristics that impact the baseline haematological and biochemical quality of WB is limited.

This study aimed to describe baseline haematological and biochemical parameters of whole blood units at the Yaoundé University Teaching Hospital (YUTH) and to investigate potential associations with socio-demographics, lifestyle and medical background of donors.

## MATERIALS AND METHODS

### Study design and sites

This study employed a prospective cross-sectional design involving blood donors and whole blood units received at the YUTH. Data were collected using a systematic, consecutive sampling approach over four months, from May 1 to August 31, 2023. Donors whose blood bags were haemolysed, coagulated, or reactive for any transfusion-transmitted infection (TTI) were excluded.

### Pre-donation measurement of vital signs

Prior to blood donation, non-mandatory vital signs, including SpO2, RF, BMI, RBS, and temperature, were assessed, alongside routine measurements of heart rate (HR), mean arterial blood pressure (MABP), and pre-donation capillary haemoglobin level (by the photometric haemocue technic). All vital signs were measured by the same trained research staff. Additionally, information on blood donation frequency and the date of last blood donation was collected.

### Post-donation collection of donor lifestyle and medical information

To avoid reporting bias due to the fear of deferral, research questionnaires were administered only after blood donation. Enrolled participants provided socio-demographic data, including age, gender, region of origin, and profession, tobacco/alcohol consumption, and medical history (Presenting symptoms and medication taken). To mitigate recall bias, inquiries were restricted to the week preceding blood donation. Further, questions were open-ended and posed without prejudice so as to prompt a more genuine recollection and unbiased responses.

### Lifestyle information

Lifestyle variables assessed included regular physical activity (defined as ≥ 30 minutes of exercise at least three times per week), alcohol consumption (≥ 3 bottles of beer or 14 glasses of wine per week for men; ≥ 1 bottle of beer or 8 glasses of wine per week for women), and tobacco use (any quantity of cigarette smoking). Medical background information included past medical history, reported symptoms, and current or recent medication use.

### Blood collection

WB was collected from participants into 450 ml single blood bags containing 63 ml of Citrate phosphate dextrose adenine (CPDA-1) anticoagulant. Following the donation, 4 mL of blood was drawn from the bag tubing, which was already mixed with CPDA-1, into EDTA and dry tubes for laboratory analysis. This approach may introduce pre-analytical variability due to the combined effect of CPDA-1 and additional anticoagulants.The remaining content of the blood bag was processed under the routine standard operating procedures of the YUTH.

### Laboratory analysis

Blood in the EDTA tube was used for haematological analyses. A complete blood count was done using an automated cell counter (HumaCount 30 TS, HUMAN Diagnostics Worldwide Co., Ltd., Magdeburg, Germany). This measured white blood cells (WBC), red blood cells (RBC), platelets, haemoglobin (Hb), mean cell haemoglobin (MCH), mean cell volume (MCV) and mean corpuscular haemoglobin concentration (MCHC). Subsequently, rapid haemoglobin-S screening was performed using the Itano haemoglobin solubility test (Anamol Laboratories PVT. LTD., Palghar, India). Finally, peripheral blood smears were prepared, stained according to the May-Grünwald-Giemsa method and examined under a light microscope (OLYMPUS) with 100x objective lens to detect malaria parasites and abnormally shaped red blood cells (aRBCs).

The dry tube was centrifuged at 3000g for five minutes using a tabletop centrifuge (EBA 200S, HETTICH Ltd., Tuttlingen, Germany) to obtain serum for biochemical analysis. Electrolytes (sodium, potassium, and chloride)

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were determined using an electrolyte analyser (GE 300, Genrui Biotech Co., Ltd., Shenzhen, China) and lactate dehydrogenase (LDH) was measured using a semi-automated spectrophotometer (Kenza Max Biochemistry, BIOLABO S.A.S, Les Hautes Rives, France). Serum Hb was quantified with a cell counter (HumaCount 30 TS, HUMAN Diagnostics Worldwide Co., Ltd., Magdeburg, Germany), and baseline haemolysis was calculated using the formula: Haemolysis (%) = [(100 - haematocrit) × (serum Hb (g/dL))] ÷ whole blood Hb (g/dL).

**Statistical analysis**

Data analysis was conducted using IBM SPSS Statistics for Windows version 23. Frequency tables were generated, and parameters were categorised as normal or abnormal based on reference ranges [17]. Comparative analysis was done with Pearson's chi-square test or Fisher's exact test, where appropriate. Associations between donor characteristics and laboratory findings were made by calculating odds ratios at a 95% confidence interval. Statistical significance was defined as $p < 0.05$.

## RESULTS

During the study period, 131 individuals were accepted as blood donors at the YUTH. Eighteen were missed by research staff, three were excluded due to haemolysis, and five were excluded for reacting to one or more TTIs. A total of 105 blood donors were retained for this study. Eighty-four (80%) were voluntary donors, while 21 (20%) were replacement donors. Fifty-three (50.5%) were first-time donors, and 52 (49.5%) were frequent donors. The median last blood donation was 12 months (inter-quartile range 4-24 months), and ten (9.6%) donors had given blood three or more times in the past year.

Of 105 included blood donors, 74 were male (70.5%). Participants' ages ranged from 19 to 58 years, with a mean of 30 (SD 8) years. Forty-eight participants (45.7%) identified as students, while 57 (54.3%) were employed. Of 105 respondents, two-thirds (67.5%) reported regular physical exercise; a third (39%) reported regular alcohol consumption, and four (3.8%) reported smoking.

Table 1. Frequency of normal and abnormal laboratory parameters of whole blood units at baseline.

| Variable | Reference Range | Mean (min-max) | Classification | Total (N=105) | Percentage |
|---|---|---|---|---|---|
| WBC ($x10^9$/L) | 4.0- 10.0 | 4.53 (2.24-9.50) | Low | 41 | 39.05 |
| | | | Normal | 64 | 60.95 |
| RBC ($x10^{12}$/L) | 3.5-5.5 | 4.67 (3.01-7.68) | Low | 7 | 6.69 |
| | | | Normal | 88 | 83.79 |
| | | | High | 10 | 9.52 |
| Haemoglobin (g/dL) | 12.5-18 | 13.50 (8.00-18.41) | Low | 15 | 14.28 |
| | | | Normal | 88 | 83.81 |
| | | | High | 2 | 1.91 |
| MCV(fL) | 80-100 | 83.25 (47.70-94.42) | Low | 25 | 23.81 |
| | | | Normal | 80 | 76.19 |
| MCH (pg) | 27-34 | 29.0 (16.10-33.90) | Low | 23 | 21.90 |
| | | | Normal | 82 | 78.14 |
| MCHC (g/dL) | 32-36 | 34.73 (27.32-37.84) | Low | 12 | 11.43 |
| | | | Normal | 76 | 72.38 |
| | | | High | 17 | 16.19 |
| Platelet ($x10^9$/L) | 150-400 | 224 (119-391) | Low | 7 | 6.72 |
| | | | Normal | 98 | 93.34 |
| aRBCs (%/field) | <10 | 14 (0-30) | Normal | 51 | 48.57 |
| | | | High | 54 | 51.43 |
| Haemolysis (%) | <0.8 | 0.01(0.0-0.3) | Normal | 105 | 100 |
| | | | High | 0 | 0 |
| Sodium (mEq/L) | 137-150 | 140.31 (125.50-159.42) | Low | 22 | 20.95 |
| | | | Normal | 81 | 79.05 |
| | | | High | 2 | 1.91 |
| Potassium (mEq/L) | 3.4-5.8 | 3.82 (2.87-6.19) | Low | 25 | 23.73 |
| | | | Normal | 77 | 73.33 |
| | | | High | 3 | 2.94 |
| Chloride (mEq/L) | 98-109 | 106.13 (86.01-126.00) | Low | 11 | 10.48 |
| | | | Normal | 74 | 70.48 |
| | | | High | 20 | 19.04 |
| LDH (IU/L) | 225-450 | 431.89 (221.04-765.21) | Normal | 74 | 70.49 |
| | | | High | 31 | 29.52 |

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Table 2. Comparison between donor characteristics and cell counts of whole blood at baseline

| Donor Characteristics | WBC ($x10^9$/L) | | RBC ($x10^{12}$/L) | | PLT ($x10^9$/L) | |
|---|---|---|---|---|---|---|
| Total (n, %) | <4 | 4-10 | <3.5 | 3.5-7.5 | <150 | 150-400 |
| | 41 (39.0) | 64 (61.0) | 8 (7.6) | 97(92.4) | 7(6.7) | 98 (93.3) |
| Age (years) | | | | | | |
| 18-34 (79,75.2) | 26 | 53 | 8 | 71 | 5 | 74 |
| 35-65 (26,24.8) | 15 | 11 | 0 | 26 | 2 | 24 |
| OR(CI);p-value | 0.36( 0.15-0.89);0.03 | | 0.90 (0.84-0.97);0.09 | | 0.81 (0.15-4.45).0.08 | |
| Gender | | | | | | |
| Male (74,70.5) | 34 | 40 | 0 | 74 | 7 | 67 |
| Female (31,29.5) | 7 | 24 | 8 | 23 | 0 | 31 |
| OR(CI);p-value | 2.91 (1.12-7.60); 0.03 | | 1.35(1.10-1.66);0.001 | | 0.91 (0.84-0.98);0.08 | |
| Profession | | | | | | |
| Student (49,46.7) | 18 | 31 | 7 | 42 | 3 | 46 |
| Worker (56,53.3) | 23 | 33 | 1 | 55 | 4 | 52 |
| OR(CI);p-value | 0.83(0.38-1.83);0.65 | | 9.17 (1.09-77.40);0.02 | | 0.85(0.18-3.99);0.83 | |
| Alcohol intake | | | | | | |
| Yes(41,39.0) | 20 | 21 | 0 | 41 | 4 | 37 |
| No(64,61.0) | 21 | 43 | 8 | 56 | 3 | 61 |
| OR(CI);p-value | 1.95(0.87-4.36);0.10 | | 1.14(1.04-1.25);0.02 | | 2.20(0.47-10.37);0.31 | |
| Random blood sugar | | | | | | |
| <1.26 g/l (99,94.6) | 39 | 60 | 8 | 91 | 5 | 94 |
| 1.26-2.2 g/l (6, 5.7) | 2 | 4 | 0 | 6 | 2 | 4 |
| OR(CI);p-value | 1.30(0.23-7.44);0.77 | | 0.92(0.87-0.97);0.47 | | 0.11(0.02-0.73);0.007 | |

Note: n = 105. P-values calculated using Pearson's Chi-squared test and Fisher's exact test where more than 20% of the cell count is less than 5. Bold values indicate statistically significant results.
Abbreviations: MCV, mean cell volume; MCH, mean cell haemoglobin; OR, Odds ratio; CI, confidence interval; VD, Voluntary donor; RD, Replacement donor.

Table 3. Comparison between donor characteristics and red blood cell indices of whole blood at baseline.

| Donor characteristics | Red blood cell indices | | | | | |
|---|---|---|---|---|---|---|
| | Haemoglobin (g/dL) | | MCV (fL) | | MCH (pg) | |
| Total (n, %) | <8-12.5 | 12.5-19.5 | <80 | 80-100 | <27 | 27-34 |
| | 36 (34.3) | 69 (65.7) | 25 (23.8) | 80(76.2) | 23(21.9) | 82 (78.1) |
| Age (years) | | | | | | |
| 18-34 (79,75.2) | 28 | 51 | 21 | 58 | 20 | 59 |
| 35-65 (26,24.8) | 8 | 18 | 4 | 22 | 3 | 23 |
| OR(CI);p-value | 1.2(0.48-3.20);0.66 | | 1.99(0.64-6.46);0.25 | | 2.60(0.70-9.59);0.14 | |
| Gender | | | | | | |
| Male (74,70.5) | 14 | 60 | 17 | 57 | 16 | 58 |
| Female (31,29.5) | 22 | 9 | 8 | 23 | 7 | 24 |
| OR(CI);p-value | 0.10(0.036-0.25);0.001 | | 0.86(0.33-2.26);0.76 | | 0.95(0.35-2.59);0.91 | |
| Profession | | | | | | |
| Student (49,46.7) | 12 | 37 | 10 | 39 | 10 | 39 |
| Worker (56,53.3) | 24 | 32 | 15 | 41 | 13 | 43 |
| OR(CI);p-value | 0.43(0.19-0.99);0.04 | | 0.70(0.28-1.75);0.44 | | 0.85(0.33-2.15);0.73 | |
| Donor type | | | | | | |
| VD (84,80.0) | 25 | 59 | 15 | 69 | 15 | 69 |
| RD (21,20.0) | 11 | 10 | 10 | 11 | 8 | 13 |
| OR(CI);p-value | 0.39(0.15-1.02);0.051 | | 0.24(0.09-0.67);0.004 | | 0.35(0.13-1.00);0.04 | |
| Medication taken | | | | | | |
| None(90,85.7) | 27 | 63 | 21 | 69 | 18 | 72 |
| Yes (15,14.3) | 9 | 6 | 4 | 11 | 5 | 10 |
| OR (CI);p-value | 0.28(0.09-0.88);0.023 | | 0.84(0.24-2.91);1.00 | | 0.50(0.15-1.65);0.25 | |

Note: n= 105. P-values calculated using Pearson's Chi squared test and Fischer's exact test where more than 20% of cell count is less than 5. Bold values indicate statistically significant results.
Abbreviations: LDH, Lactate dehydrogenase; OR, Odds ratio; CI, confidence interval; VD, Voluntary donor; RD, Replacement donor.

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Table 4. Comparison of donor characteristics and indices of whole blood hemolysis at baseline.

| Donor characteristics | Haemolysis indices | | | | | |
|---|---|---|---|---|---|---|
| | LDH (IU/L) | | Potassium (mEq/L) | | Haemolysis (%) | |
| | 225-450 | >450 | <3.4 | 3.4-6.2 | 0 | 0.1-0.8 |
| Total (n, %) | 74(70.5) | 31 (29.5) | 25 (23.8) | 80(76.2) | 103(98.1) | 2(1.9) |
| Age (years) | | | | | | |
| 18-34 (79,75.2) | 56 | 23 | 19 | 60 | 77 | 28 |
| 35-65 (26,24.8) | 18 | 8 | 6 | 20 | 26 | 20 |
| OR(CI);p-value | 1.08(0.41-2.84);0.87 | | 1.0(37-3.01);0.92 | | 0.98(0.94-1.01);0.62 | |
| Gender | | | | | | |
| Male (74,70.5) | 51 | 23 | 18 | 56 | 72 | 7 |
| Female (31,29.5) | 23 | 8 | 7 | 24 | 31 | 0 |
| OR(CI);p-value | 0.77(0.30-1.98);0.59 | | 1.11(0.41-2.98);0.85 | | 0.97(0.94-1.01);0.36 | |
| Profession | | | | | | |
| Student (49,46.7) | 32 | 17 | 10 | 39 | 49 | 0 |
| Worker (56,53.3) | 42 | 14 | 15 | 41 | 54 | 2 |
| OR(CI);p-value | 0.63(0.27-1.46);0.28 | | 0.70(0.28-1.75);0.44 | | 1.04(0.99-1.09);0.18 | |
| Donor type | | | | | | |
| VD (84,80.0) | 55 | 29 | 20 | 64 | 84 | 0 |
| RD (21,20.0) | 19 | 2 | 5 | 16 | 19 | 2 |
| OR(CI);p-value | 0.20(0.04-0.92);0.03 | | 1.00(0.33-3.07);1.00 | | 1.12(0.96-1.27);0.004 | |
| Tobacco intake | | | | | | |
| Yes(4,3.8) | 3 | 1 | 1 | 3 | 3 | 1 |
| No(101,96.2) | 71 | 30 | 24 | 77 | 100 | 1 |
| OR(CI);p-value | 1.27(0.13-12.68);0.84 | | 1.07(0.11-10.76);0.96 | | 0.30(0.01-0.60);0.001 | |
| Alcohol intake | | | | | | |
| Yes(41,39.0) | 28 | 13 | 16 | 25 | 40 | 1 |
| No(64,61.0) | 46 | 18 | 9 | 55 | 63 | 1 |
| OR(CI);p-value | 0.84(0.36-1.98);0.60 | | 3.91(1.52-10.05);0.003 | | 0.64(0.04-10.44);0.75 | |

Table 5. Comparison between donor characteristics and abnormally shaped red blood cells, sodium and chloride ions of whole blood at baseline

| Donor characteristics | aRBCs, Sodium and Chloride | | | | | |
|---|---|---|---|---|---|---|
| Total (n, %) | ≤10 | >10 | <137 | 137-160 | 86-109 | >109 |
| | 41 (39.0) | 64 (61.0) | 22(21.0) | 83(79.0) | 72(68.6) | 33 (31.4) |
| Age (years) | | | | | | |
| 18-34 (79,75.2) | 35 | 44 | 15 | 64 | 56 | 23 |
| 35-65 (26,24.8) | 6 | 20 | 7 | 19 | 16 | 10 |
| OR(CI);p-value | 2.65(0.96-7.31);0.05 | | 0.64(0.23-1.79);0.39 | | 1.52(0.60-3.85);0.37 | |
| Gender | | | | | | |
| Male (74,70.5) | 28 | 46 | 18 | 56 | 51 | 23 |
| Female (31,29.5) | 13 | 18 | 4 | 27 | 21 | 10 |
| OR(CI);p-value | 0.84(0.36-1.98);0.70 | | 2.17(0.67-7.04);0.29 | | 1.06(0.43-2.60);0.91 | |
| Profession | | | | | | |
| Student (49,46.7) | 23 | 26 | 11 | 38 | 30 | 19 |
| Worker (56,53.3) | 18 | 38 | 11 | 45 | 42 | 14 |
| OR(CI);p-value | 1.87(0.85-4.13);0.12 | | 1.18(0.46-3.03);0.72 | | 0.53(0.23-1.21);0.13 | |
| Donor type | | | | | | |
| VD (84,80.0) | 32 | 52 | 19 | 65 | 53 | 31 |
| RD (21,20.0) | 9 | 12 | 3 | 18 | 19 | 2 |
| OR(CI);p-value | 0.82(0.31-2.16);0.69 | | 1.75(0.47-6.60);0.55 | | 0.18(0.039-0.83):0.017 | |
| Alcohol intake | | | | | | |
| Yes(41,39.0) | 16 | 25 | 11 | 30 | 23 | 18 |
| No(64,61.0) | 25 | 39 | 11 | 53 | 49 | 15 |
| OR(CI);p-value | 0.99(0.45-2.30);0.99 | | 1.77(0.68-4.56);0.24 | | 0.39(0.17-0.91)0.03 | |
| BMI (kg/m$^2$) | | | | | | |
| 18.5-25 kg/m$^2$ (73,69.5) | 34 | 39 | 18 | 55 | 49 | 24 |
| >25 kg/m$^2$ (32,30.5) | 7 | 25 | 4 | 28 | 23 | 39 |
| OR(CI);p-value | 3.11(1.20-8.10);0.02 | | 2.29(0.71-7.42);0.20 | | 0.70(0.32-1.99);0.63 | |

Note: n= 105. P-values calculated using Pearson's Chi squared test and Fisher's exact test where more than 20% of cell count is less than 5. Abbreviations: aRBC, abnormally shaped red blood cells; OR, Odds ratio; CI, confidence interval; BMI, body mass index; VD, Voluntary donor; RD, Replacement donor.

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Past medical history in decreasing order of frequency included smoking (6.7%), surgery (5.7%), allergies (5.7%), rheumatism (2.9%), sexually transmitted infections (1.9%), depression (1.9%), asthma (1.9%), hypertension (1.9%), and coronavirus infection (1.9%). Forty-six (43.8%) participants reported no symptoms a week to blood donation, and 59 (56.2%) reported symptoms including fatigue (33.3%), heartburn (8.6%), abdominal bloating (9.8%), flu (4.8%) and allergic reactions (1.9%). Fifty (47.6%) participants did not take any medication, and 55 (52.4%) reported taking painkillers (47.6%), antibiotics (4.8%) and flu drugs (2.9%). Upon haemoglobin-S and malaria screening done for the purpose of this study, twelve donors (11.4%) were healthy malaria carriers, and 24 (22.9%) were sickle cell carriers.

The mean values of all haematological and biochemical parameters measured lay within normal ranges, yet certain extremes were observed, notably anaemia, thrombopenia, hyperkalemia and hyperlactatemia. Hemolysis was observed in certain blood units, but none was above the 0.8% permissible limit. Abnormally shaped red blood cells were identified on peripheral blood smears. These included dacrocytes (teardrop-shaped or pear-shaped cells), elliptocytes (cigar-shaped cells), echinocytes (crenated cells with multiple spicules), drepanocytes (elongated or S-shaped cells with pointed ends), schistocytes (fragmented cells with a jagged appearance), codocytes (cells with a bull's-eye appearance), and ovalocytes (egg-shaped cells).

WBCs were lower in older donors and in men. RBCs were higher in men, in workers and in non-alcohol drinkers, while platelets were lower in persons with high blood sugar. Haemoglobin was lower in women, students, and donors who had taken medication. MCV and MCH were lower in replacement donors than in voluntary donors. LDH was higher in replacement donors. Potassium was lower in alcohol consumers, whereas percentage of haemolysis was higher in smokers. Abnormally shaped RBCs were higher in overweight donors, while chloride was lower in replacement donors and alcohol drinkers.

## DISCUSSION

In this study, the mean values for all haematological and biochemical parameters lay within normal ranges, but several outliers were identified. This observation corroborates previous research indicating that certain haematological parameters in healthy Cameroonians tend to be lower than typical ranges suggested by haematology analysers [18,19]. The extreme levels of abnormally shaped RBCs, Na, K and LDH noted could impair the storage capacity and compromise transfusion outcomes of whole blood units [5,8,20,21].

During our study period, test strips for rapid haemoglobin meters were sometimes out of stock in the YUTH. In such instances, blood bank staff adopted conjunctival colouration of the blood donor as an alternative indicator of pre-donation haemoglobin. On subsequent full blood count analysis done for the purpose of this study, we found that one donor selected as such had a low haemoglobin level of 8g/dL. This highlights the limitation of conjunctival colouration in predicting haemoglobin levels, particularly in individuals with darker skin tones [22]. In this study, we observed that low WBCs related to male sex and older age, while low RBCs were associated with female sex and a student profession. Recent research has indicated that while the normal range of WBCs is wider in women than in men [23-24], the overall range is comparable between both sexes [25]. Lower RBCs in females are explained by regular blood loss through menstruation [26].

We found low platelet count to be associated with higher RBS. Contrasting findings were made by Bhatta et al., who reported higher platelets in hyperglycemic individuals [27]. Future research should be conducted on a larger sample so as to provide deeper insight into the association between donor blood sugar and platelet count. Based on research conducted in high-income countries, replacement blood donations, often deemed unsafe and unethical, are discouraged by international organisations [28]. However, recent studies in SSA have shown that family donors are equally valid and essential to the blood supply as voluntary donors. Similar to voluntary donations, altruism motivates replacement donations, with many replacement donors subsequently becoming repeat voluntary donors [29]. Moreover, the rates of TTIs are comparable between both donor groups in SSA, and, unlike what is generally assumed, African replacement donors hardly report coercion or pressure to donate [30]. Our study found significantly lower levels of RBC indices in family donors and significantly higher levels of LDH in voluntary donors. This can be explained by the fact that family donors usually step in for their relatives in emergency situations without having prepared themselves nutrition-wise [28]. Larger studies are required to examine the tendency of LDH in voluntary donors and to elucidate the actual differences if any, in transfusion outcomes when using blood from voluntary versus replacement donors.

We observed higher aRBCs in overweight donors compared to healthy weight donors, corroborating findings by Sparrow et al. [32], who reported increased hemolysis in overweight-obese males and attributed this to greater mechanical fragility of RBCs in such donors. In this study, haematological and biochemical parameters of WB were similar between malaria-positive and malaria-negative donors. This contrasts with the findings of Aninanghei et al. [40], who reported lower RBC and higher hemolysis in blood from asymptomatic malaria carriers at baseline. Nevertheless, in our study, as in that of Aninanghei, the permissible haemolysis limit of 0.8% was not observed in any blood unit at baseline. We also did not observe any association between SCT and hemato-biochemical parameters of WB. This differs from the observations of Lee et al. [41], who observed reduced elasticity and increased sphero-echinocytosis of RBCs from SCT donors.

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This could be explained by differences in study methods: our study assessed laboratory parameters at baseline only, while Aninanghei and Lee evaluated these parameters during storage. However, differing donors with malaria and/or SCT are contentious in SSA due to the high prevalence of both conditions and the low blood supply. Nevertheless, to ensure transfusion safety, it may be an option to adjust the shelf life of blood from malaria-positive and SCT donors to a point where non-permissible biological quality degradation does not occur.

In our study, mandatory vital signs lay within normal ranges, while non-mandatory vital signs exhibited extremes. This underscores the potential benefit of expanding the panel of vital signs to screen out blood donors with underlying medical conditions that could impact the quality of blood units. Additionally, during post-donation interviews conducted for this study, blood donors reported to have experienced mild symptoms, such as fatigue, flu and gastric pain, a week before donation. Such donors should have been deferred during the regular selection process of the YUTH. That this did not happen highlights the crucial need for continuous training of blood bank staff on rigorous donor selection methods.

The principal limitation of this study, common to all descriptive investigations, lies in its inability to establish causal relationships. Future research should include a large cohort study with repeated analysis of haematological and biochemical parameters of blood throughout storage. Despite these limitations, this preliminary study in SSA has raised pertinent questions on the variability of haematological and biochemical parameters across diverse blood donor demographics.

### Conclusion

The mean haematological and biochemical parameters of blood units were normal, but notable outliers were identified that could accelerate storage degradation and compromise post-transfusion efficacy. Haematological and biochemical parameters were associated with donor lifestyle, medical background, and vital signs, particularly non-mandatory signs such as RF, SPO2 and RBS. Further research is needed to inform donor education initiatives, refine donor selection criteria, and improve blood safety.

## DECLARATIONS

### Ethical consideration

This study received approval from the ethics committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I (Approval No. 5023/UYI/FMBS/VDRC/DAASR/CSD dated February 6, 2023). Written informed consent was obtained directly from all study participants, none of whom was a minor. Participants presenting with abnormal clinical or laboratory findings were referred to appropriate physicians for further evaluation.

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest

### Author contribution

SYIW, TTC and MFW developed study questions and designs. SYIW and NND administered questionnaires. SYIW and ATP coordinated sample analysis. SYIW, ATP, NND, MM and BA analysed data and drafted the initial manuscript. TTC and MFW edited the manuscript. All authors approved the final manuscript.

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### Availability of data

Data is available upon request to the corresponding author

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# Economic cost of oral conditions to patients attending the dental department of the Korle Bu Teaching Hospital, Ghana

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**Abstract**

***Background:*** Providing and utilising oral health care services are essential to achieving a high quality of life. However, oral conditions present both physical and economic burdens to individuals, households, and governments.

***Objective:*** This study sought to estimate the economic costs incurred by patients accessing oral health services at the Korle-Bu Teaching Hospital in Ghana.

***Methods:*** A cross-sectional cost-of-illness study was conducted at the Korle Bu Teaching Hospital, involving 224 participants. A structured questionnaire was used to collect data on direct and indirect costs. Intangible costs were assessed using a 5-point Likert scale. Descriptive statistics were employed in summarising the costs. Sensitivity analysis was performed with 3%, 5%, and 7% variations in medication costs and wage rates. Differences in mean costs across socioeconomic statuses were analysed using independent t-tests and one-way ANOVA. $P < 0.05$ was considered statistically significant.

***Results:*** The estimated total economic cost was GHS 532,154.06 (US$ 44,346.17). The estimated annual average direct and indirect cost of oral health services were approximately GHS 2,129.98 (US$ 177.50) and GHS 245.70 (US$ 20.48), representing 89.7% and 10.3% of the total economic cost, respectively. Sensitivity analysis revealed a varied increase in total costs, with variations in medication costs and wage rates. Intangible cost was found to be low, with many patients experiencing no to mild burden.

***Conclusion:*** The economic burden of oral health on patients is significant, particularly in terms of direct costs. There is a need for policymakers to develop policies and interventions to mitigate the costs of oral health care. The National Health Insurance Authority should consider expanding insurance coverage for more oral conditions to alleviate the economic burden and improve access to care.

**Keywords:** Oral health, cost of illness, Intangible cost, Quality of life

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## INTRODUCTION

Oral health is a critical aspect of an individual's physical health and a determinant of overall well-being, and quality of life [1,2]. According to the World Health Organisation (WHO), oral health is defined as the condition of the mouth, teeth, and orofacial structures that enables an individual to carry out essential functions, including eating, breathing, speaking, and maintaining psychosocial well-being [3].

Oral disorders are a significant public health concern globally, as they frequently heighten susceptibility to non-communicable diseases such as cardiovascular diseases and

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diabetes [3]. The 2022 Oral Health Status Report estimated that 3.5 billion people worldwide are impacted by oral health issues [3,4]. They are a major cause of pain and discomfort and have a significant socioeconomic impact, leading to diminished productivity, lower academic performance, and disruption of social interactions [4,5]. It also substantially influences the physical and mental health, social relationships, and economic standing of individuals across various age groups and socioeconomic status [6,7]. These conditions have substantial financial consequences for health systems, patients and families [8].

The Global Burden of Disease study has highlighted the substantial economic burden of oral health problems, with an estimated annual expenditure on dental care of US$ 442 billion [9]. Out of this, approximately US$298 billion (about 4.6% of global health spending) is attributed to direct treatment expenses, with the remaining US$ 144 billion ascribed to indirect expenditures, including productivity loss [9]. In many countries, including Ghana, oral healthcare remains an under-prioritised area of healthcare, despite its fundamental impact on the health and well-being of the population. Despite being fundamentally preventable, oral health conditions in Ghana are highly prevalent and characterised by limited public investment in preventive and therapeutic interventions, socioeconomic disparities and high patient expenditures [10,11].

In 2019, the WHO reported that approximately 70% of sub-Saharan African countries spent less than US$ 1 per person annually on treatment costs for oral healthcare [12]. This limited investment and financial burden associated with treating dental ailments is a significant obstacle to the utilisation of oral care services [13,14]. According to Deh et al. [15], patients in Ghana are responsible for covering the expenses associated with treating dental problems. An economic cost study in Ghana estimated the total cost of oral care to be US $6,248.59, with an average cost of US $35.75, a significant amount for many Ghanaians, especially those categorised under lower socioeconomic status [15]. The financial burden of oral health care often leads to delayed or avoided treatment, exacerbating the progression of oral diseases and resulting in negative consequences for individuals and the health system. While multiple studies have highlighted the substantial economic burden associated with oral health services [15,16], a gap remains in comprehensively assessing indirect costs, including productivity loss and intangible costs such as pain and suffering.

This study aimed to investigate this gap by capturing the broader cost implications of oral healthcare, including direct and indirect costs borne by patients and the Korle Bu Teaching Hospital (KBTH), as well as intangible costs experienced by patients. By providing a comprehensive understanding of the economic burden, this study aimed to inform effective health policies that improve access to affordable oral healthcare and reduce disparities in treatment across Ghana.

# MATERIALS AND METHODS

### Study design and sites

A cross-sectional cost-of-illness study to estimate the economic costs of oral healthcare among patients at the Maxillofacial Department of the Korle-Bu Teaching Hospital in Accra. The study was conducted from March to April 2023. Korle Bu Teaching Hospital is a premier tertiary healthcare facility in Ghana with an approximate 2000-bed capacity, 21 clinical and diagnostic departments, and three centres of excellence. The Maxillofacial unit is a subsidiary of the Dental department. The department handles an average of 20-30 new cases daily, encompassing a range of dental diseases.

### Study population and sample size

The study population consisted of individuals aged 18 years or above who presented with dental conditions to the dental department of the KBTH. The sample size for this study was determined using the Cochran (1977) formula for estimating sample sizes for finite populations. Using a finite population of 500 patients per month at the dental department. A final sample size of 224 patients was determined, including an additional 10% to account for potential non-responses.

### Inclusion criteria and exclusion criteria

All patients aged 18 years and above who presented to the Maxillofacial Department of Korle-Bu Teaching Hospital (KBTH) for oral health services and provided written informed consent were included in the study. Patients were excluded if they were acutely ill during the data collection period (e.g., hemodynamically unstable, critically unwell, or requiring emergency resuscitation) or if they had not accessed dental care at the Maxillofacial Unit within the past 12 months.

### Sampling technique

A simple random sampling technique was used to select participants receiving care at the dental department. This approach was employed to ensure equal chances of selection for all members of the study population. Using the balloting method, ‘yes’ and ‘no’ were written on paper, then folded and placed into a box. Patients at the department were asked to pick one piece of paper each. Those who picked ‘yes’ were included in the study after providing written informed consent. This process was repeated on each clinic day.

### Data Collection

The data collection period for this study was from March to April 2023. This timeframe was selected to ensure adequate time to recruit the required sample size of 224 participants, considering the daily patient flow at the KBTH Dental Department. The department handles approximately 20-30 new cases daily, and over the two months, this enabled the inclusion of a diverse and representative sample of patients. The questionnaire, which included both closed-ended and open-ended questions, covered five sections; the first section collected the socio-demographic characteristics.

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The second section on oral health conditions collected data on the type of dental condition, its duration, treatment modality, and payment method. The third section recorded the direct medical and non-medical costs associated with seeking care for the oral condition. The fourth section collected data on the indirect costs of seeking care. The time lost due to illness and the time lost by caregivers were collected (travel time, waiting time, lost workdays). All costs were measured from the patient's perspective. The final part covered intangible costs, which measured the level of pain and emotional suffering when receiving oral healthcare. Intangible costs were measured using a 5-point Likert scale (1 = Strongly Disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly Agree). The questionnaire captured comprehensive data on the costs, focusing on events and costs incurred over the previous 12 months.

### Data processing and analysis

The data collected was entered into Microsoft Excel 2016, checked, and cleaned. Data was imported into STATA version 16 for further analysis. Descriptive statistics such as means, standard deviations, and proportions were used to summarise socio-demographic data and cost-related information. All costs were calculated in both Ghanaian cedis (GHS) and US dollars (US$), using the Bank of Ghana's interbank exchange rate of US$ 1 = GHS 12 (as of March 10, 2023).

### Economic cost estimation

#### Total economic cost

The outcome variable "total economic cost" was estimated by summing all direct and indirect costs of oral care.

### Direct cost estimation

The total direct cost was estimated by summing both medical and non-medical costs incurred by the patients. Direct medical costs comprised consultation fees, diagnostic tests, treatments and medications. The direct non-medical costs comprised transportation, food and drinks, accommodation for accompanying relatives and communication costs. The average direct cost was estimated by dividing the overall direct cost by the total number of participants.

### Indirect cost estimation

Indirect costs were estimated using the human capital approach (HCA), which assigns monetary value to time lost due to illness. These costs comprised productivity loss for patients and their accompanying caregivers, estimated based on the number of workdays lost, travel time, and waiting time. Workdays lost were defined as the total number of working days lost by employed patients during diagnosis and treatment. Productivity loss due to travel was calculated by summing the total time spent by patients and their relatives commuting to and from the hospital. Productivity loss due to waiting time was based on the average time spent waiting for oral care services at the hospital. The total waiting time was multiplied by Ghana's minimum wage of GHS13.53 (as of 2022) to estimate the monetary value. The total indirect cost was calculated by aggregating productivity losses for patients and caregivers.

### Intangible cost

A five-point Likert scale was used to describe intangible costs rather than assign monetary value to them. There were five different responses: "strongly disagree," "disagree," "neutral," "agree," and "strongly agree." Patients reported emotional and physical discomfort, speaking difficulty, changes in eating habits, persistent worry about their oral condition, difficulty smiling, and avoiding social situations because of dental disease. These responses were summarised as percentages and presented descriptively.

### Sensitivity analyses

A one-way and multi-way sensitivity analysis was conducted. Wages and medication costs were varied by +3%, +5%, and +7% to evaluate their impact on overall cost estimates. These key variables were used in the sensitivity analyses due to the uncertainty associated with them.

## RESULTS

### Socio-demographic characteristics of respondents

A total of 224 patients participated in the study, with more than half (58.0%) being males. The mean age of participants was 37.9 (± 13.4) years. Approximately 36% of the participants had completed tertiary education, while over half (53.6%) of the participants were unmarried, and 73.7% of the participants were employed. About 90% of participants had a valid National Health Insurance Scheme (NHIS) card.

### Oral conditions and type of treatment

Table 1 presents the various oral conditions experienced by the participants, along with the type of treatment received. Dental caries was the most prevalent oral condition (54.4%), while oral cancers were the least prevalent (1.8%) among participants. In relation to the type of treatment, extraction was the most common (31.7%), while root canal therapy was the least common (1.8%) among study participants.

### Economic cost of oral health services

#### Direct cost of oral health services

As shown in Table 2, the total direct cost of oral care was approximately GHS 477,116.50 (US$ 39,759.71) for the 12-month period. The direct cost comprised medical and non-medical costs, estimated at GHS 445,348.00 (US$ 37,112.33) and GHS 31,768.50 (US$ 2,647.38), respectively. The average direct medical costs for registration and consultation was GHS 55.38 (US$ 4.62), diagnostics were GHS 274.24 (US$ 22.85), treatment was GHS 1,472.12 (US$ 122.68), and medication was GHS 186.42 (US$ 15.54). The average direct non-medical costs were highest for transportation at GHS 121.02 (US$ 10.09), followed by food at GHS 14.96 (US$ 1.25), and drinks and water at GHS 5.85 (US$ 0.49). On average, a patient spent an estimated GHS 2,129.98 (US$ 177.50) as a direct cost

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on oral health services, of which medical costs constituted 93.4% in the past 12 months.

Table 1. Oral conditions of Participants and type of treatment received

| Oral Condition | Frequency | Percentage (%) |
|---|---|---|
| Dental caries (Apical periodontitis, reversible pulpitis, irreversible pulpitis, class 1 cavity) | 122 | 54.4 |
| Gingivitis | 33 | 14.7 |
| Periodontitis | 10 | 4.5 |
| Impacted tooth/pericoronitis | 6 | 2.7 |
| Oral cancers | 4 | 1.8 |
| Complicated crown fracture | 15 | 6.7 |
| Partial edentulism | 13 | 5.8 |
| Others e.g., Ameloblastoma, mandibular fracture, Keloid. | 21 | 9.4 |
| Type of treatment | | |
| Scaling and polishing/cleaning | 32 | 14.3 |
| Dentures | 13 | 5.8 |
| Medications | 46 | 20.5 |
| Biopsy | 5 | 2.2 |
| Extraction | 71 | 31.7 |
| Crown | 7 | 3.1 |
| Fillings | 38 | 17.0 |
| Root canal therapy | 4 | 1.8 |
| Surgery under general anaesthesia | 8 | 3.6 |

**Indirect cost of oral health services**

The total indirect cost of oral health services was GHS 55,037.56 (US$ 4,586.46) in the past 12 months. The total productivity loss for the patient was GHS 27,747.55 (approximately US$ 2,312.30), while caregivers recorded a loss of GHS 27,290.01 (approximately US$ 2,274.17). Also, on average, the patients' estimated cost of days absent from work was GHS 50.98 (US$ 4.25), the period of travelling to and from the health facility was GHS 61.12 (US$ 5.09), and the waiting time to be attended by a dentist was GHS 11.78 (US$ 0.98) (Table 3). Furthermore, on average, caregivers estimated the cost of days absent from work at GHS 8.82 (US$ 0.74) over the past 12 months, and the cost of travelling to and from the health facility was GHS 113.01 (US$ 9.42). On average, a patient spent an estimated GHS 245.70 (US$ 20.48) as a total indirect cost on oral health services, of which patient productivity lost constituted 50.4%. The estimated total economic cost of oral health services was GHS 532,154.06 (US$ 44,346.17) over the 12-month period. Thus, most of the cost of oral health services (89.7%) was direct costs, while 10.3% was attributed to indirect costs.

**Sensitivity analysis of the cost of oral health services**

The one-way and multi-way sensitivity analyses of cost were conducted using the costs of medication and wages. A definite increase in the cost of medication also leads to a rise in total cost. As shown in Table 4, a 3% increase in medication leads to a 0.24% increase in total cost. Similarly, a 5% and 7% increase in medication costs over a

Table 2. Direct Cost Estimates

| Costs | Sum GHS (US$) | Mean GHS (US$) | SD GHS (US$) | Min GHS (US$) | Max GHS (US$) | Cost Profile (%) |
|---|---|---|---|---|---|---|
| Direct Medical | | | | | | |
| Registration & Consultation | 12,405.00 (1033.75) | 55.38 (4.62) | 22.93 (1.91) | 0.00 (0.00) | 130.00 (10.83) | 2.6 |
| Diagnostics | 61,430.00 (5,119.17) | 274.24 (22.85) | 644.67 (53.72) | 40.00 (3.33) | 5,000.00 (416.67) | 12.9 |
| Treatment | 329,755.00 (27,479.58) | 1,472.12 (122.68) | 8,182.81 (681.90) | 59.00 (4.92) | 120,000.00 (10,000.00) | 69.1 |
| Medication | 41,758.00 (3,479.83) | 186.42 (15.54) | 428.27 (35.69) | 10.00 (0.83) | 4,000.00 (333.33) | 8.8 |
| Total direct medical | 445,348.00 (37,112.33) | 1,988.16 (165.68) | 8484.15 (707.01) | 199.00 (16.58) | 121,620.00 (10,135.00) | 93.4 |
| Direct non-medical | | | | | | |
| Transportation | 27,108.00 (2,259.00) | 121.02 (10.09) | 220.33 (18.36) | 0.00 (0.00) | 1,440.00 (120.00) | 5.7 |
| Food | 3,350.00 (279.17) | 14.96 (1.25) | 10.80 (0.9) | 0.00 (0.00) | 68.00 (5.67) | 0.7 |
| Drinks and Water | 1,310.50 (109.21) | 5.85 (0.49) | 4.01 (0.33) | 0.00 (0.00) | 20.00 (1.67) | 0.3 |
| Total Direct non-medical | 31,768.50 (2,647.38) | 141.82 (11.82) | 221.24 (18.44) | 0.00 (0.00) | 1,455.00 (121.25) | 6.6 |
| Total Direct | 477,116.50 (39,759.71) | 2,129.98 (177.50) | 8,545.26 (712.11) | 238.00 (19.83) | 122,111.00 (10,175.92) | 100.0 |

Note: SD = Standard Deviation, Min = Minimum Value, Max = Maximum Value

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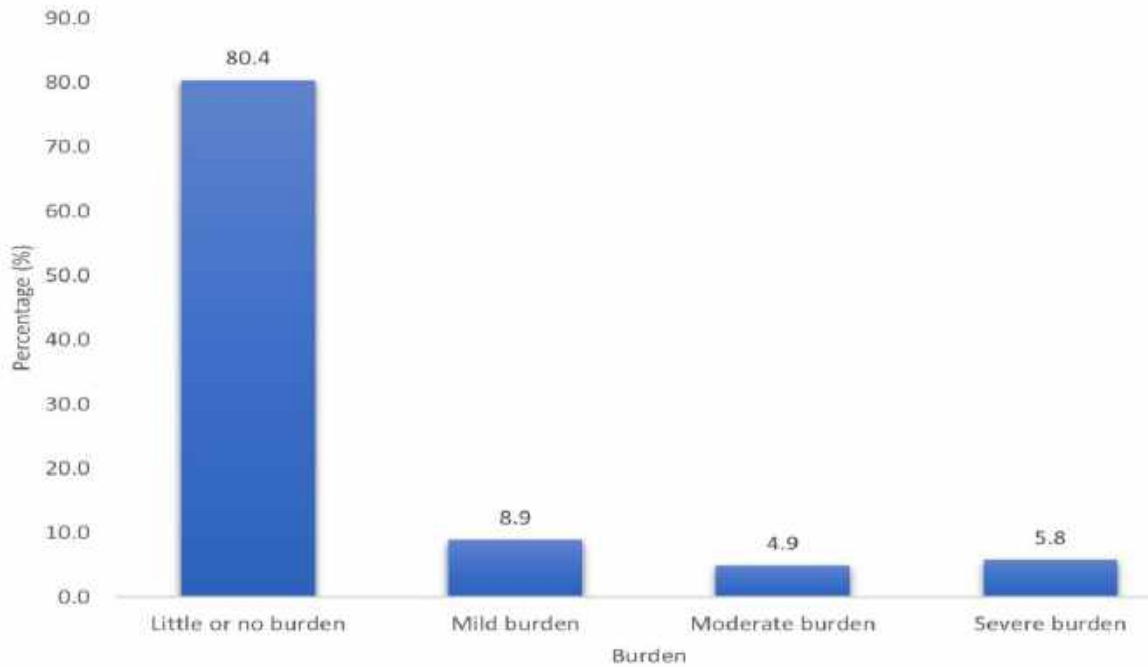


Figure 1. Intangible burden on patients

Table 3. Indirect cost estimates

| Costs | Sum GHS (US$) | Mean GHS (US$) | SD GHS (US$) | Min GHS (US$) | Max GHS (US$) | Cost Profile (%) |
|---|---|---|---|---|---|---|
| Patient Indirect | | | | | | |
| Days absent from work | 11,419.32 (951.61) | 50.98 (4.25) | 108.51 (9.04) | 0.00 (0.00) | 811.80 (67.65) | 20.75 |
| Traveling time | 13,690.33 (1,140.86) | 61.12 (5.09) | 62.93 (5.24) | 3.38 (0.28) | 649.44 (54.12) | 24.87 |
| Waiting time | 2,637.90 (219.83) | 11.78 (0.98) | 6.62 (0.55) | 0.23 (0.02) | 40.59 (3.38) | 4.79 |
| Total patient indirect | 27,747.55 (2,312.30) | 123.88 (10.32) | 148.35 (12.36) | 10.82 (0.90) | 1,068.87 (89.07) | 50.4 |
| Relatives/friends Indirect | | | | | | |
| Days absent from work | 1,975.38 (164.62) | 8.82 (0.74) | 23.78 (1.98) | 0.00 (0.00) | 189.42 (15.79) | 3.6 |
| Traveling time | 25,314.63 (2,109.55) | 113.01 (9.42) | 68.97 (5.75) | 13.53 (1.13) | 676.50 (56.38) | 46.0 |
| Total Relatives/friends Indirect | 27,290.01 (2,274.17) | 121.83 (10.15) | 73.31 (6.11) | 13.53 (1.13) | 744.15 (62.01) | 49.6 |
| Total Indirect | 55,037.56 (4,586.46) | 245.70 (20.48) | 200.38 (16.70) | 31.57 (2.63) | 1,813.02 (151.09) | 100.0 |

Note: SD = Standard Deviation, Min = Minimum Value, Max = Maximum Value

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Table 4. Sensitivity analysis of the cost of oral health services

| | | | | | % of the total cost | | % change in the total cost | |
|---|---|---|---|---|---|---|---|---|
| | Cost component GHS (US $) | % change in parameter | Total cost GHS (US$) | % change in the total cost | Direct | Indirect | Direct | Indirect |
| Scenario | | | | | | | | |
| Basic Scenario | | 0 | 532,154.06 (44,346.17) | | 89.7 | 10.3 | 0 | 0 |
| Variation (One-way sensitivity analysis) | Medication | | | | | | | |
| | 41,758.00 (3,479.83) | 3 | 533,406.80 (44,450.57) | 0.24 | 89.7 | 13.3 | 0.0 | 29.1 |
| | | 5 | 534,241.96 (44,520.16) | 0.39 | 89.7 | 15.3 | 0.0 | 48.5 |
| | | 7 | 535,077.12 (44,589.76) | 0.55 | 89.7 | 17.3 | 0.0 | 68.0 |
| Variation (One-way sensitivity analysis) | Wage rate | | | | | | | |
| | 11,419.32 (951.61) | 3 | 532,496.64 (44,374.72) | 0.06 | 92.6 | 13.3 | 3.2 | 29.1 |
| | | 5 | 532,725.03 (44,393.75) | 0.10 | 94.6 | 15.3 | 5.5 | 48.5 |
| | | 7 | 532,953.41 (44,412.78) | 0.15 | 96.5 | 17.3 | 7.6 | 68.0 |
| Multi-way sensitivity analysis) | Medication & Wage rate | | | | | | | |
| | 53,177.32 (4,431.44) | 3 | 533,749.38 (44,479.12) | 0.30 | 92.4 | 13.3 | 3.0 | 29.1 |
| | | 5 | 534,812.93 (44,567.74) | 0.50 | 94.2 | 15.3 | 5.0 | 48.5 |
| | | 7 | 535,876.47 (44,656.37) | 0.70 | 96.0 | 17.3 | 7.0 | 68.0 |

Note: USD 1.00 equivalent to GHS 12 (Bank of Ghana interbank exchange rate, 10 March 2023).
The national minimum wage per day of GHS13.53 (US $ 1.13) as of December 2022 was used to value productivity days and time lost to patients.

Table 5. The various burdens experienced by the study participants

| Burden | SD n (%) | D n (%) | N n (%) | A n (%) | SA n (%) |
|---|---|---|---|---|---|
| Severe Pain | 91 (40.6) | 81 (36.1) | 6 (2.7) | 17 (7.6) | 29 (13.0) |
| Difficulty smiling | 41 (18.3) | 151 (67.4) | 6 (2.7) | 11 (4.9) | 15 (6.7) |
| Change Diet | 96 (42.9) | 98 (43.8) | 5 (2.2) | 11 (4.9) | 14 (6.2) |
| Always worried about the condition | 55 (24.6) | 136 (60.7) | 15 (6.7) | 5 (2.2) | 13 (5.8) |
| Are embarrassed to smile in social situations | 43 (19.2) | 148 (66.1) | 13 (5.8) | 5 (2.2) | 15 (6.7) |
| Difficulty in speaking | 50 (22.3) | 147 (65.7) | 5 (2.2) | 9 (4.0) | 13 (5.8) |
| Sleepless nights | 88 (39.3) | 93 (41.5) | 13 (5.8) | 13 (5.8) | 17 (7.6) |
| Low self-confidence | 31 (13.8) | 153 (68.3) | 23 (10.3) | 2 (0.9) | 15 (6.7) |
| Avoid the company of others | 31 (13.8) | 160 (71.4) | 15 (6.7) | 2 (0.9) | 16 (7.2) |

Note: n = Frequency, SD = Strongly Disagree, D = Disagree, N = Neutral, A = Agree, SA = Strongly Agree

year results in a 0.39% and 0.55% increase in total cost, respectively. When the wages were increased by 3%, the economic cost of oral health services increased by 0.06%. The direct cost increased by 0.0% (thus from 89.7% to 89.7%), and the indirect cost component decreased by 29.1% (thus from 10.3% to 13.3%) when varied by 3%.

**Intangible Cost**

More than 50% of the participants either disagreed or strongly disagreed with experiencing severe pain, difficulty smiling, changing diet, worrying about the condition always, feeling embarrassed to smile in social situations, having difficulty speaking, sleepless nights, low self-confidence and avoiding the company of others (Table 5). Figure 1 shows the overall intangible burden among patients. Most patients (80.4%) experienced little to no burden. Approximately 9% of patients had a mild burden, while only 4.9% and 5.8% had moderate and severe burdens, respectively.

## DISCUSSION

The provision of oral health care in Ghana exerts a substantial financial burden on the patients. The study's findings indicate that patients encounter a substantial financial burden when seeking oral health services. The average direct cost incurred over a 12-month period was GHS 2,129.98, which was equivalent to US$ 177.50. The average direct cost in this study is higher than the cost of US$ 33.78 reported in another study in Ghana [15]. The study site in this current study is a tertiary facility that treats more advanced oral health conditions, which could be a contributing factor to the observed difference. In Sonoma County, United States, a study reported an average direct cost of US$283 for the prevention and early treatment of dental disease [17]. The average cost reported in the United States was higher than the average costs in this study. Authors noted in a global cross-region and country analysis that the highest levels of expenditure on dental conditions were reported in high-income countries in North America, Australia, Western Europe and East Asia (18). The average medical cost in this study was estimated to be GHS 1,988.16 (approximately US$ 165.68), which exceeds the average medical cost of US$ 29.33 in the United States [17]. Meanwhile, the average non-medical cost was GHS 141.82 (approximately US$ 11.82). The findings of this study indicate that direct costs were the largest proportion of overall expenditures, aligning with previous studies in Ghana [15] and other countries [18]. While the present study, along with previous studies on the cost of oral diseases [15], focused on estimating the costs associated with oral health services as perceived by patients, Warmerdam et al. [17] investigated a broader societal viewpoint by considering costs borne by both patients and healthcare providers [17]. Furthermore, it should be noted that the costs estimated in the present study were calculated on a monthly basis, whereas Deh et al. [15] and Warmerdam et al. [17] conducted their analyses over a period of ten days and one year, respectively [15,17]. Thus, the disparities observed can be ascribed to the varying sampling time in these investigations.

The findings of this study indicate that most patients seek medical care at the hospital for curative procedures, such as medication, extraction, and filling, which are associated with higher direct costs compared to indirect costs. This finding is consistent with previous studies [15,16], which indicate that a significant proportion of individuals seeking oral health care received therapeutic interventions such as medication, tooth extraction, and dental fillings. This implies that the expenses associated with oral health treatments in Ghana are substantial, potentially resulting in a considerable economic strain on households. Studies have noted that out-of-pocket expenses on oral health care are among the main drivers of catastrophic health expenditures [19,20]. A study in Ghana explained that the absence of a comprehensive national oral health preventative programme may lead to the emergence of elevated treatment costs, as evidenced in this study [15]. Given the prevailing daily minimum wage of GHS 13.35 (approximately US$1.12), it is evident that many households with limited incomes may face significant financial burdens due to oral disorders, as indicated by the average treatment cost of GHS 1,472.12 (approximately US$122.68) observed in this study. On average, the per-patient annual indirect cost of oral healthcare amounted to GHS 245.70 (approximately US$ 20.48). The indirect cost recorded in this study is more than 20 times the mean indirect cost of GHS 8.12 (US$ 0.68)reported in a previous study in Ghana [15]. This cost variation may be attributed to the characteristics of the research location, which offers a limited range of services and encounters a lower volume of complex patients compared to a tertiary hospital setting. In the present study, a proportion of patients expressed dissent about modifying their dietary habits. They consistently reported feelings of anxiety, embarrassment in social interactions, impaired speech, diminished self-esteem, and a tendency to isolate themselves due to their oral health issues. This finding affirms that most patients who utilise oral health services encounter minimal to moderate levels of burden. Patients' experience of a minimal to moderate burden can be attributed to the fact that a proportion of them seek treatment, such as medication, extraction, and filling, at the oral health department. Patients who seek surgical procedures at the oral health department tend to feel a higher level of pain in comparison to those who visit for routine procedures such as polishing or cleaning. The present observation aligns with previous findings wherein a subgroup of patients had challenges in executing the act of smiling [21].

The present study revealed a statistically significant disparity between the average indirect costs incurred by employed patients and those incurred by unemployed patients. This phenomenon can be attributed to the fact that working individuals may experience a greater degree of productivity loss due to their absence from work compared to individuals who are unemployed. This is also evidenced in studies in Japan [22,23] and Canada [24]. According to the study's findings, the mean number of days lost over the 12-month period seeking care for the disease was 3.8 days. The observed value exceeded the productivity loss of 1.6 days reported by Deh et al. [15]. Studies on oral disease and productivity loss have reported that there exists a correlation between inadequate dental health and reduced work hours, potentially impacting an individual's overall productivity [22,23]. This association has also been reported in the United States [25]. In Southern Brazil, these associations were reported, with a linkage between poor oral health and poor academic performance and absenteeism [26]. There is, thus, a need for evidence-informed policymaking on oral health [27] to mitigate excessive out-of-pocket payments, leading to catastrophic health expenditures, and to increase productivity.

### Strengths and limitations

The study, conducted in Ghana's largest referral hospital, ensured a representative sample of individuals from diverse

areas and broadened the analysis by including intangible costs. However, the single facility may limit generalizability. Recalling bias could have affected the accuracy of data from the past 12 months. Using the daily minimum wage instead of actual income could lead to an underestimation of the true economic cost of oral care. The study's cross-sectional design limits the ability to establish causality. These limitations, however, do not negatively impact the overall findings.

### Conclusion

The study highlights a substantial economic burden of oral healthcare in Ghana, with direct medical costs, particularly treatment and diagnostics, being the largest expense for patients. Indirect costs, though smaller, also contribute to the overall burden on both patients and caregivers. To address these issues, policies should aim to expand the scope of oral health disorders under the National Health Insurance Scheme, which will help reduce treatment costs and improve access. Further studies are necessary to track the economic burden over time and identify cost-effective strategies for oral healthcare in low- and middle-income countries.

## DECLARATIONS

### Ethical consideration

The study obtained ethical approval from the Korle Bu Teaching Hospital Scientific and Technical Committee/Institutional Review Board (KBTH STC/IRB/000174/2022). The informed consent process was carefully designed to ensure participants fully understood the study's purpose, procedures, risks, and benefits. Participants were provided with a detailed explanation of the study in either English or their preferred local language. For those unable to read or write, the consent form was explained by a research assistant or a witness. Participants were allowed to ask questions and clarify doubts before providing consent. Two copies of the signed or thumb-printed consent form were provided, one for the participant to keep and one for the research team. Participants were assured that their participation was voluntary and that they could withdraw from the study at any time without any consequences. All data collected was anonymised and securely stored to protect participant confidentiality.

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest

### Author contribution

MT, RO, and MOB conceived the study. MT, RO, and IA designed the study and data collection instruments, and SAB and MOB supervised data collection. MT, RO, and DDO contributed to data analysis. MT, SAB, IA and DDO drafted the manuscript. All authors reviewed and approved the final manuscript.

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### Availability of data

Data is available upon request to the corresponding author

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# Efficacy of anthropometric measures in predicting hypertension among adult Ghanaians: A community-based cross-sectional study

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**Abstract**

***Background:*** As global rates of hypertension continue to rise, especially in developing countries, there is an urgent need for effective screening tools. Anthropometry offers a practical approach to assessing the risks associated with hypertension due to its simplicity and cost-effectiveness.

***Objective:*** This study aimed to evaluate the efficacy of waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR) and body mass index (BMI) in predicting hypertension among adults in the Cape Coast metropolis in Ghana.

***Methods:*** This analytical cross-sectional study involved 390 adults from three local communities. Anthropometric data were collected using standardised equipment, and hypertension was defined based on the WHO blood pressure classification. The validity of the anthropometric measures was assessed using positive predictive value (PPV) and negative predictive value (NPV), as well as specificity and sensitivity. IBM SPSS version 26 was used for statistical analyses. Chi-square and linear regression models were used to determine the associations between anthropometric measures and hypertension.

***Results:*** Among 390 participants (mean age: 34.6 ± 13.8 years; 50% female), WC and WHtR were significantly associated with hypertension (WC: β = 0.256, 95% Confidence Intervel [CI]: 0.173 - 0.445, p = 0.011; WHtR: β = 0.310, 95% CI: 0.210 - 0.458, p = 0.024), whereas body mass index (BMI) was not (β = 0.034, p = 0.466). WHtR demonstrated the highest sensitivity (88.4%), while WC had the highest specificity (81.7%) for predicting hypertension.

***Conclusion:*** This study highlights the importance of WC and WHtR as valuable and effective anthropometric measures for predicting hypertension in a clinical setting. Incorporating these measures into routine health assessments could enhance the early detection and management of hypertension, thereby contributing to better public health outcomes. Further research is needed to confirm these findings in diverse populations and longitudinal studies.

**Keywords:** Anthropometry, hypertension, waist circumference, waist-to-height ratio, public health

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## INTRODUCTION

Obesity is increasingly recognised as a significant chronic health condition that greatly contributes to both morbidity and overall mortality rates [1]. This is particularly concerning as the incidence of obesity in some developing nations surpasses that in developed countries, and continues to escalate rapidly [2]. Given the critical health implications of obesity, it is essential to have reliable methods for measuring body composition, which is a focal point of epidemiological, clinical, and population studies

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[3]. Although advanced imaging techniques like dual-energy x-ray absorptiometry, magnetic resonance imaging, and computed tomography offer accurate measurements, anthropometry remains the most widely utilised method due to its portability, non-invasiveness, cost-effectiveness, and suitability for field studies [4,5].

Despite the availability of more precise techniques, these are often unsuitable for general use due to high costs and risk factors and are therefore reserved for specific research contexts [5]. Consequently, simple anthropometric measures serve as practical proxies for assessing obesity in clinical settings and large-scale epidemiological studies [5]. The Body Mass Index (BMI), which correlates weight with height, is the simplest and most prevalent obesity metric [5]. Although a high BMI is directly associated with increased risks of cardiovascular disease (CVD) and hypertension [5], it does not reflect variations in body fat distribution, particularly abdominal fat, which can significantly differ among individuals and within narrow BMI ranges [6]. Research has shown that cardiovascular risk factors such as hypertension, lipid levels, and glucose concentrations have a stronger association with abdominal adiposity, measured through waist circumference (WC) and waist-to-hip ratio (WHR), than with overall adiposity indicated by BMI [7]. Despite this, BMI remains a critical indicator for major health issues like type 2 diabetes and hypertension [2]. As a result, both WC and WHR are extensively used in clinical and research settings to provide a clearer picture of intra-abdominal and total body fat [8].
Further complicating the evaluation of obesity's impact on health are the differential effects of fat distribution. Upper-body obesity is more often associated with adverse cardiovascular and metabolic outcomes than lower-body obesity [9]. The challenge remains in determining the most effective cut-off points for WC and WHR to identify at-risk individuals. Proposals vary, with some suggesting gender-specific cut-offs based on BMI-defined overweight and obesity thresholds, while others recommend universal cut-offs that vary by age [5].

Moreover, certain populations, such as Asians, demonstrate higher metabolic and cardiovascular risks at lower BMI thresholds [10]. Hsuan et al. [11] provided evidence that abdominal obesity, rather than overall body mass, significantly contributes to metabolic and cardiovascular risks in this demographic, highlighting the importance of WHR, especially when BMI falls within a normal range. In studies conducted in China, different anthropometric measures were evaluated for their effectiveness in identifying cardiovascular disease (CVD) risk factors [12]. The findings indicated that while BMI and WC were the most effective for men, WC and WHR were more suitable for women [12, 13]. This underscores the necessity of using tailored anthropometric measurements that reflect both general and central obesity to enhance the predictive accuracy of nutrition-related non-communicable diseases (NR-NCDs) such as hypertension.

Given the complexities of determining the most effective anthropometric measure for predicting NR-NCDs, ongoing research comparing WHR and BMI is essential. Such research is crucial to ascertaining which method best predicts the individuals at greatest risk of NR-NCDs, thus aiding in the early detection and management of these diseases. Nutritionists, dietitians, public health practitioners, and other stakeholders must understand which measurement is more relevant for early detection and intervention. Therefore, this study aims to assess the efficacy of WHR, WHtR, WC and BMI as predictors of hypertension among adults in the Cape Coast Metropolis, providing critical data to inform public health strategies and improve health outcomes in the region.

## MATERIALS AND METHODS

### Study design and location

This community-based analytical cross-sectional study was conducted in the Cape Coast Metropolis, which serves as the regional capital of the Central Region of Ghana. Cape Coast spans an area of 122 square kilometres. Data collection occurred from June 5, 2020, to July 28, 2020, involving 390 randomly selected adult participants aged 18 years and older. These participants were from three communities within the metropolis: Amamoma, Kwaprow, and Abura, comprising 195 females and 195 males.

### Study population and sampling procedure

A convenience sampling approach was used, with an added element of randomness. All seats at the screening centres in the three selected communities were numbered, and a subset of seats was randomly tagged. Adults who were present, sat on tagged seats, and consented to participate were included in the study.

### Anthropometric measurements and data collection

Anthropometric data were collected using standard equipment. Participants' height and weight were measured with a stadiometer and a weighing scale, respectively, after they had removed their footwear and any heavy clothing. The Omron BF-511 full-body sensor body composition monitor and scale were utilised to assess BMI. Waist and hip circumferences were measured with a non-stretchable tape. Additionally, a structured questionnaire was used to obtain demographic information from the subjects.

### Measurement and definition of hypertension

Blood pressure (BP) measurements were taken using a mercury sphygmomanometer (Reishter, Germany) tailored to the arm circumference of the subjects by a skilled nurse. Participants were seated, having rested for 10 minutes, and were instructed to abstain from smoking or consuming caffeine for at least 30 minutes prior to blood pressure measurement, which was in line with standard WHO recommendations. Two consecutive BP readings were taken 10 minutes apart, during which participants remained seated with their left hand at heart level and palms facing upward. The average of these two measurements was

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recorded as the final BP. Hypertension was defined based on the first Korotkoff sound (systolic blood pressure, SBP) and the disappearance of the last Korotkoff sound (diastolic blood pressure, DBP), with thresholds set at SBP > 140 mmHg or DBP > 90 mmHg. In addition, individuals who self-reported current use of antihypertensive medication were classified as hypertensive, regardless of their measured blood pressure.

**Data analysis**

The data analysis was conducted using IBM SPSS version 26.0 software (Chicago, Illinois, USA). Categorical variables were presented as percentages, and continuous variables were expressed as means ± standard deviations. The Chi-square test was utilised to analyse the association between anthropometric parameters and hypertension. Additionally, linear regression analysis was employed to evaluate the impact of various anthropometric indicators on blood pressure. Sensitivity, specificity, positive predictive value, negative predictive value, and relative risk were computed for each anthropometric variable using cross-tabulation and standard formulas for diagnostic test evaluation. All tests were considered significant at a p-value of less than 0.05.

## RESULTS

Gender distribution was even, with each sex constituting 50% (195 individuals) of the sample (Table 1). Age-wise, the sample was predominantly youthful, with the 18 - 29 years age group representing the largest segment at 39.4% (154 individuals). The age group with the least number of participants was 70 - 89 years (10.7%). A significant majority, 57.2% (223 individuals), had attained higher education, underscoring a well-educated demographic. Occupational data revealed a diverse economic background among the participants. Civil servants formed the largest group at 43.1% (n = 168), reflecting strong public sector employment. This was followed by self-employed individuals at 20.3% (n = 79), traders at 19.0% (n = 74), and farmers at 17.7% (n = 69). With regard to marital status, over half of the participants were single, accounting for 54.1% (n = 211).

**Anthropometric and clinical characteristics of the respondents**

Table 2 summarises the anthropometric and clinical characteristics of the study participants. The average height and weight were 1.65 ± 0.10 m and 64.00 ± 12.50 kg, respectively. Participants had a mean body mass index (BMI) of 23.80 ± 5.00 kg/m², waist circumference of 88.50 ± 15.00 cm, and hip circumference of 95.20 ± 15.00 cm. The average waist-to-hip ratio was 0.95 ± 0.10, while the waist-to-height ratio was 0.56 ± 0.10. Mean systolic and diastolic blood pressure values were 135 ± 25 mmHg and 84 ± 12 mmHg, respectively. Males exhibited slightly higher values in terms of height, WHtR, and WHR ($p < 0.05$).

**Prevalence of hypertension**

Figure 1 illustrates the prevalence of hypertension among respondents, categorised by gender. Of the respondents, 25.38% were hypertensive. The graph indicates that 73.33% of the females were normotensive and 26.67% were hypertensive. In comparison, the male population showed a slightly higher percentage of normotensive individuals at 75.9%, with 24.1% being hypertensive.

**Association between anthropometric measurements and hypertension**

Table 3 presents the results of a chi-square analysis examining the relationship between various anthropometric

Table 1. Socio-demographic characteristics

| Characteristic | Frequency (n) | Percentage (%) |
|---|---|---|
| Sex | | |
| Female | 195 | 50.0 |
| Age group | | |
| 18-29 years | 154 | 39.4 |
| 30-49 years | 126 | 32.2 |
| 50-69 years | 69 | 17.6 |
| 70-89 years | 42 | 10.7 |
| Educational Level | | |
| None | 48 | 12.3 |
| Primary | 29 | 7.4 |
| Middle/JHS | 34 | 8.7 |
| Secondary/SHS | 56 | 14.4 |
| Higher | 223 | 57.2 |
| Occupation | | |
| Civil Servant | 168 | 43.1 |
| Farming | 69 | 17.7 |
| Trading | 74 | 19.0 |
| Self-employed | 79 | 20.3 |
| Marital Status | | |
| Married | 142 | 36.4 |
| Divorced | 7 | 1.8 |
| Widowed | 30 | 7.7 |
| Single | 211 | 54.1 |

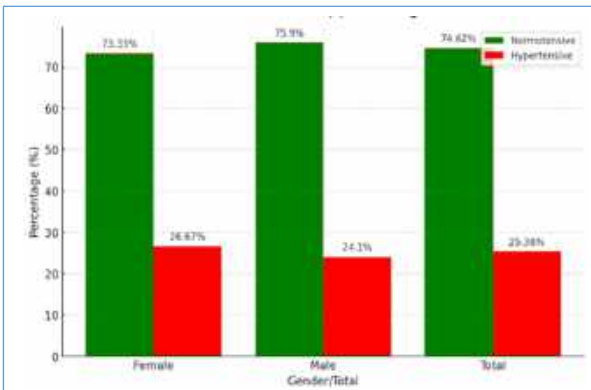


Figure 1. Prevalence of normotension and hypertension by gender

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parameters (WC, WHR, WHtR, and BMI) and hypertension. The chi-square test indicates a statistically significant association ($p < 0.05$) between these anthropometric variables and hypertension.

**Linear regression analysis of the relationship between anthropometric measurements and hypertension**

Table 4 presents the results of a linear regression analysis examining the relationship between various anthropometric measurements and hypertension. The data indicated that only WC and WHtR show significant associations with hypertension ($p = 0.011$ and $p = 0.024$, respectively), while WHR and BMI were not statistically significant ($p = 0.458$ and $p = 0.466$, respectively). Specifically, the WC variable had a standardised coefficient of 0.293. WHtR showed a stronger association, with a standardised coefficient of 0.325. Both variables had statistically significant t-values, indicating a strong influence on the likelihood of hypertension. Conversely, WHR and BMI did not show statistically significant associations with hypertension. This suggests that they are not reliable predictors of hypertension in this analysis.

Table 2: Anthropometric and clinical characteristics of the respondents

| Variables | General (n = 390) | Male (n = 195) | Female (n = 195) | t-statistic | p-value |
|---|---|---|---|---|---|
| Height (m) | 1.65 ± 0.10 | 1.70 ± 0.12 | 1.60 ± 0.08 | 9.682 | 0.007 |
| Weight (kg) | 64.00 ± 12.50 | 68.00 ± 14.00 | 60.00 ± 11.00 | 6.274 | 0.249 |
| BMI (kg/m²) | 23.80 ± 5.00 | 24.00 ± 5.50 | 23.60 ± 4.50 | 0.786 | 0.432 |
| Waist Circumference (cm) | 88.50 ± 15.00 | 89.00 ± 16.00 | 88.00 ± 14.00 | 0.656 | 0.512 |
| Hip Circumference (cm) | 95.20 ± 15.00 | 94.00 ± 16.00 | 96.40 ± 14.00 | 1.576 | 0.116 |
| Waist-Hip Ratio | 0.95 ± 0.10 | 0.96 ± 0.11 | 0.94 ± 0.09 | 4.965 | 0.044 |
| Waist-Height Ratio | 0.56 ± 0.10 | 0.57 ± 0.11 | 0.55 ± 0.09 | 6.965 | 0.039 |
| SBP (mmHg) | 135 ± 25 | 137 ± 26 | 133 ± 24 | 1.578 | 0.116 |
| DBP (mmHg) | 84 ± 12 | 85 ± 13 | 83 ± 11 | 1.640 | 0.102 |

The table presents detailed comparisons of height, weight, Body Mass Index (BMI), waist and hip circumferences, waist-hip ratio, waist-height ratio, and blood pressure values (both systolic and diastolic) between males and females.
n = number, m = meters, kg = kilogram, cm = centimeter, and mmHg = millimeters of mercury

Table 3: Association between anthropometric measurements and hypertension

| Variables | Categories | Normal (n1 = 291) | Hypertensive (n2 = 99) | $\chi^2$ | P-value |
|---|---|---|---|---|---|
| Waist Circumference (cm) | Normal | 233 | 58 | 15.34 | 0.021 |
| | Abnormal | 58 | 41 | | |
| Hip Circumference (cm) | Normal | 240 | 60 | 12.76 | 0.052 |
| | Abnormal | 51 | 39 | | |
| Waist-Hip Ratio | Normal | 247 | 64 | 18.89 | 0.009 |
| | Abnormal | 44 | 35 | | |
| Waist-Height Ratio | Normal | 251 | 69 | 13.55 | 0.033 |
| | Abnormal | 40 | 30 | | |

*Chi-Square ($\chi^2$) Analysis of Anthropometric Measurements and Hypertension

Table 4: Linear regression analysis of the relationship between anthropometric measurements and hypertension

| model | Unstandardized | | Standardized Coefficients | | | |
|---|---|---|---|---|---|---|
| | B | S.E. | B | t | 95% CI | P-value |
| Constant | 0.612 | 0.113 | — | 4.59 | 0.295 – 0.743 | 0.031 |
| WC | 0.299 | 0.069 | 0.256 | 4.48 | 0.173 – 0.445 | 0.011 |
| WHR | -0.054 | 0.040 | -0.045 | -0.57 | -0.152 – 0.084 | 0.458 |
| WHtR | 0.388 | 0.063 | 0.310 | 5.33 | 0.210 – 0.458 | 0.024 |
| BMI | 0.039 | 0.062 | 0.034 | 0.56 | 0.157 – 0.087 | 0.466 |

*The table provides a regression analysis summary with coefficients for different anthropometric measures (WC, WHR, WHtR, BMI) and a constant. Each model parameter includes an unstandardized coefficient (B), standard error (S.E.), standardised coefficient (Beta), t-statistic, 95% confidence interval (CI), and p-value. WC = waist circumference, WHR = waist-hip-ratio, WHtR = waist-to-height ratio, BMI = body mass index

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Table 5: Specificity, sensitivity, predictive values, and relative risk

| Parameters | SEN | SPE | PPV | NPV | OR |
|---|---|---|---|---|---|
| BMI | 34.2 | 76.95 | 49.4 | 65.55 | 1.596 |
| WHR | 62.7 | 57 | 46.55 | 71.25 | 1.862 |
| WC | 57.95 | 81.7 | 68.4 | 75.05 | 3.23 |
| WHtR | 88.35 | 46.55 | 49.4 | 87.4 | 6.175 |

The table presents diagnostic accuracy parameters for four anthropometric measures: BMI, WHtR, WC, and WHR. Each measure is evaluated by its Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Odds Ratio. WC = waist circumference, WHR = waist-hip-ratio, WHtR = waist-to-height ratio, BMI = body mass index, SEN = sensitivity, SPE = specificity, PPV = positive predictive value, NPV = negative predictive value and OR = odds ratio.

**Specificity, sensitivity, predictive values, and relative risk**

Table 5 revealed diverse diagnostic efficiencies of anthropometric measures for hypertension. Body Mass Index (BMI) exhibited relatively low sensitivity (34.2%) but higher specificity (76.95%), suggesting it better identified individuals without hypertension. Its moderate predictive values, with a Positive Predictive Value (PPV) of 49.4% and a Negative Predictive Value (NPV) of 65.55%, implied a modest risk increase, indicated by an odds ratio of 1.596. WHR displayed moderate sensitivity (62.7%) and lower specificity (57%), leading to an odds ratio of 1.862, suggesting a higher relative risk. WC showed better specificity (81.7%), high PPV (68.4%), and NPV (75.05%), marking it as a strong predictor. Waist-to-height ratio topped in sensitivity (88.35%) but had the lowest specificity (46.55%), with the highest odds ratio (6.175), thus presenting as the most significant risk indicator.

## DISCUSSION

Hypertension remains a major risk factor for cardiovascular disease and a significant cause of death among adults in Ghana and worldwide, commonly referred to as a silent killer because it frequently goes unnoticed in its early stages or presents without a known cause. When a specific cause, like renal arterial stenosis, is determined, it is termed secondary hypertension. The effects of hypertension, both on individuals and the wider population, are profound; numerous individuals silently succumb to this condition due to late or absent diagnosis and treatment, highlighting the critical need for careful monitoring and prompt intervention [14]. The primary purpose of this study was to evaluate the effectiveness of various anthropometric indices, specifically BMI, WC, WHR, and WHtR, in predicting the risk of hypertension among adults in the Cape Coast Metropolis. By identifying which of these measures most accurately correlates with elevated blood pressure, the study aimed to provide evidence for the integration of practical and cost-effective tools into routine clinical assessments. This objective aligns with the broader public health goal of enhancing early detection and timely intervention for hypertension, especially in resource-limited settings where advanced diagnostic tools may not be readily available.

A study identified WHtR as an effective predictor of hypertension, noting its ability to account for the distribution of abdominal fat, which is closely linked to cardiovascular risk and an important indicator of central obesity[15]. Screening tests confirm WHtR as the superior predictor of hypertension risk [16]. The ability of WHtR to predict cardiovascular risk and hypertension has been highlighted in several studies [5]. A study among Brazilians discovered that WC and BMI are not as good indicators of hypertension as WHtR [17]. This can be attributed to several key factors. Unlike BMI, which reflects general body mass without considering fat distribution, and WC, which does not account for individual height differences, WHtR adjusts WC relative to height. This adjustment allows WHtR to more accurately reflect central (abdominal) adiposity (a stronger predictor of cardiovascular and metabolic risks). Abdominal fat, especially visceral fat, is closely linked to insulin resistance, inflammation, and increased arterial pressure, all of which contribute to hypertension. Therefore, WHtR serves as a better risk indicator by capturing the impact of fat distribution in relation to the body frame, making it more sensitive to cardiovascular risk than BMI or WC alone. This is particularly true when evaluating the distribution of abdominal fat, which is strongly associated with cardiovascular diseases [5,18].

The use of WHtR over other anthropometric measurements is further supported by the Korean ARIRANG study, which showed a substantial correlation between elevated WHtR and an increased risk of hypertension [19]. The importance of WHtR as a simple yet effective method for identifying people at risk of hypertension and related cardiovascular disorders has been severally investigated [5]. Conversely, BMI is significantly less effective in predicting hypertension compared to WC and WHtR. Body mass index, which measures global obesity, does not distinguish between fat and muscle and does not specifically measure central adiposity. The findings from this study, supported by similar hospital and population-based studies, demonstrate that indices of central obesity (WC and WHtR) are more predictive of hypertension risk than BMI. This supports theories of obesity-related hypertension and underscores the value of these anthropometric measurements as screening tools, particularly in a primary care setting [15]. Studies have indicated that WC and WHtR are more predictive of hypertension than BMI [5]. Research has demonstrated that central obesity markers, such as WC and WHtR, are superior to BMI in predicting the risk of hypertension. In contrast to BMI, WHtR exhibited a higher Area Under the Receiver Operating Characteristic (AU-ROC) curve, which suggests that it has a greater predictive potential for hypertension risk, according to the ARIRANG study [19]. Waist-to-height

ratio is a superior test for hypertension prediction because it takes into account the distribution of abdominal fat, which is an important indication of cardiovascular risk [19]. Visceral fat is more strongly associated with hypertension and other cardiovascular disorders. Measurements of central obesity, such as WC and WHtR, are substantially correlated with visceral fat [5,13,19].

The robust predictive capability of WC and WHtR over BMI in determining hypertension underscores the need for healthcare providers, especially those in primary care settings, to incorporate these measurements into routine assessments, as this may enhance the early identification of individuals at higher cardiovascular risk due to central obesity [5, 19]. Additionally, the application of these anthropometric indices aligns with current healthcare strategies aimed at combating cardiovascular diseases through preventive measures. By prioritising the assessment of WHtR and WC, medical practitioners can better target interventions and educate patients on the specific risks associated with abdominal obesity, thus fostering a more informed and health-conscious community [11].

This strategic shift in focus from global to central obesity indicators could also pave the way for more tailored public health initiatives. As the evidence mounts in favour of WHtR and WC as critical markers for hypertension and related cardiovascular risks, health policies might evolve to include these measurements in standard health check-ups and public health screenings. This could potentially lead to earlier intervention and management strategies, which are crucial in mitigating the long-term effects of hypertension and reducing the overall burden of cardiovascular diseases [11]. Moreover, by integrating WHtR and WC into public health programs, educational campaigns can more effectively communicate the specific dangers of central obesity to the broader population. Such targeted education could empower individuals to make informed lifestyle choices that focus on reducing abdominal fat, such as specific dietary adjustments and appropriate physical activities, thus improving overall health outcomes.

### Limitations of the study

The study was conducted in the Cape Coast Metropolis and may not be representative of other regions or populations. This geographical limitation could affect the generalizability of the findings to other settings or ethnic groups, as the sample is confined to a specific locale and demographic. Additionally, the cross-sectional nature of the study limits the ability to establish causality between anthropometric measurements and hypertension. Longitudinal studies would be more effective in determining causal relationships and the dynamics of changes in anthropometric measures and their impact on hypertension over time.

### Strengths of the study

Firstly, the study utilises a robust and detailed methodology for collecting and analysing anthropometric data. The use of standard equipment for measuring height, weight, waist and hip circumferences, and blood pressure ensures accuracy and reproducibility of results. Furthermore, employing statistical tools like chi-square tests and linear regression analysis to evaluate the relationships between anthropometric measurements and hypertension enhances the scientific rigour of the findings. Secondly, the study adheres to strong ethical standards, with approval from the Institutional Review Board and informed consent obtained from all participants. This commitment to ethical research practices not only enhances the integrity of the study but also respects the rights and well-being of the participants. The community-based approach, involving local populations in Cape Coast, fosters community engagement and may improve participant compliance and the relevance of the findings to the local context.

### Conclusion

In conclusion, the findings from this study reinforce the critical role of precise anthropometric assessments in clinical and public health frameworks. By focusing on central obesity measures like WHR, WHtR and WC, healthcare providers can achieve a more accurate and early diagnosis of hypertension, ultimately leading to better preventive care and management of cardiovascular health. This approach enhances individual patient care and contributes to the broader goal of reducing the prevalence and impact of hypertension within communities.

## DECLARATIONS

### Ethical consideration

Ethical approval for this study was obtained from the Institutional Review Board of the University of Cape Coast (UCCIRB/CHAS/2020/07). Informed consent was secured from each participant before their inclusion in the study. All anthropometric measurements adhered to established standard protocols, ensuring the ethical integrity of the research.

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest

### Author contribution

KA and ARA conceptualised and designed the research; KA and ARA implemented the research; SOA, ARA, and IA-M conducted the analysis; KA, SOA, AD, MDA, IA-M and ZH wrote the draft manuscript; all authors reviewed the draft manuscript and approved the final version.

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**Availability of data**

Data is available upon request to the corresponding author

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# Female healthcare professionals' knowledge of vasectomy and attitudes toward partner uptake: A cross-sectional analysis of physicians and nurses

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**Abstract**

***Background:*** Permanent contraception is a key method used by individuals who have completed their families or do not seek to have children. Common methods include bilateral tubal ligation in females and vasectomy in males. Vasectomy involves cutting and sealing each of the vas deferens to prevent sperm movement, leading to sterilisation. Despite being safer, more effective, relatively cheaper, and associated with fewer complications, vasectomy is not as commonly utilised as bilateral tubal ligation. The reasons for this disparity are unclear.

***Objective:*** The study assessed female doctors and nurses/midwives' knowledge of vasectomy and determined their acceptance of this procedure as a permanent contraceptive method for their male partners.

***Methods:*** This cross-sectional study involved the completion of self-administered online questionnaires by 308 female doctors and nurses/midwives at the Korle-Bu Teaching Hospital. Data were collected in Microsoft Excel and analysed using IBM SPSS version 25. The data was analysed by using descriptive statistics, Chi-square tests, and multiple logistic regression. A p-value < 0.05 was considered statistically significant.

***Results:*** The 308 participants had a mean age of 32.7 ± 6.6 years. Nurses/midwives comprised 55.8%, and the rest were doctors. Only 33.8% of the participants demonstrated good knowledge of vasectomy (defined as a knowledge score greater than 80%). Thirty-nine percent were willing to allow their partners to undergo a vasectomy. Factors associated with this willingness included their inclination to recommend vasectomy as a contraception method generally, adjusted odds ratio of 13.01 (95% CI 4.66, 36.33), and having family members indifferent about their partners undergoing vasectomy, adjusted odds ratio of 2.01 (95% CI 1.02, 3.97).

***Conclusion:*** There is low knowledge of vasectomy among female doctors, nurses and midwives. Only about two-fifths of female doctors and nurses/midwives were willing to allow their male partners to undergo the procedure, and factors associated with this willingness included their inclination to generally recommend vasectomy as a contraception method and family indifference towards the procedure. More education on vasectomy is needed, including its incorporation into medical and nursing training curricula.

**Keywords:** Vasectomy, Female healthcare professionals, Partner attitudes, Knowledge

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## INTRODUCTION

Unintended pregnancy rates varied widely across geographical regions, from 35 per 1000 women in Europe and Northern America to 91 per 1000 women in sub-Saharan Africa in 2015 - 2019. In this same period, the global abortion rate remained relatively stable at 39 per 1000 women. Notably, the proportion of unintended pregnancies ending in abortion increased from 51% to 61% over the same period [1,2]. These high rates of unplanned pregnancies and, consequently, unsafe abortions contribute

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significantly to poor neonatal and maternal health outcomes [3,4]. For couples who have completed their families, permanent contraception methods offer a reliable solution to prevent unplanned pregnancies. Vasectomy is a surgical procedure that prevents the normal flow of sperm by occluding the vas deferens, serving as a safe method for male sterilisation [5]. Female sterilisation, or tubal ligation, is an alternative permanent method. Compared to female sterilisation, vasectomy is markedly less invasive, typically performed under local anaesthesia in an outpatient setting, resulting in reduced surgical risks and a shorter recovery period. It is also more cost-effective. Despite its effectiveness, safety, and relative affordability, vasectomy remains underutilised compared to female sterilisation methods. Data from the United States 2006 - 2008 National Survey of Family Growth revealed that among married individuals aged 15 - 44 years, 13.1% of men reported having a vasectomy, while 21.1% of women reported having a tubal ligation. Interestingly, vasectomy was more common among those with higher education and income, whereas tubal sterilisation was more prevalent among those with lower incomes and educational levels [7]. In Ghana, about 30% of currently married women want no more children. Incidentally, the most commonly used modern methods are injectables and implants (8% each), pills (4%) and female sterilisation (3%).

In contrast, less than 0.5% of the partners of women opt for vasectomy [8]. Studies have also shown varying attitudes towards vasectomy in Ghana. A qualitative study in the Western and Central regions revealed that many women opposed vasectomy, citing religious reasons, concerns about male promiscuity, fears of reduced sexual gratification, and beliefs that the procedure weakens men physically and reduces their productivity [9]. However, another study in the Central Region found that while initial knowledge of vasectomy was low (32%), after receiving information, 66.3% of women preferred their partners to undergo vasectomy compared to 50% before the study [10]. Modern studies have also focused on healthcare workers' knowledge and perceptions regarding vasectomy and other contraceptive methods. This emphasis is crucial because healthcare professionals are presumed to have more comprehensive knowledge about reproductive health and contraception. Their understanding, attitudes, and recommendations can significantly influence patients' contraceptive choices and can provide insights into potential barriers to vasectomy acceptance within the medical community itself. This study sought to establish the perceptions of female doctors and nurses concerning the uptake of vasectomy as a permanent method of contraception, potentially influencing its underutilisation.

## MATERIALS AND METHODS

### Study design and setting

This analytical cross-sectional study was conducted among female doctors and nurses/midwives at Korle Bu Teaching Hospital - the largest healthcare facility in Ghana and the primary tertiary referral centre for the country's southern region. KBTH is a public teaching hospital in the Ablekuma South Metropolitan Assembly, Accra, affiliated with the University of Ghana Medical School (UGMS). Established on October 9th, 1923, KBTH is currently the third-largest referral centre in Africa. The hospital has about 2000 beds in capacity, 21 clinical and diagnostic departments, and three centres of excellence. This expansive and diverse clinical setting, therefore, allowed access to a wide range of female healthcare professionals across various specialties and departments.

### Study population

The study population consisted of female doctors and nurses at Korle Bu Teaching Hospital. The inclusion criteria were

- Being female doctors, nurses and midwives
- Being currently married or in a sexual relationship

Female doctors, nurses, or midwives whose partners had already undergone vasectomy were excluded.

### Sample size determination and sampling method

The sample size for this study was determined using the Cochrane formula:

$n = [Z^2\alpha/2 * p(1-p)] / d^2$

Where:

n = required sample size

$Z^2\alpha/2 = 1.96$ (for 95% confidence level)

p = proportion of the study sample who accept vasectomy as a permanent procedure

d = absolute error or precision as 0.05

From a study by Ohn Mar et al. [11], 76% of clinical medical students accepted vasectomy as a permanent method of contraception, p = 0.76.

Using this formula, the minimum required sample size was calculated to be 280. The number was increased by 10% to account for potential non-response, resulting in a final targeted sample size of 308. A purposive sampling technique was employed to recruit participants for this study. Female doctors and nurses were selected from various departments across Korle-Bu Teaching Hospital.

### Data collection method and instruments

An online questionnaire was developed using Google Forms and distributed via various digital platforms accessible to female doctors and nurses at Korle-Bu Teaching Hospital. Responses were collected electronically through a designated email address. Respondents used their initials rather than their full names to ensure participant anonymity. All data retrieved was stored on a password-protected personal laptop to maintain confidentiality and data security.

### Data processing and analysis

Initial data organisation and summarisation were performed using Microsoft Excel 2010. Subsequent statistical analysis was conducted using IBM SPSS software (version 25). The study examined several key variables. The primary

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outcome variable was the knowledge of female doctors and nurses regarding vasectomy. The secondary outcome variable was the acceptance of vasectomy by male partners of female doctors and nurses as a permanent contraceptive method. Determinant variables included socio-demographic characteristics such as age and occupation, as well as obstetric and gynaecological characteristics, particularly parity and vasectomy-specific characteristics such as source of information on vasectomy.

The data analysis proceeded in three stages. First, univariate analysis was conducted to determine the frequencies and percentages of participant responses, providing a descriptive overview of the data. Subsequently, bivariate analysis was performed using the chi-square test. This allowed for the examination of associations between the primary outcome variable (female doctors' and nurses' acceptance of vasectomy by their male partners as a permanent method of contraception) and various determinant variables, including the socio-demographic, obstetric, and gynaecological characteristics of the respondents. Finally, to adjust for possible confounding factors, multiple logistic regression was used to determine the factors associated with female doctors' and nurses' acceptance of vasectomy by their male partners as a permanent method of contraception. Throughout all statistical analyses, a p-value $< 0.05$ was considered statistically significant.

## RESULTS

The study included 308 female healthcare professionals, with a mean age of 32.7 (SD 6.6) years. The majority (54.2%, n = 167) were between 30 and 39 years old. Nurses/midwives comprised 55.8% (n = 172) of the participants, while doctors comprised 44.2%. Most participants (58.8%, n = 181) were married, and most (94.5%, n = 291) identified as Christian. A significant proportion (71.9%, n =164 ) were living with their partners (Table 1). Regarding parity, 43.8% (n =135) of participants had no children, while 22.7% (n = 70) had two children. Among participants with children, 66.5% (n = 107) had fewer than three children with their current partner. Over half of the participants (61.4%, n = 189) reported using contraception previously, with pills 25.4% (n = 48) and IUDs (31.2%, n = 59) being the most common methods (Table 2). Only 14.9% (n = 46) of participants knew a male who had undergone a vasectomy. The primary sources of information about vasectomy were literature (48.7%, n =150) and other health workers (34.4%, n = 106). Regarding family approval of vasectomy, 37.7% (n = 116 ) believed their families would disapprove, while 31.8% (n = 98) were unsure (Table 3). The study assessed vasectomy knowledge using a 14-item questionnaire. Only 33.8% (n =104) of participants scored above 80%, indicating good knowledge. Most participants correctly identified vasectomy as a permanent (94.5%, n = 291), effective (95.8%, n = 295) method, and it does not affect sexual performance (89.9%, n = 277). However, there were notable knowledge gaps. For instance, 62.7% (n =193) incorrectly believed all vasectomies involved a scalpel, and 57.8% (n = 178) could not correctly identify the typical duration of the procedure (Tables 3 and 4). Only 39% (n = 120) of participants were willing to allow their partners to undergo a vasectomy. The main reasons for opposition included concerns about promiscuity (17.9%), religious beliefs (12.9%), and the desire for more children in the future (10.1%) (Tables 3 and 5). In the adjusted analysis, participants who were willing to recommend vasectomy as a contraceptive option had 13 times higher odds of accepting it for their partners compared to those who were not willing to recommend it, [aOR 13.01 (95% CI 4.66, 36.33)].

Participants who perceived their families to be indifferent towards vasectomy had twice the odds of accepting compared to those who did not know whether their family members would approve of it or not [aOR 2.01 (95% CI 1.02, 3.97)]. No statistically significant associations were found between vasectomy acceptance and the department professionals belonged to, the cadre of the professional, [aOR 1.23 (95% CI 0.65, 2.36)], source of vasectomy information, or vasectomy knowledge score, [aOR 1.12 (95% CI 0.59, 2.14) ] (Table 6).

Table 1. Socio-demographic characteristics of participants

| Variable | Frequency (n = 308) | Percentage |
|---|---|---|
| Age, in years: Mean (±SD) | | 32.7 (± 6.6 years) |
| Age, in years | | |
| 20-29 | 102 | 33.1 |
| 30-39 | 167 | 54.2 |
| 40+ | 39 | 12.7 |
| | | |
| Department | | |
| O&G | 70 | 22.7 |
| Surgery | 103 | 33.4 |
| Child Health | 49 | 15.9 |
| Medicine | 57 | 18.5 |
| Polyclinic | 15 | 4.9 |
| Dental | 5 | 1.6 |
| Other | 9 | 2.9 |
| | | |
| Occupation | | |
| Doctor | 136 | 44.2 |
| Nurse | 172 | 55.8 |
| | | |
| Relationship Status | | |
| Single | 80 | 26 |
| Married | 181 | 58.8 |
| In a relationship | 47 | 15.3 |
| | | |
| Living partner | | |
| Yes | 164 | 71.9 |
| No | 64 | 28.1 |
| Religion | | |
| | | |
| Christian | 291 | 94.5 |
| Islam | 15 | 4.9 |
| Agnostic | 2 | 0.6 |

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Table 2. Obstetric and contraceptive characteristics of participants

| Variable | Frequency (n = 308) | Percentage |
|---|---|---|
| Parity | | |
| 0 | 135 | 43.8 |
| 1 | 45 | 14.6 |
| 2 | 70 | 22.7 |
| 3+ | 58 | 18.8 |
| Participants with children | | |
| < 3 | 115 | 66.5 |
| >/= 3 | 58 | 33.5 |
| Used contraception | | |
| Yes | 189 | 61.4 |
| No | 119 | 38.6 |
| Past Contraceptive Method | | |
| Pills | 48 | 25.4 |
| IUD | 59 | 31.2 |
| Injectables | 19 | 10.1 |
| Implant | 24 | 12.7 |
| Condom | 26 | 13.8 |
| BTL | 2 | 1.1 |
| Natural | 11 | 5.8 |

Table 3. Vasectomy-specific characteristics of participants

| Variable | frequency | Percentage |
|---|---|---|
| Knowledge of any male who has had a vasectomy | | |
| Yes | 46 | 14.9 |
| No | 262 | 85.1 |
| Source of information about vasectomy | | |
| Mass Media | 25 | 8.1 |
| Friends & Family | 3 | 1.0 |
| Health workers | 106 | 34.4 |
| Literature | 150 | 48.7 |
| School | 24 | 7.8 |
| Perceived family approval of vasectomy | | |
| I do not know | 98 | 31.8 |
| They will approve of it | 13 | 4.2 |
| They will be indifferent | 81 | 26.3 |
| They won't approve of it | 116 | 37.7 |
| Willing to recommend vasectomy to others | | |
| Yes | 235 | 76.3 |
| No | 73 | 23 |
| Vasectomy knowledge score > 80% | | |
| Yes | 104 | 33.8 |
| No | 204 | 66.2 |
| Participant's desire for partner or future partner to undergo vasectomy | | |
| Yes | 120 | 39 |
| No | 188 | 61 |

Table 4. Vasectomy knowledge questionnaire: item analysis and response patterns

| Vasectomy knowledge assessment items | Correctly answered: n (%) |
|---|---|
| Vasectomy increases the risk of Prostate cancer | 213 (69.2) |
| Vasectomy is the same as castration | 235 (76.3) |
| Will a man need to use another contraceptive method after a vasectomy is done to prevent pregnancy in the first 3 months? | 183 (59.4) |
| Vasectomy is a permanent method of contraception | 291(94.5) |
| Vasectomy affects sexual performance | 277 (89.9) |
| Vasectomy can cause Erectile dysfunction | 252 (81.8) |
| Performing a vasectomy will reduce testosterone levels | 197 (64.0) |
| All vasectomies involve the use of a knife or scalpel | 115(37.3) |
| Vasectomy does not prevent sexually transmitted infections | 280 (90.9) |
| How long does a vasectomy procedure usually take? | 130 (42.2) |
| Vasectomy has less complications than Bilateral tubal ligation | 135 (43.8) |
| Vasectomy is an easily reversible procedure | 237 (76.9) |
| Vasectomy is for couples who want to have more children | 303 (98.4) |
| Vasectomy is a very effective procedure | 295 (95.8) |

Table 5. Reasons influencing female doctors and nurses' opposition to partner vasectomy

| Reasons for not accepting vasectomy | n (%) |
|---|---|
| No reason | 69 (36.7) |
| He will be promiscuous | 25 (13.3) |
| It is against my religious beliefs | 18 (9.6) |
| We may want to have more children in the future | 14 (7.5) |
| Not necessary (I will do BTL, I'm in my menopause, there are less invasive options available, I will do family planning) | 12 (6.4) |
| It is expensive | 9 (4.8) |
| I do not like it | 9 (4.8) |
| The procedure has too many complications | 9 (4.8) |
| He will lose his physical strength | 6 (3.2) |
| It's irreversible | 4 (2.1) |
| My partner won't be interested | 4 (2.1) |
| Personal preference | 3 (1.6) |
| Haven't thought about it | 3 (1.6) |
| It's his decision | 2 (1.1) |
| It might undermine his ego | 1 (0.5) |

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## DISCUSSION

Vasectomy is a safe and effective surgical procedure for male sterilisation, involving the occlusion of the vas deferens to prevent sperm flow [5]. This study evaluated the knowledge of vasectomy among female doctors and nurses and assessed their acceptance of this method as a permanent contraceptive option for their male partners. Our findings reveal important insights into healthcare professionals' perspectives on vasectomy and highlight areas for improvement in education and promotion of this contraceptive method.

### Knowledge of vasectomy

Our study revealed limited knowledge of vasectomy (33.8%) among participants, primarily sourced from the literature. This finding contrasts with research from diverse cultural contexts. In Nigeria, studies among health professionals showed higher vasectomy knowledge among health workers [12,15]. Similarly, research from Latin America, particularly among medical students, demonstrated varied but generally more comprehensive understanding across different countries [16]. While our Ghanaian sample showed limited knowledge, the discrepancy might be attributed to differences in population characteristics, educational curricula and information dissemination strategies across various healthcare systems. Our study also revealed knowledge gaps similar to those in less-resourced contexts. These gaps may reflect participants' professional backgrounds; most of the study participants were nurses with limited specialised training. Only 42.2% (n = 130 ) correctly identified the vasectomy procedure duration, and merely 43.8% (n = 135) recognised its lower complication rate compared to bilateral tubal ligation (BTL). This is consistent with a study where non-surgical residents demonstrated similar knowledge limitations compared to the surgical professionals, although overall knowledge was high in their study [17].

### Acceptance of vasectomy

Compared to tubal ligation, vasectomy remains underutilised despite its effectiveness. Notably, vasectomy is more commonly observed among individuals with higher education and income in high-resource settings [7]. Our study, however, presents a remarkable contrast, which highlights that higher education does not correlate with greater acceptance of vasectomy in low-resource settings. Despite being healthcare professionals with advanced medical knowledge, 61% of participants were unwilling to consider vasectomy for their partners. This finding aligns with a study conducted in Nigeria among female health workers, where only 21.0% of the respondents would encourage their spouses or partners to undergo vasectomy after completion of family size [18]. In another Nigerian study, despite the reasonable level of knowledge among their respondents, acceptance of vasectomy as a contraceptive method also remained low. A combined 60% of respondents would not recommend vasectomy to patients or were unsure about recommending it [12].

This discrepancy between professional status and personal acceptance of vasectomy was attributed to several factors in this study: a lack of clear motivation (36.7%, n = 69), fear of promiscuity by partners (13.3%, n = 25), religious influences (9.6%, n = 18), desire for more children (7.5%, n = 14), irreversibility and personal preference for reversible methods (2.1%, n = 4). These correlate with several sociocultural, religious, and psychological reasons reported for vasectomy aversion in multiple studies in Nigeria [14,15]. Interestingly, while our study focused on practising female healthcare professionals, it is worth noting the contrast with medical students' attitudes towards vasectomy. Although not yet fully-fledged health workers, medical students are immersed in the medical field and often demonstrate a different pattern of acceptance. Studies have shown that medical students' acceptance of vasectomy is typically less influenced by sociocultural factors and more closely aligned with their knowledge of the procedure [19,20]. This suggests that their views are shaped primarily by the scientific information they receive during their training. The researchers, however, acknowledged that despite good knowledge and acceptance, undetected variables may influence this decision and are worth investigating.

### Factors influencing vasectomy acceptance

Two key factors were significantly associated with the acceptance of vasectomy among female healthcare professionals for their partners. Firstly, participants who were willing to recommend vasectomy as a contraceptive method were 13 times more likely to accept it for their partners compared to those who were not willing to recommend it. This strong association suggests that overcoming personal biases to recommend vasectomy professionally may also facilitate personal acceptance. Secondly, participants who perceived their families to be indifferent towards vasectomy were twice as likely to accept it compared to those who did not know whether their families would approve or disapprove of it. This finding underscores the persistent influence of family attitudes on contraceptive choices, even among healthcare professionals. Notably, our study found no statistically significant associations between vasectomy acceptance and factors such as the department they worked in, the cadre of the professional, the source of vasectomy information, or the vasectomy knowledge score. This lack of association between knowledge and acceptance aligns with our earlier discussion about the disconnect between clinical knowledge and personal acceptance of vasectomy. It reinforces the understanding that sociocultural factors, rather than mere knowledge, play a crucial role in the aversion to vasectomy.

This study was limited to female health workers in Korle Bu Teaching Hospital and may not represent all hospitals in Ghana or accurately reflect knowledge and acceptance of vasectomy among the general population. Self-reported data through online questionnaires could introduce

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response bias, while the sample, predominantly young nurses/midwives, might skew attitudinal findings.

### Conclusion

This study evaluated the knowledge of vasectomy among female doctors and nurses and assessed their acceptance of this method as a permanent contraceptive option for their male partners. Our findings reveal that both knowledge and acceptance of vasectomy were generally low among the study population. A significant proportion of female healthcare professionals expressed reluctance towards their partners undergoing vasectomy, which may contribute substantially to the underutilisation of this contraceptive method among couples. Two key factors were found to be associated with the willingness of female doctors and nurses to consider vasectomy for their partners: their likelihood to recommend vasectomy as a contraceptive method to others and the presence of indifferent family views towards vasectomy. These findings underscore the complex interplay of personal, professional, and social factors influencing attitudes toward vasectomy among female healthcare providers.

These results highlight the need for improved education about vasectomy among healthcare professionals, as well as broader efforts to address cultural and social barriers to its acceptance. Future interventions should focus on enhancing knowledge, challenging misconceptions, and promoting open discussions about vasectomy as a viable contraceptive option, both within the healthcare community and the broader population.

## DECLARATIONS

### Ethical consideration

This study was conducted per established ethical guidelines. Administrative approval was obtained from the Korle-Bu Teaching Hospital (approval number: ADM/00114/2022). Furthermore, the research protocol was reviewed and approved by the University of Ghana Medical School Department of Community Health Research Committee (Approval ID: UGMS-CHDRC/071/2023). These approvals ensured that the study adhered to institutional and ethical standards for conducting research involving human subjects

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest.

### Author contribution

AOK and BOT designed and conducted this study. AOK, BOT, GA, TMS, BT, NM, and MK did data analysis and interpretation. The manuscript was drafted by AOK, BOT, and TMS and reviewed for intellectual content by BT, NM, and MK. All authors read and approved the final version of the manuscript.

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### Availability of data

Data is available upon request to the corresponding author.

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# Human Strongyloidiasis in Ghana: A scoping review of prevalence and geographic distribution (2003–2023)

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**Abstract**

***Background:*** Human strongyloidiasis is a neglected tropical disease with global public health concerns. Despite several interventions geared towards the prevention, control, and elimination of human strongyloidiasis in Ghana, infection and reinfection continue to occur, negatively impacting the health of affected populations. Lifelong autoinfection and fatal hyperinfection syndrome in immunocompromised individuals are often reported.

***Objective:*** This scoping review aims to map and synthesise existing evidence on the prevalence and geographic distribution of human strongyloidiasis in Ghana between 2003 and 2023, identify research gaps and inform future priorities regarding control and elimination of the infection.

***Methods:*** Original peer-reviewed studies published in English (2003 - 2023) that investigated human strongyloidiasis in Ghana were systematically searched and retrieved from six electronic databases and included in this review. Additional studies were identified from the reference lists of the reviewed articles. Relevant data were extracted from the included articles and presented in narrative and tabular formats.

***Results:*** Twenty (20) articles that met the inclusion criteria were reviewed under broad subthemes: geographic distribution, prevalence, laboratory diagnostic methods, target population, and nature of public health intervention. Ten (50.0%) studies were conducted in the southern, six (30.0%) in the middle belt, and four (20.0%) in the northern sectors. Overall, 17 studies used cross-sectional designs, two retrospective, and one case-control method. The reported prevalence of human strongyloidiasis in Ghana ranged between 0.1% and 41.1%. However, a prevalence of 0.1% - 2.2% was reported in children, 0.5% - 41.1% in adults, 0.4% in HIV seropositive individuals, and 2.9% in food vendors. The geographical prevalence of human strongyloidiasis ranged between 0.1% - 21.2%, 0.4% - 2.9%, and 0.3% - 41.1% in the Northern, Middle belt, and Southern sectors, respectively. The direct wet mount and formal-ether concentration technique (70.0%), PCR (15.0%), and culture and other diagnostic techniques (5.0%) were used.

***Conclusion:*** The national prevalence of strongyloidiasis in Ghana, based on this review, is low-to-moderate (median 1.45%), but extreme geographic heterogeneity exists, with localised hyperendemic regions (e.g., 21.2% and 41.1%) accounting for an increase in the mean to 4.5%. Population-weighted studies are essential for accurate national estimates, and targeted interventions are urgently needed to address high-transmission hotspots and underlying drivers of transmission. This review proposes further research and targeted interventions relevant to Ghana's efforts to meet the WHO's human strongyloidiasis elimination target by 2030.

**Keywords:** Strongyloidiasis, Ghana, *Strongyloides stercoralis*, Neglected tropical parasite, Scoping review

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## INTRODUCTION

Human strongyloidiasis is a soil-transmitted helminthic infection of the gut, caused mainly by the rhabditid nematode, *Strongyloides stercoralis (S. stercoralis)*, which is globally distributed. It is predominantly found in tropical and subtropical countries in Sub-Saharan Africa, Central and South America, and Southeast Asia [1,2]. *Strongyloides stercoralis* is a neglected tropical parasite that infects human beings but occasionally parasitises primates and dogs [3]. Different species within the genus cause disease in amphibians, birds, primates, reptiles, and livestock. The rarer human-infecting species of Strongyloides comprises the zoonotic *S.*

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*fuelleborni (fülleborni)* subsp. *fuelleborni* and also *S. fuelleborni* subsp. *kellyi*, for which humans are the only known host currently [4], although they were initially thought to be a subspecies of *Strongyloides fuelleborni* [5]. Whereas Strongyloides *fuelleborni kellyi* is limited to Papua New Guinea in terms of distribution, animal reservoirs of the parasite are yet to be identified. Strongyloides *fuelleborni felleborni* is generally zoonotic with a wide geographical distribution [4].

Strongyloidiasis is endemic in tropical and subtropical regions of the world and has been reported to account for about 30-100 million infections annually [6, 7]. With the advent of highly sensitive diagnostic techniques, *S. stercoralis* infection is estimated to affect 613.9 million people worldwide, especially in Africa, Southeast Asia, and the Western Pacific regions [8]. Strongyloidiasis has been grossly underestimated and under-reported due to poor diagnosis [2]. The major public health challenge posed by human strongyloidiasis is, most often, its asymptomatic presentation that could last for years in immunocompetent individuals, thus making diagnosis and treatment difficult [9]. The life cycle of *S. stercoralis* is shown in Figure 1.

The most at-risk population of strongyloidiasis live in endemic areas with humid and warm climatic conditions, poor social infrastructure, and economic deprivation [11]. The presence of faecal contaminants in the environment may lead to its prevalence among farmers, migrants, mental health patients, prisoners, and people who live in areas with poor environmental sanitation [12]. Other at-risk persons include alcoholics, immigrants, travellers, malnourished individuals, people with malignancies, diabetic patients, chronic renal disease patients, and chronic obstructive pulmonary disease patients [13,14]. Individuals at increased risk of hyperinfection include those on immunosuppressants or corticosteroids, with immune deficiency disorders such as HTLV-1 or HIV/AIDS, and donors or recipients of organ transplantation [7,15]. Even though *Strongyloides stercoralis* infection is prevalent among HIV-AIDS patients who live in endemic communities, hyperinfection syndrome is seldom noticed [15].

Strongyloidiasis may present with acute, chronic, or hyperinfection syndrome, mostly characterised by low larval output. Although acute infections are rarely reported, individuals may experience local inflammation at the site of larval penetration, causing urticaria and itching around the feet, groin, buttocks, or trunk. Infected travellers may present with skin rashes and incessant diarrhoea [16]. Severe gastrointestinal infection can lead to anorexia, constipation, diarrhoea, abdominal pain, and occult intestinal bleeding. Clinical symptoms of pulmonary larval migration may also result in shortness of breath, cough, wheezing, or Loeffler's syndrome. Chronic cases of strongyloidiasis are common among people in endemic areas and are periodically detected in refugees and international travellers [17].

Hyperinfection of *Strongyloides stercoralis* is due to accelerated autoinfection (disseminated syndrome) when the larvae migrate to other internal organs of the host beyond the lung-autoinfective cycle [18]. Disseminated strongyloidiasis is common among individuals on immunosuppressants, alcoholics, HTLV-1 carriers,

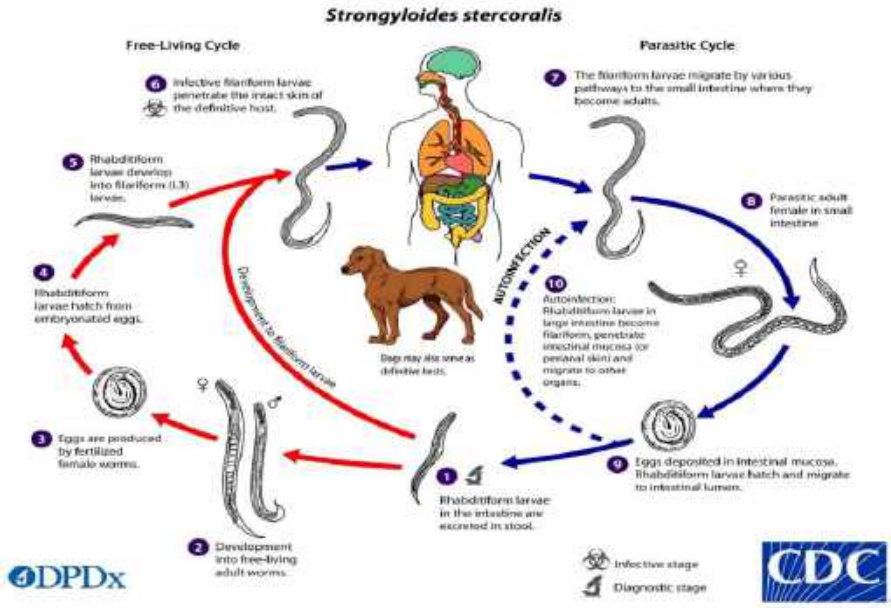


Figure 1. The life cycle of Strongyloides stercoralis.
Unique features include, irregular movement of autoinfective larvae, development of rhabditiform larvae from embryonated egg, and single generation of male and female free-living adults [10]

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diabetic patients, organ transplant recipients, and those with haematological malignancies [15].

In Ghana, studies showed a varied prevalence of *Strongyloides stercoralis* infection: 4.8% (n = 26/538) and 39.5% among malnourished persons in Ga West Municipality in Accra [19], 0.45% (n = 3/861) in Berekum District [20], 43.0% of vegetables sold in open-air markets and a supermarket in Accra [21], 0.9% in the Middlebelt of Ghana (Kintampo South District and Kintampo North Municipality) [22], and 0.3% (n = 1/300) among school children within the Accra Metropolitan Area [23].

**Disease diagnosis**

Wet mount microscopy, nutrient agar plate culture (Koga agar plate), and the Baermann funnel techniques are common diagnostic tools to detect *Strongyloides stercoralis*. However, these tools demonstrate moderate sensitivity and poor diagnostic accuracy. Serious limitations of the Koga agar plate culture and Baermann's technique include their laborious and time-consuming nature and the inability to deploy them on a large scale [24, 25]. The polymerase chain reaction (PCR) is increasingly used as a routine diagnostic technique for *Strongyloides stercoralis* detection in stool samples, although there are concerns about sensitivity and limited data on its application to bodily fluids [26].

Stool samples from cases of *S. stercoralis* infection typically contain larvae rather than eggs, distinguishing them from other helminthic parasites. In chronic cases, the larvae are often present in limited numbers, which may result in counts falling below the detection threshold of available diagnostic tests [27,28]. Although it is common to find larvae in stool during heavy infections in endemic areas [14,29], intermittent and fewer larvae are produced in chronic situations [30]. Diagnosis of strongyloidiasis is fraught with challenges, such as low parasite load and low or irregular larval output, leading to underdiagnosis and underreporting of its prevalence [26].

Serological assays are comparatively more sensitive for detecting *Strongyloides stercoralis*; in developed countries, where they are available and used to determine therapeutic success [31]. Disadvantages of serological diagnosis include false-negative results in immunocompromised individuals and those with recent infections[32,33], false-positive results in persons with other parasitic infections, cross-reactivity with filarial worms [34,35] and the need for careful interpretation of results in Strongyloides-endemic areas [36]. Incidentally, real-time polymerase chain reaction remains the most sensitive diagnostic tool for the detection of *Strongyloides stercoralis* in stool samples [37].

**Current treatment regimen and ivermectin resistance**

The goals for therapy against *S. stercoralis* infections are to clear the parasite completely, thereby eliminating the risk of autoinfection, address symptomatic infection, and prevent complications associated with asymptomatic infections [38]. Evidence supports the efficacy of ivermectin and benzimidazoles (thiabendazole, mebendazole, and albendazole) for treating chronic strongyloidiasis [39]. The development of ivermectin from avermectin as a nematicide [40,41], has significantly contributed to the drastic reduction of onchocerciasis, lymphatic filariasis, soil-transmitted helminthiasis, scabies, and potentially malaria [16]. Although albendazole is recognised for its low efficacy and therapeutic effect on the parasite, mebendazole is not recommended for treating strongyloidiasis in the general population, particularly among pregnant women, due to its limited activity [39]. Thiabendazole is effective in the treatment of intestinal parasitic infections, but side effects such as malaise, nausea and or dizziness have been reported [42]. It is posited that an insufficient dosing regimen of ivermectin may result in incomplete parasite clearance, which could be misinterpreted as emerging resistance [43,44]. Ivermectin is effective against strongyloidiasis in immunosuppressed individuals; however, reinfection presents challenges to the elimination and eradication of the disease [45]. Poor diagnosis may not be easily differentiated from reinfection. A study has indicated potential ivermectin resistance in livestock, which could pose risks to humans [39,46]. To mitigate drug resistance, the combination of ivermectin and albendazole has been tested and shown to be effective in controlling other soil-transmitted helminths [47,48].

**Study aim and research questions**

Given the public health impact of strongyloidiasis on at-risk populations, it is important to understand the burden and associated factors driving transmission in Ghana. The knowledge of the prevalence and epidemiology of *S. stercoralis* infections would inform public health interventions aimed at improving health outcomes in strongyloidiasis-endemic areas. Therefore, this scoping review aimed to map and synthesise existing evidence on the prevalence and geographic distribution of human strongyloidiasis in Ghana between 2003 and 2023, identify research gaps and inform future priorities. To our knowledge, this is the first scoping review on the prevalence and epidemiology of human strongyloidiasis in Ghana. Consequently, this review was conducted based on the scoping review framework [49,50] by implementing a systematic methodology to provide a preliminary assessment of the quantity, quality, and key characteristics of the study design of available studies. Four primary research questions framed the review:

1. What are the reported prevalence, geographic distribution, and temporal trends of human strongyloidiasis in Ghana from 2003 to 2023?
2. What diagnostic methods have been used to detect *Strongyloides stercoralis* in Ghana, and how do they vary across regions or study populations?
3. What interventions (treatment, public health measures) have been implemented to control strongyloidiasis in Ghana between 2003 and 2023, and what is their reported impact on prevalence or geographic spread?

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4. What are the key methodological, geographic, or population-related gaps in the current literature on strongyloidiasis in Ghana from 2003 to 2023?

## MATERIALS AND METHODS

### Study design and sites

This study focused on reviewing existing literature on human strongyloidiasis in Ghana. Ghana is a tropical country in West Africa with a total land mass area of 239,000 km$^2$ and is located between latitudes 4.5 °N and 11.5 °N and longitudes 3.5 °W and 1.5 °E. Ghana is bounded to the west by the Republic of Côte d'Ivoire, to the east by the Republic of Togo, to the north by the Republic of Burkina Faso, and to the south by the Gulf of Guinea. Annually, the average temperature of Ghana is 26 °C (79 °F), with the tropical monsoon typically defining the climatic condition of the country [51,52]

### Search strategy and selection process

A systematic search was conducted across multiple databases, including African Journals Online, Cochrane Library, Google Scholar, Web of Science, PubMed, and ScienceDirect, between January 2003 and December 2023. The search strategy was based on the PRESS 2015 Guideline Statement and ensured sensitivity, accuracy, and precision [53]. The search terms were combined using predetermined search terms, including Medical Subject Headings (MeSH) and relevant keywords. The strategy was validated by an information specialist and employed Boolean operators ("AND," "OR") to create relevant search queries and controlled vocabulary, such as "*Strongyloides stercoralis*" [MeSH] OR "strongyloidiasis" [MeSH] OR "Strongyloides" [tiab] OR "strongyloidiasis" [tiab], AND ("Ghana" [MeSH] OR Ghana[tiab]), AND ("humans" [MeSH] OR human*[tiab]), NOT (animal*[tiab] OR veterinary[tiab]). Truncation (*) was utilised to broaden search terms (e.g., human* to include humans), while field tags [tiab] and [MeSH] were used to target title/abstract and indexed terms, respectively.

Duplicate records were removed using Zotero, and screening was conducted with Rayyan QCRI [54]. Additionally, manual reference tracking was employed to identify further relevant studies. The methodological quality of the individual studies was assessed, and animal and human strongyloidiasis were differentiated. No restrictions were applied to the study design or region.

### Eligibility criteria

Full-text peer-reviewed studies conducted in Ghana on human strongyloidiasis that reported primary data in English and were published between 2003 and 2023 were included. All studies reporting data on prevalence, diagnostics, control, treatment methods at local or regional levels, and intensity of infections in Ghana were included. No restrictions were placed on the geography, sex, age, or education level of the study population, provided the study was conducted in Ghana. Published articles that were not peer-reviewed (grey literature, book chapters), included secondary data, or were opinion pieces were excluded. Original studies or secondary data on animal strongyloidiasis were also excluded. All published articles were thoroughly screened and reviewed according to the eligibility criteria. Duplicates were removed, and published articles on any intervention for strongyloidiasis control in Ghana aimed at breaking the transmission were considered relevant and included in this study. The quality of the individual studies and the data underlying the publications was assessed prior to inclusion in this review (Figure 2).

### Screening of studies and data extraction

The screening was conducted in a stepwise process. Initial screening of studies was done based on the title and abstract of retrieved articles; the same authors (CYD, JPK, PBT-Q, and IA) conducted a full-text assessment of included studies when the abstracts were deemed insufficient to conclude. A review panel assessed the quality of individual studies and resolved by consensus any uncertainties or disagreements between the two full-text assessors on the inclusion of an article.

The extraction of relevant data from each paper after the full-text screening was summarised on data extraction forms. The full-text assessment evaluated and recorded the lead author's name, country of origin, study design, study settings, sample size, participants' characteristics/recruitment, strongyloidiasis intervention reported data analysis, key findings, conclusions, and recommendations. For studies that were excluded, the reasons were recorded. Data on prevalence, distribution, treatment or control method, demographics, year of study, and study design were vital for this review. Studies on WASH intervention for *Strongyloides stercoralis* infection control were included. Strongyloidiasis control measures adopted by different countries in Africa were also critically examined for their effectiveness.

### Data synthesis

As a result of heterogeneity in the study design, study settings, study population, and the nature of the intervention, a thorough synthesis was done to address the objective of this review. Findings of the studies were tabulated, highlighting the prevalence, target population, population size, nature of the intervention, study period, and year the study was published, among others. Data on the intensity and prevalence of human strongyloidiasis were extremely important for this review. Data on infected and non-infected humans was considered and included. Also, data on the geographic location, demographics, year of the study, and diagnostic technique used were all recorded where available. Most of the studies were cross-sectional.

### Patient and Public Involvement

This was a scoping review, and no personal data from patients, clients, or members of the public was collected or generated.

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## RESULTS

A total of 154 articles related to strongyloidiasis in Ghana were retrieved. Of these, 75 were duplicates and hence removed. After a thorough screening of the titles and abstracts, 79 articles remained for full-text assessment for eligibility. A further 55 were excluded, leaving 20 articles published between 2003 and 2023 across Ghana included in this review (Fig.2). Details of the coverage of this review include 10 (50.0%) studies conducted in the southern sector, 6 (30.0%) in the middle-belt and 4 (20.0%) in the northern sector. Of these, 17 studies used cross-sectional designs, 2 were retrospective studies, and 1 case-control study (Figure 3 and Table 1).

Most of the *Strongyloides stercoralis* infections reported in the studies included in this review were among children (5-16 years) with prevalence ranging from 0.1% to 2.2%. Pregnant women (15 - 49 years) had a prevalence range between 1.9% and 3.1% while food vendors (10 - 70 years) had 2.9% prevalence. For community-based studies involving children and adults, the age ranges from 5 to 100 years with a prevalence rate between 0.9% and 4.8%. The prevalence of strongyloidiasis infection in HIV seropositive

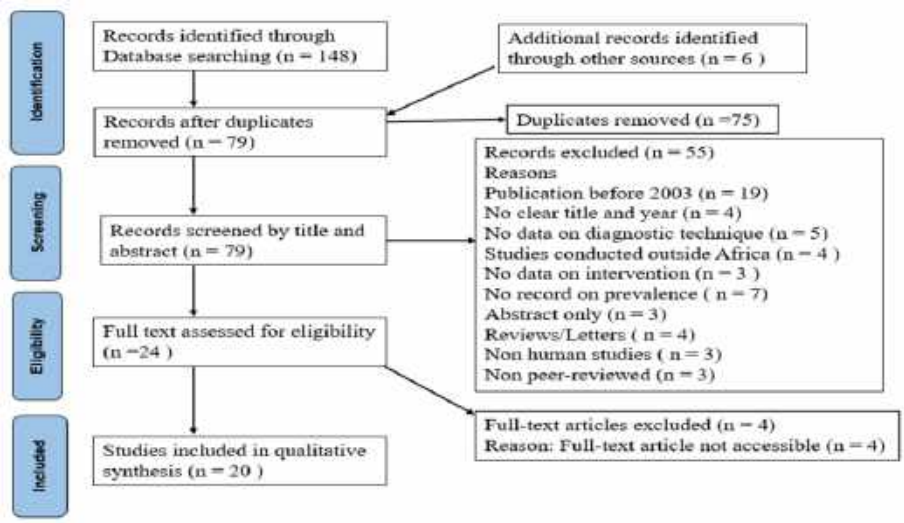


Figure 2. PRISMA Extension for Scoping Reviews (PRISMA-ScR)[55,56]

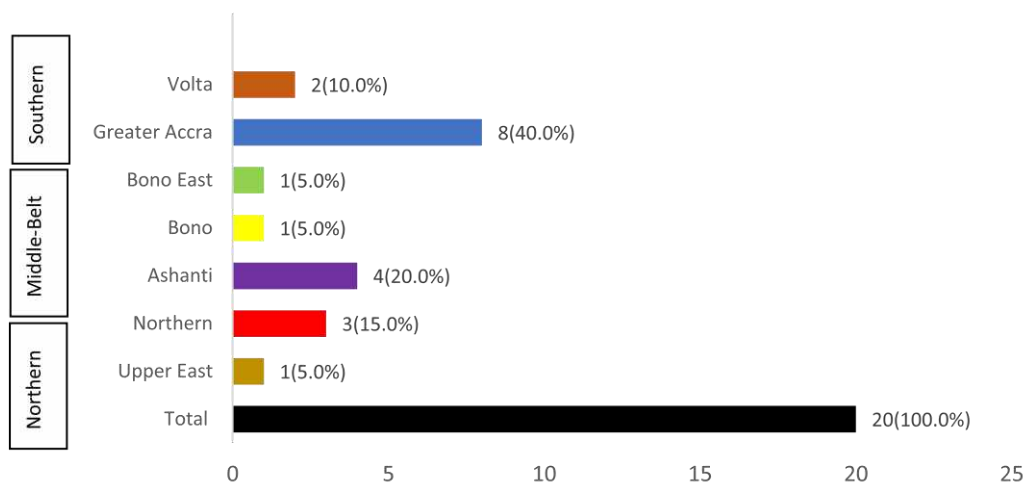


Figure 3. Regional distribution of studies on human strongyloidiasis in Ghana.

Table 1. Prevalence, diagnostic technique, and nature of intervention regarding strongyloidiasis in Ghana

| Sector | Region | District | Study site | % Prevalence | Diagnostic technique | Study type | Target population (years) | Targeted population size | Nature of Intervention | Study period | Year Study published | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Northern | Northern | Not stated | Not stated | 21.2 (45/212) | PCR, Culture /Baermann | Cross sectional | Mixed (adults and children) | 212 | Not stated | Not stated | 2009 | [57] |
| | Upper East | Kassena-Nankana | Navrongo War Memorial Hospital | 2.3 (7/300) | FEC | Cross sectional | Pregnant women | 300 | Not stated | Aug - Nov 2005 | 2010 | [58] |
| | Northen /North East/Savannah/ Upper West | Not stated | Nothern Ghana | 0.1 | Multiplex Bead Assay | Cross sectional /cluster | Children (1-9) | 10840 | Not stated | Nov 2015-April 2016 | 2022 | [59] |
| Middle-belt | Ashanti | Kumasi Metropolis | KNUST food stalls/canteen, | 2.9 (4/140) | DWT, FEC | Cross sectional | Food vendors (10-70) | 140 | Not stated | Feb-April 2011 | 2014 | [60] |
| | Ashanti | Kumasi Metropolis | Kumasi | 0.4 (3/800) | DWT, FEC | Cross sectional | HIV seropositive &negative adults (≤ 20 > 50) | 800 | Not stated | April - December 2008 | 2012 | [61] |
| | Ashanti | Kumasi Metropolis | Komfo Anokye Teaching Hospital, Kumasi | 0.5 (2/380) | DWT | Cross sectional | Women | 760 | Not stated | Not stated | 2015 | [62] |
| | Ashanti | Not stated | KNUST Hospital, Kumasi | 2.0 (41/77) | PCR | Retrop ective | Children (≤13) | 2046 | Not stated | 2007-2008 | 2022 | [63] |
| | Ashanti | Asante Akim North municipal | Not stated | 0.9 (4/548); 1.1(6/651)* | DWT, FEC, ELISA, PCR | Case-control | Children (≤13) | 1234 | Treatment (Albendazole (400 mg) | June 2007-October 2008 | 2015 | [64] |
| | Bono | Banda | Asante Akim North municipal | 2.2 (6/275) | FEC | Cross sectional | Children (5-16) | 275 | Treatment Albendazole (400 mg) | 2021 | 2023 | [65] |
| | Bono East | Kintampo North & Kintampo | 7 basic schools | 0.9 (14/1569) | DWT, KK, FEC | Cross sectional | Community based (<8-100) | 1826 | Not stated | Sep 2015 - August 2016 | 2018 | [22] |
| Southern | Greater Accra | Dangme East | Kintampo North Municipality and Kintampo South District | 1.9 (7/375) | FEC | Cross sectional | Pregnant women (15-49) | 375 | Not stated | April - July 2012 | 2017 | [66] |
| | Greater Accra | Accra metropolis | Sege, Bonikope & Anyamam Health Centre | 41.1 (37/90) | DWT, FEC | Cross sectional | Adult (≤18) | 336 | Not stated | Jan – Aug 2021 | 2023 | [67] |
| | Greater Accra | Accra metropolis | Korle-Bu | 0.3 (1/300) | DWT, FEC | Cross sectional | Children (2-9) | 300 | Not stated | Mar-July, 2016 | 2017 | [23] |
| | Greater Accra | Accra metropolis | Odododiodio | 2.0 (2/101) | DWT, FEC | Cross sectional | Mixed (5-22) | 101 | Not stated | April-June 2012 | 2015 | [68] |
| | Greater Accra | Ga West Municipal | Osu Orphanage | 4.8 (26/538) | FEC | Cross sectional | Mixed (6-≥40) | 538 | Treatment Albendazole (400 mg) | Sept 2019-Mar 2020 | 2020 | [19] |

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Table 1. Cont.

| Sector | Region | District | Study site | % Prevalence | Diagnostic technique | Study type | Target population (years) | Targeted population size | Nature of Intervention | Study period | Year Study published | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Greater Accra | Accra metropolis | Osu Orphanage | 2.0 (2/101) | DWT, FEC | Cross sectional | Mixed (5-22) | 101 | Not stated | April-June 2012 | 2015 | [68] |
| | Greater Accra | Ga West Municipal | Opah, Otuaplem, Dedeman, Onyansana, & Manchie | 4.8 (26/538) | FEC | Cross sectional | Mixed (6-≥40) | 538 | Treatment Albendazole (400 mg) | Sept 2019-Mar 2020 | 2020 | [19] |
| | Greater Accra | Accra metropolis | Accra Psychiatric hospital | 0.9 (1/111) | DWT, FEC | Cross sectional | Psychiatric Patients (25–60) | 111 | Not stated | May-Aug 2012. | 2015 | [69] |
| | Greater Accra | Accra metropolis | Mamprobi Polyclinic, James Town Maternity Home &Achimota Hospital. | 3.1 | DWT, FEC | Cross sectional | Pregnant women ( ≤20 -≥40 ) | 1000 | Not stated | Jan-June 2007 | 2008 | [70] |
| | Volta | Ho Municipal | Ho Teaching Hospital | 0.6 | DWT, FEC | Retrospective | Patients ( <10 - >59) | 7045 | Not stated | Aug 2017-Jan 2018 | 2019 | [71] |
| | Volta | Ho Municipal | Klave, Hoe, Freetown, Dave, Godokpe | 0.7 (1/150) | DWT, FEC | Cross sectional | Asymptomatic Children (4-59 months) | 150 | Not stated | Not stated | 2020 | [72] |
| | Greater Accra | Accra metropolis | BA, WR, Ashanti, Central, GR, Volta, Eastern, UE, UW, Northern | 1.0 | PCR | Cross sectional | Ghanaian Global Polio Laboratory Network (GPLN) (0-17+) | 448 | Not stated | 2016 | 2018 | [73] |

Key: DWT-Direct Wet mount, KK – Kato-Katz, FEC -Formal-ether Concentration, PCR-Polymerase chain reaction; Case-Control*

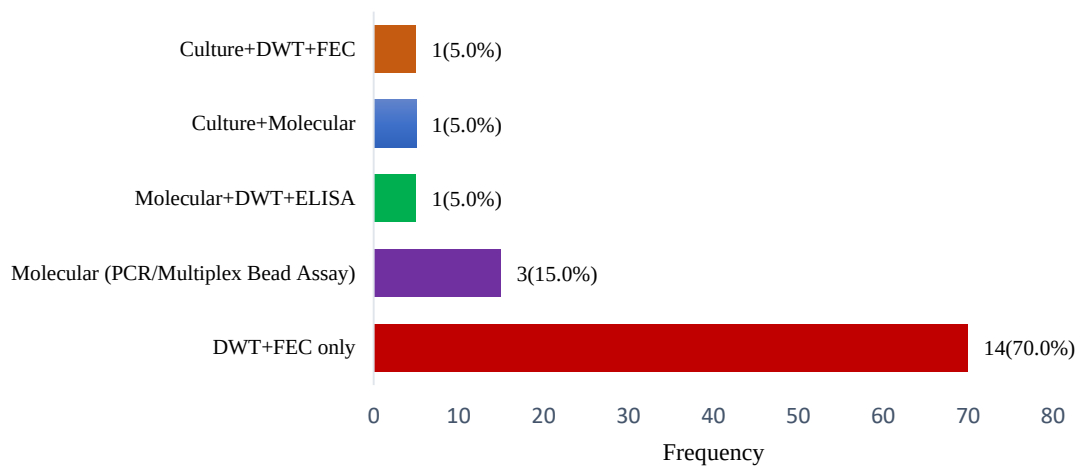


Figure 4. Diagnostic techniques used to detect *S. stercoralis*

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individuals (between 20 and 50 years) was 0.4%. The distribution of strongyloidiasis prevalence revealed 0.1% - 21.2%, 0.9% -2.9%, and 0.3% - 41.1% for northern, middle-belt, and southern sectors, respectively. Various techniques have been utilised to detect S. stercoralis in stool specimens during the period of this review. The direct wet mount and formal-ether concentration techniques were the most common, accounting for 70.0% of the cases, molecular methods, including PCR and Multiplex Bead Assay, represented 15.0%, and the combination of different techniques accounted for only 5.0%, as illustrated in Figure 4. The national prevalence of human strongyloidiasis in Ghana is low to moderate (median 1.45%), but extreme geographic heterogeneity exists, with localised hyperendemic regions (21.2% and 41.1%) inflating the mean to 4.5%. Different prevalence rates are reported across the regions, which is graphically represented to

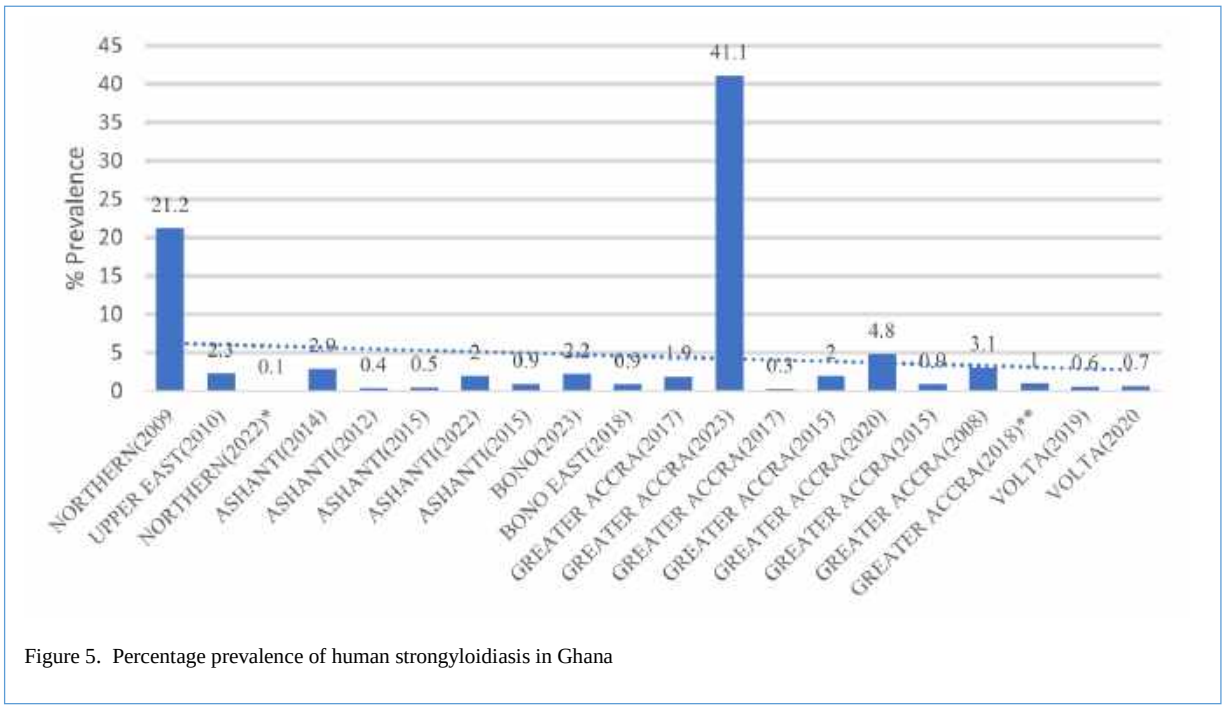


Figure 5. Percentage prevalence of human strongyloidiasis in Ghana

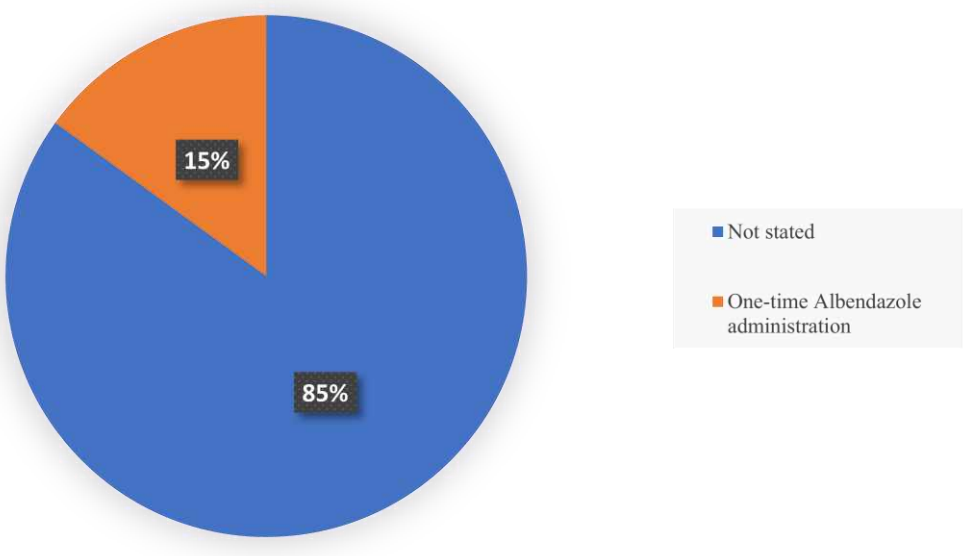


Figure 6. Proportion of studies that reported strongyloidiasis control intervention in Ghana

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enhance identifying areas that may require public health interventions (Figure 5).

Albendazole and mebendazole administration for preventive and curative purposes remain the single most implemented control measure reported in three (3) studies, while seventeen (17) studies did not state the nature of the intervention (Figure 6).

## DISCUSSION

Human *Strongyloides stercoralis* infection remains endemic and under-reported in many resource-limited settings, including Ghana, with the most at-risk population being children. This review assesses the prevalence and epidemiological data of human strongyloidiasis across Ghana to estimate the approximately twenty-year period prevalence of infection, suggests a need for further primary research, informs public health intervention, and the possibility of its elimination by 2030 as projected by the WHO.

**Diagnostic technique, prevalence, and demographic characteristics**

The prevalence of *Strongyloides stercoralis* infection in Ghana is low to moderate. Geographically, Ghana's southern, northern, and middle belts have the highest, moderate and least prevalence in that order. Unsafe water, poor personal and environmental sanitation, and poverty were factors that accounted for the transmission in resource-limited settings. The findings of this study are consistent with other similar studies in Ethiopia [74], Cambodia [75] and Brazil [76]. The sensitivity of the diagnostic technique used is vital to detecting *S. stercolaris* infection. In the present study, only five out of the 20 studies reported the use of molecular techniques for parasite detection. Such observation in a resource-poor setting demonstrates that the true prevalence of *Strongyloides stercoralis* infection is globally underestimated and under-reported due to the use of diagnostic techniques with poor sensitivity [26]. Stool microscopy and Kato-Katz techniques, which are commonly used for *Strongyloides stercoralis* detection, have poor diagnostic sensitivity and, hence, account for the underestimation of the global prevalence of the infection.

The concentration methods, such as the formol-ether concentration technique, Kogar agar plate culture and Baermann techniques, although quite better, have unsatisfactory sensitivity. Serological techniques provide a better alternative albeit with concerns regarding their specificity. Molecular techniques, such as polymerase chain reaction (PCR), albeit with a high parasite detection rate, are expensive and require technical expertise in their application. This challenge is further compounded by the delayed diagnosis of infection as a result of the non-presentation of specific gastrointestinal signs and symptoms, irregular larval output and low parasite load [77].

A study conducted in Kuwait [78] showed the prevalence of 7% and 1.45% out of 384 stool specimens examined for *S. stercoralis* using stool examination and ELISA-based serology techniques for individuals from endemic and non-endemic areas, respectively. A study conducted [79] in the Amhara region of Ethiopia revealed varied prevalence rates of strongyloidiasis based on the sensitivity of the diagnostic technique used. The prevalence based on the comparison of five diagnostic techniques reported 39.0%, 28.8%, 10.9%, 10.3%, 4.0% and 2.0% by real-time polymerase chain reaction (RT-PCR), agar plate culture (APC), Baermann concentration technique (BCT), spontaneous tube sedimentation technique (STST), and formol-ether concentration technique (FECT) respectively. Prevalence rates of 48.2%, 45.0%, and 41.1% were reported in children between 12-14 years, males and rural dwellers, respectively. A similar investigation conducted by Amor et al. [80] in north-western Ethiopia among school-aged children showed 3.5%, 12.1% and 13.4% by conventional stool concentration (formol-ether), Baermann and PCR, respectively. These comparable study outcomes further indicate that S. Stercoralis is under-reported and under-reported due to reliance on conventional diagnostic methods.

Non-molecular methods do not discriminate between the genetically diverse human pathogenic species: *Strongyloides stercoralis*, S. fuelleborni fuelleborni, and *S. fuelleborni kellyi* and other non-human species. Additionally, *S. fuelleborni* eggs in the stools of infected individuals may be misidentified as hookworm eggs since they have similar morphology. This poses another layer of challenge for accurate diagnosis and treatment in resource-limited areas. This speciation and identification were necessary for the detection of the pathogenic *S. fuelleborni* in a Belgian student returning from the Democratic Republic of Congo [81]. Precise knowledge of the biology of *S. fuelleborni* is required to aid the diagnosis. The ova of *S. fuelleborni* only hatch in the external environment, and the infective larvae are not detected in stool specimens, hence making autoinfection impossible [78].

The treatment of strongyloidiasis is oral ivermectin or benzimidazoles (thiabendazole, mebendazole, and albendazole). Although albendazole and thiabendazole are only considered alternatives to ivermectin, albendazole, and thiabendazole combination therapy is highly recommended in *Strongyloides stercoralis* endemic areas [39,47]. Mebendazole is contraindicated in pregnant women, while albendazole or ivermectin are better tolerated than thiabendazole, in humans [33,85]. As part of the global elimination strategy of strongyloidiasis and other soil-transmitted helminths, the World Health Organization (WHO) recommended the use of mass drug administration (MDA) to disrupt transmission and the disease burden in endemic areas. To this end, ivermectin is part of a triple-drug regimen (ivermectin, diethylcarbamazine and albendazole) instead of the two-drug regimen (diethylcarbamazine and albendazole or ivermectin and

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albendazole) currently being practised [82]. The direct target of this treatment regimen is the control of Lymphatic filariasis albeit providing ancillary benefit towards reducing the burden of strongyloidiasis [83]. There is a dearth of information regarding the resistance of *Strongyloides stercoralis* to ivermectin or benzimidazoles globally. Although an insufficient dosing regimen resulting in incomplete parasite clearing, low sensitive diagnostic technique, and reinfection could be misinterpreted as emerging resistance [46], non-human *Strongyloides stercoralis* resistance has been reported [39, 46]. Nonetheless, none of the studies included in this review reported treatment failure, emerging resistance, or poor tolerance of any of the recommended drugs for the treatment of strongyloidiasis. It is unclear if the drugs of choice remain efficacious in treating the parasite in Ghana.

Strongyloidiasis has a negative impact on the health and wellness of individuals, particularly children and pregnant women, in resource-limited settings, including Ghana [31, 84]. The lack of safe water, adequate sanitation, and proper personal and environmental hygiene practices are significant risk factor associated with the transmission of Strongyloides ster*coralis* and other soil-transmitted helminth infections [71]. While these factors are prevalent in both urban and rural areas of Ghana, a disproportionate number of studies have been conducted in southern Ghana, resulting in a critical research gap regarding the actual epidemiology of human strongyloidiasis.

**Strengths and weaknesses of this review**

This review is the result of a comprehensive search using general and inclusive terms with a well-structured synthesis of available data. Data on the control, prevention, and elimination of strongyloidiasis as a neglected tropical disease in Ghana were included. The limitation of this study is the exclusion of studies not carried out in Ghana and articles published earlier than 2003 and after December 2023, leading to the omission of potentially valuable research articles for this review. Furthermore, the exclusion of non-English studies may have led to language bias.

**Knowledge and research gaps identified**

1. Effective control and elimination of strongyloidiasis as a neglected tropical disease can only be achieved based on the evidence of current national epidemiological data. This will guide the planning, implementation, monitoring, and evaluation of any preventive chemotherapeutic measures such as mass drug administration.

2. Animal strongyloidiasis reported elsewhere in cattle, dogs, and cats is an evolving phenomenon that must engage the attention of researchers. Studies on this will provide the needed information on the detection, population structure, genetics, interrelatedness of human and animal strongyloidiasis, and zoonotic potential.

3. Molecular study of *S. stercoralis* and genomic analysis of *S. stercoralis* isolates is currently lacking in Ghana. Molecular data will provide information on the susceptibility or resistance of Ghanaian *S. stercoralis* isolates to ivermectin and benzimidazoles (albendazole and thiabendazole).

**Conclusion**

The national prevalence of strongyloidiasis in Ghana is low to moderate (median 1.45%), but there are areas with extreme geographic heterogeneity, including hyperendemic regions (21.2% and 41.1%), thus increasing the mean to 4.5%. Population-weighted studies are essential for accurate national estimates, and targeted interventions are urgently needed to address high-transmission hotspots and underlying drivers of transmission. With further research and targeted interventions, Ghana is likely to meet the WHO's elimination target by 2030.

## DECLARATIONS

**Ethical consideration**

Not Applicable

**Consent to publish**

All authors agreed on the content of the final paper.

**Funding**

None

**Competing Interest**

The authors declare no conflict of interest

**Author contribution**

GBK, PBT-Q, PFA-K, and CYD conceived the study. CYD, PBT-Q, JPK and IA reviewed relevant literature. CYD drafted the manuscript which was critically reviewed by JPK, IA, GBK, PBT-Q, and PFA-K. All authors read, edited, and approved the manuscript.

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**Availability of data**

Data is available upon request to the corresponding author

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# Occurrence and Antimicrobial Resistance of Extended-Spectrum Beta-Lactamase Producing Bacteria in Diabetic Foot Infections at Korle-Bu Teaching Hospital

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**Abstract**

***Background:*** Common complications of diabetes mellitus include foot infections, which lead to increased healthcare cost and delayed wound healing. Diabetic foot infections (DFIs) can be caused by Gram-negative, Extended-Spectrum Beta-Lactamase (ESBL) producing bacteria which are resistant to a wide range of antibiotics used in clinical medicine. This presents a significant challenge to the treatment of DFIs. However, identifying the bacterial species involved can be critical for effective management and targeted therapy.

***Objective:*** The study investigated the antimicrobial resistance and molecular characteristics of ESBL-producing bacteria from diabetic foot infections at Korle Bu Teaching Hospital (KBTH) using disk diffusion and Polymerase Chain Reaction (PCR).

***Methods:*** From January to September 2018, tissue samples, aspirates, or pus were collected from diabetic patients from the ulcer room at the department of surgery, KBTH. Patients' demographics were gathered using a data collection tool. Bacterial culture, antimicrobial susceptibility testing and PCR detection of ESBL genes were performed.

***Results:*** In total, 138 Gram-negative isolates were recovered from the 50 study participants enrolled. Majority of the isolates were resistant to ciprofloxacin (55.79%, n = 77/138) but susceptible to meropenem (97.82%, n = 135/138). Among the isolates, 41 (29.71%) were phenotypically positive for ESBL production using CHROMagar ESBL. The *CTX-M* gene was predominantly identified in *E. coli* (9/19) by PCR.

***Conclusion:*** ESBL-producing Gram-negative bacteria continue to pose a major challenge in Ghana, with the *CTX-M* gene identified as the most prevalent among ESBL-positive isolates. Notably, a majority of the isolates remained susceptible to meropenem, suggesting its potential as an effective treatment option. Continued surveillance is crucial to monitor the emergence and dissemination of AMR pathogens in DFIs.

**Keywords:** Diabetic foot infection, ESBL, AMR, Ghana

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## INTRODUCTION

Diabetic foot infection (DFI) is a major complication among diabetic patients which often leads to prolonged wound healing and hospitalization, amputations and in extreme cases death. Several factors including neuropathy, poor blood circulation, and a weakened immune system all of which are prevalent in diabetic patients contribute to these infections [1]. A crude estimate of diabetes in Ghana shows a prevalence of 6.30% with foot infections, gangrene, abscess, and cellulitis being the most common surgical complications [2,3]. DFIs can be either

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polymicrobial or monomicrobial, however, majority are complex polymicrobial infections commonly caused by *Escherichia coli, Klebsiella spp, Proteus spp, Pseudomonas aeruginosa* and obligate anaerobes such as *Bacteroides spp* [1,4,5,6].

Early and appropriate antibiotic treatment targeting the most likely etiological agent is vital in the management of these foot infections. However, the emergence of antimicrobial resistance particularly among Enterobacterales and *Pseudomonas spp* producing Extended-Spectrum Beta-Lactamase (ESBL) complicates the process [1,7,8,9]. In Ghana, a nationwide survey of ESBL prevalence showed a fast-growing silent pandemic with rates ranging from 41.50% to 50.50% [10-13]. This rise is compelling clinicians to prescribe second- and third-generation antimicrobials, which are typically in the reserve group for clinical use, especially in deep seated infections with poor healing history such as diabetic foot infections. The excessive reliance on these antibiotics accelerates the emergence of resistant bacterial strains, reducing therapeutic options and increasing treatment failures. Given these challenges, investigating resistance patterns and the genetic mechanisms underlying ESBL production is crucial. A deeper understanding of these factors can aid in optimizing antibiotic therapy, enhancing patient outcomes, controlling the spread of resistant bacteria, and informing public health strategies. This study investigated the antimicrobial resistance patterns and genetic determinants of resistance in ESBL-producing bacterial species recovered from diabetic foot infections.

## MATERIALS AND METHODS

### Study Site, Study Design and Sampling

In this prospective cross-sectional study, 50 diabetic patients with inframalleolar foot infections including ulcer, cellulitis, gangrene, plantar fasciitis and necrotising fasciitis were enrolled at the ulcer room of the department of surgery at the Korle-Bu Teaching Hospital (KBTH). The Perfusion, Extent, Depth, Infection and Sensation (PEDIS) index as described by the Infectious Diseases Society of America and International Working Group on the Diabetic Foot was used to establish colonisation, contamination and infection, ensuring careful selection of participants for the study [14].

After obtaining informed consent, tissue biopsies were collected during debridement by a qualified surgeon. Localised anaesthesia was administered using a subcutaneous injection of 2% w/v lidocaine by a qualified nurse anaesthetic before collection. For patients with deep-seated pus, aspirates or fluid from fluctuant areas were collected using sterile syringes. Patients' treatment histories were collected for the period between January and October 2018. Additionally, demographic data, including age, gender, and empirical antibiotic treatment were also obtained. Patients' blood sugar and blood pressure were also checked and recorded.

### Sample Preparation and Transport

Tissue samples, pus and aspirates collected were quickly dispensed into a glass bottle containing thioglycolate broth, capped, sealed with parafilm and transported (within 4 hours of sampling) to the Bacteriology Department of the Noguchi Memorial Institute for Medical Research, for analysis.

### Bacterial identification

The broth sample mixture was incubated aerobically for 18-24 hours at 37 ºC prior to subculture. The samples were then plated on Blood agar and MacConkey agar and incubated aerobically for 18-24 hours at 37 ºC. Preliminary identification of bacteria was done by colonial morphology and Gram staining. Bacterial identification was confirmed using the Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF-MS) (Bruker Daltonics, Germany). Briefly, colonies from fresh overnight cultures were spotted on the target plate. One microliter of formic acid was then added and allowed to dry for 15 minutes. One microliter of matrix preparation was then placed on each sample and left to dry for about 15 minutes. The target plate was then introduced into the machine. Within the machine, the ionization peaks (spectra) generated were matched against the integrated reference library of the MALDI system for confirmation of bacteria species.

### Antibiotic Susceptibility Testing and ESBL phenotypic screening

Antibiotic susceptibility testing was performed by the Kirby-Bauer disk diffusion method and interpreted according to the Clinical Laboratory Standards Institute (CLSI 2018) guidelines [15]. Gram-negative organisms recovered were screened for production of ESBL using CHROMagar ESBL (Biomerieux, France). The isolates were inoculated on the agar and incubated aerobically for 18 - 24 hours at 37ºC. The plates were observed for growth and colony appearance after incubation. ESBL-positive strain *K. pneumoniae* NCTC 13368 (ATCC 700603) and ESBL-negative strain *E. coli* ATCC 25922 were used as Controls.

### Polymerase Chain Reaction (PCR) Detection of ESBL genes (*CTX-M, SHV and TEM-1*)

Multiplex PCR was performed on presumptive ESBL-producing isolates to determine ESBL genes (*CTX-M, SHV and TEM-1*) as described by Sharma et al., (2013) [16]. Briefly, crude DNA was obtained by transferring three freshly prepared colonies of bacteria into 200µl of molecular-grade nuclease-free water and boiled for 5 minutes at 98 °C. The resulting mixture was frozen in -20 ºC for 10 minutes. The mixture was then centrifuged for 5 minutes at 4 °C and the supernatant was transferred into Eppendorf® tubes and used as DNA template for the PCR. For PCR amplification, each reaction-mix of 25 µL consisted of 12.5 uL of Green PCR Master Mix (2×) (DreamTaq, Thermo Scientific, Waltham, MA, USA), 4.5 µL of primer mix, 6 µL of molecular-grade nuclease-free

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water and 2 µL of crude DNA template, as previously demonstrated by Khurana et al., 2018. [17]. Table 1 shows the primers used for the PCR. The cycling conditions included initial denaturation at 95 °C for 5 minutes, followed by denaturation at 95 °C for additional 30 seconds and template annealing for 30 seconds and elongation at 72 °C for 2 minutes and final elongation for 10 minutes. All PCR amplicons were analyzed with gel-electrophoresis in a 2% (weight/volume) agarose gel (SeaKem®GTG®Agarose, Lonza, Basel, Switzerland) using Tris/Acetate/EDTA buffer.

**Data Analysis**

Data collected were entered into Microsoft excel version 2016. The data were checked for consistency and then transferred into Epi Info Version 7.2.6 software for statistical analysis. This was presented as frequencies and percentages in tables.

## RESULTS

In total, 50 patients comprising nine (9) in-patients and 41 out-patients were recruited in this study. There was a gender balance of (50.00%, n = 25) males and (50.00%, n = 25) females. Majority of the participants (38.00%, n = 19) fell in the 60 years to 70 years age group. The nature of infections seen included ulcers (80.00%, n = 40), abscess (6.00%, n = 3), cellulitis (10.00%, n = 5) and plantar fasciitis (2.00%, n = 1). Table 2 shows the demographic characteristics of patients involved in the study. Random blood sugar was

Table 1. List of primer sets showing the oligonucleotides

| Gene | Primer set | Expected amplicon size (bp) |
|---|---|---|
| *TEM*-1 | F:5′-GAGACAATAACCCTGGTAAAT-3′ | 459 |
| | R:5′-AGAAGTAAGTTGGCAGCAGTG-3′ | |
| *CTX*-M | F:5′-GAAGGTCATCAAGAAGGTGCG-3’ | 560 |
| | R:5′-AGAAGTAAGTTGGCAGCAGTG-3′ | |
| *SHV* | F:5’-GTCAGCGAAAAACACCTTGCC-3’ | 383 |
| | R:5’-GTCTTATCGGCGATAAACCAG-3’ | |

Table 2. Demographic table (showing distribution of age, sex and infection type)

| Characteristics | Group | Frequency (%) |
|---|---|---|
| Sex | Female | 25(50.00%) |
| | Male | 25(50.00%) |
| Department | IPD | 9(18.00%) |
| | OPD | 41(82.00%) |
| Age | ≤60 | 25(50.00%) |
| | ≥60 | 25(50.00%) |
| Type of infection | Ulcers | 40(80.00%) |
| | Abscess | 3(6.00%) |
| | Cellulitis | 5(10.00%) |
| | Plantar fasciitis | 1(2.00%) |

Table 3. Empirical Antibiotic Treatment of Various Infections with Associated ESBL Genes

| ESBL bacteria | Patient ID | Sex | Infection | Empirical antibiotic given | Phenotypic antibiotype | ESBL gene |
|---|---|---|---|---|---|---|
| *Escherichia coli* | 1G | M | Ulcer | CLN | AMC/MEM/GEN/PIP | *TEM/CTX/SHV* |
| | 2A | M | Ulcer | NI | AMC/MEM/GEN/PIP | *CTX* |
| | 3N | M | Ulcer | NI | AMC/MEM/GEN/PIP | *CTX* |
| | 4J | F | Ulcer | NI | AMC/MEM/GEN/PIP | *CTX* |
| | 6B | F | Abscess | FLU | MEM/CHL/GEN/CFT/PIP | *TEM* |
| | 9B | F | Cellulitis | AMC | MEM/GEN/PIP | *CTX* |
| | 11B | M | Ulcer | CLN | AMC/MEM/GEN/CIP | *SHV* |
| | 17D | M | Ulcer | CLN | MEM/GEN/PIP | *TEM/CTX* |
| | 18B | M | Ulcer | CLN | MEM/GEN/PIP | *SHV/CTX* |
| | 21C | M | Ulcer | | MEM/GEN/CIP/CFT | *CTX* |
| | 27A | M | Ulcer | CLN | CFX/AMC/MEM/CTM/CFP/GEN/PIP | *CTX* |
| *Enterobacter kobei* | 7C | F | Ulcer | CLN | MEM/CHL/CEF/GEN/CIP | *TEM/CTX* |
| *Klebsiella pneumoniae* | 4K | F | Ulcer | NI | MEM/CHL/CFT | *TEM/CTX/SHV* |
| | 5G | F | Ulcer | NI | TET/CHL/GEN | *TEM/CTX/SHV* |
| *Morganella morganii* | 14B | F | Cellulitis | CLN/CIP | CTM/MEM/CFP/GEN/PIP | *SHV/TEM* |
| *Proteus mirabilis* | 5D | F | Ulcer | NI | AMC/MEM/CTM/CFP/GEN/CFT/PIP | *CTX* |
| | 40A | F | Ulcer | CLN/CIP | MEM/GEN/CFT/PIP | *TEM/CTX* |
| *Providencia stuartii* | 27I | M | Ulcer | CLN | MEM/CFP/GEN/PIP | *SHV/CTX* |
| *P. aeruginosa* | 10J | F | Plantar fasciitis | AMC | MEM/TET/CFT/CFP/GEN/CIP/PIP | *TEM/CTX/SHV* |
| | 27C | M | Ulcer | CLN | MEM/TET/CHL/CFP/GEN/CIP/CFT/PIP | *TEM/CTX/SHV* |
| | 47A | M | Ulcer | CIP/CLN | MEM/CFP/GEN/CIP | *CTX* |

*AMC-Amoxicillin/Clavulanate, CLN- Clindamycin, CIP-Ciprofloxacin, FLU- Flucloxacin, NI-not indicated MEM-Meropenems, CFX-Cefuroxime, CTM-Cefotaxime, CFP-Cefepime, CFT- Ceftazidime GEN-Gentamicin, PIP-Pipercillin-tazobactam, CHL-Chloramphenicol, M-Male, F-Female

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Table 4. Distribution of bacteria isolates among wound types sampled from diabetic patients

| Bacterial Isolate | Ulcers 40(80%) | Abscess 3(6%) | Plantar Fasciitis 1(2%) | Cellulitis 5(10%) | CHROMagar ESBL Positive |
|---|---|---|---|---|---|
| *Proteus mirabilis* (n=31) | 24(22.22) | 2(18.18) | 2(33.33) | 3(23.07) | 2(6.45) |
| *Proteus vulgaris* (n=13) | 10(9.25) | 0 | 1(16.66) | 2(15.38) | 0 |
| *Klebsiella pneumoniae* (n=14) | 10(9.25) | 2(18.18) | 0 | 2(15.38) | 4(28.57) |
| *Klebsiella oxytoca* (n=8) | 4(3.70) | 2(18.18) | 1(16.66) | 1(7.69) | 1(12.50) |
| *Escherichia coli* (n=38) | 32(29.62) | 2(18.18) | 2(33.33) | 2(15.38) | 19(50.00) |
| *Enterobacter cloacae* (n=4) | 4(3.70) | 0 | 0 | 0 | 0 |
| *Pseudomonas aeruginosa*(n=24) | 19(17.59) | 3(27.27) | 0 | 2(15.38) | 9(37.50) |
| *Morganella morganii* (n=2) | 1(0.92) | 0 | 0 | 1(7.69) | 2(100) |
| *Providencia stuartii* (n=3) | 3(2.77) | 0 | 0 | 0 | 3(100) |
| *Enterobacter kobei* (n=1) | 1(0.92) | 0 | 0 | 0 | 1(100) |
| Total | 108 | 11 | 6 | 13 | 41 |

Table 5. Distribution of ESBL genes among ESBL-positive isolates

| Isolates | *SHV*(%) | *TEM-1*(%) | *CTX-M*(%) | Total No. of genes detected |
|---|---|---|---|---|
| *Escherichia coli*(n=19) | 3(33.33) | 3(30.00) | 9(50.00) | 15 |
| *Pseudomonas aeruginosa*(n=9) | 2(22.22) | 2(20.00) | 3(16.66) | 7 |
| *Klebsiella pneumoniae*(n=4) | 2(22.22) | 2(20.00) | 2(11.11) | 6 |
| *Proteus mirabilis*(n=2) | 0 | 1(10.00) | 2(11.11) | 3 |
| *Enterobacter kobei*(n=1) | 0 | 1(10.00) | 1(5.55) | 2 |
| *Morganella morganii*(n=2) | 1(11.11) | 1(10.00) | 0 | 2 |
| *Providencia stuartii*(n=3) | 1(11.11) | 0 | 1(5.55) | 2 |
| Total | 9 | 10 | 18 | 37 |

No gene was detected in *Klebsiella oxytoca* (n=1)

tested using a One-touch select glucometer, with the median blood sugar in the study being 9.85 mmol/L. Out of the 50 patients, 88.0% (n = 44) were already receiving antibiotic treatment. Four patients were on B-lactam/β-lactamase inhibitors, nine (9) were on aminoglycoside/fluoroquinolones combination therapy, and three (3) on aminoglycosides/ fluoroquinolone/β-lactamase triple therapy. Three patients received quinolone monotherapy, while aminoglycoside monotherapy was administered to 21 patients. Table 3 shows antibiotics administered to patients with ESBL-producing bacteria.

**Bacterial Isolates, Antimicrobial Resistance and ESBL Production**

A number of patients (20.00%, n = 10/50) had polymicrobial infections. A total of 138 Gram-negative bacteria species were recovered and 29.71% (n = 41) showed positivity for ESBL production using CHROM agar. Among them were *Escherichia coli* (46.34%, n = 19/41), *Pseudomonas aeruginosa* (21.95%, n = 9/41) and *Klebsiella pneumoniae* (9.75%, n = 4/41). Isolates recovered were resistant to ciprofloxacin (55.79%, n = 77/138), cefepime (44.20%, n =61/138), but susceptible to meropenem (97.82%, n = 135/138), gentamicin (97.82%, n = 135/138) and piperacillin-tazobactam (95.65%, n = 132/138). Table 4 shows the distribution of isolates recovered, type of infections as well as the proportions of ESBL positive isolates.

**Distribution of ESBL Genes Among ESBL Positive Isolates**

All three ESBL genes (*TEM-1*, *SHV*, *CTX-M*) were detected in one *E. coli*, two *K. pneumoniae*, and two *P. aeruginosa* isolates. Six isolates had both *TEM* and *SHV* genes. *TEM* and *CTX-M* genes were both present in 8 of the isolates. Both *SHV* and *CTX-M* were found in 7 isolates. Phenotypic ESBL detection indicated ESBL production in *Klebsiella oxytoca*, however, none of the genes associated with ESBL production was found in the isolate. Table 5.0 shows the distribution of ESBL genes among the ESBL-positive isolates.

## DISCUSSION

In this study, the presence of ESBL among bacterial isolates obtained from diabetic foot infections and their accompanying antimicrobial resistance patterns was investigated. DFIs present a significant and challenging complication for individuals with diabetes, often leading to severe outcomes. Ulcers were observed as being the most common diabetic foot infections. Gram-negative bacteria were isolated from the DFIs and many of the infections were polymicrobial which probably contributed to poor wound healing [4-6]. This study presents an overall ESBL-producing percentage positivity of 29.70% with *E. coli* having the highest level of ESBL positivity. Other studies in Ghana

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have reported rates of 57.80% (Kumasi), 50.50% and 43.70% (Accra) as well as 41.50% (Ho) [10-13]. In Africa, studies have recorded prevalence rates of 50.00% (Lagos, Nigeria) and 36.10% (South Africa) [18,19]. Several other African studies have also reported relatively high levels of ESBL- producing *E. coli* [20-23]. ESBL percentage positivity among *Proteus mirablilis*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were 6.45%, 28.57%, and 37.50%, respectively, which is not unexpected. The prevalence of ESBL-producing organisms observed in this study, along with findings from previous research in the country, is concerning as it significantly limits available treatment options and contributes to increased rates of therapeutic failure [13]. In light of these challenges, urgent intervention is needed, particularly the strengthening of laboratory capacity as most clinical microbiology laboratories in Ghana do not routinely test for ESBLs. The widespread practice of self-medication without prior laboratory diagnosis, coupled with the limited capacity to detect and report ESBLs at the community level, may further drive the emergence of antibiotic resistance. If not addressed, this growing threat could have serious implications, especially for patients with diabetic foot infections, where treatment options are already limited. Isolates recovered frequently demonstrated resistance to amoxicillin and ciprofloxacin, which are preferred antibiotics for managing patients with diabetic foot infections in the hospital setting. The high proportion of resistance could be as a result of indiscriminate use of these antimicrobials [24]. The low resistance to meropenem and gentamicin reflects their less frequent usage among patients. Meropenem has emerged as the antimicrobial agent of choice in the treatment of serious infections caused by ESBL-producers based on in vitro testing [11,25,26]. Preserving the efficacy of this drug is an essential measure as they belong to the category of critically needed antibiotics used to treat life-threatening infections caused by *E. coli* and other pathogens in humans. Significantly, the second and third-generation cephalosporins exhibited a resistance percentage ranging from 70% to 75%. Fortunately, they were not observed to be frequently prescribed to patients in this study. Some strains also exhibited co-resistance to aminoglycosides, quinolones, and third-generation cephalosporins. This is a significant concern, as these strains may lead to therapeutic challenges [27,28]. Among the three genes detected (*SHV, TEM-1, CTX-M*), *CTX-M* was prevalent among ESBL-producing *E. coli*, similar to the observation made among the isolates recovered in Komfo Anokye Teaching Hospital, Ghana [11]. Although *Klebsiella oxytoca* tested positive for ESBL on Chromagar, none of the ESBL genes (*CTX-M, TEM-1 and SHV*) were detected. The mode of resistance may involve efflux pumps or the utilization of cell wall transpeptidases that are insensitive to β-lactam antimicrobials [29].

### Conclusion

This study found that several organisms causing diabetic foot infections (DFIs) were ESBL producers. Among these, ESBL-positive *E. coli* had a high prevalence, with *CTX-M* and *TEM-1* identified as the predominant resistance genes. Although few in number, some ESBL isolates also exhibited resistance to meropenem, a reserve antibiotic. These findings highlight the urgent need for continuous surveillance and preventive measures to curb the spread of resistant bacteria.

## DECLARATIONS

### Ethical consideration

This work received clearance from the Ethical and Protocol Review Committee of the University of Ghana Medical School. Patients were provided with written consent before enrolment into the study. All specimen were labelled using a unique coding system to ensure confidentiality. Written consent was obtained from each patient before enrolling into the study.

### Consent to publish

All authors agreed to the content of the final paper.

### Funding

None

### Competing Interest

The authors have no conflict of interest to declare.

### Author contribution

BE, KS, and PF conceptualized the study. KS, JB, SS, and BE designed the methodology. BE, KS, JB, and SS conducted the investigation and performed formal analysis. BE, KS, NO-N, PF, JB, and SS contributed to validation. KS, BE, JB and SS handled data curation. KS and BE drafted the original manuscript. BE, KS, SS, JB, NO-N, and PF reviewed and revised the manuscript. KS, BE, JB and PF contributed to visualization. BE and PF supervised the study. BE managed the project and acquired funding. All authors read and approved the final manuscript.

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### Availability of data

Data is available upon request to the corresponding author

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# High antibiotic resistance and elevated plasma IFNγ from type 2 diabetes mellitus (T2DM) patients with uropathogens visiting Cape Coast Teaching Hospital

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**Abstract**

***Background:*** Diabetes mellitus (DM) is a polygenic metabolic disorder characterised by persistent elevated plasma glucose levels, which can lead to a range of complications, including an increased susceptibility to infections such as urinary tract infections (UTIs). Studies have shown that DM significantly increases the incidence of UTIs, and this is primarily due to a weakened immune system and the presence of glucosuria.

***Objective:*** The study aimed to determine cytokine profiles in the peripheral blood, identify common uropathogens and analyse their antibiotic susceptibility patterns in DM patients reporting for treatment at Cape Coast Teaching Hospital (CCTH).

***Methods:*** In a prospective study design, midstream urine and peripheral blood samples were collected from 202 known Type 2 diabetic patients recruited for the study. Using standard bacteriological methods, uropathogens were isolated and identified, and antibiogram testing was performed using the Kirby–Bauer disk diffusion method. Plasma concentrations of IL1β, IL6, IL10, IL17, IFNγ, and TNF-α cytokines were measured using an ELISA kit.

***Results:*** This study recorded a 43.1% prevalence of UTIs among diabetic patients, with the main uropathogens identified as Escherichia coli (18.8%), Citrobacter *spp.* (11.4%), and Enterobacter *spp.* (5.4%). The study also observed a high level of antibiotic resistance among the uropathogens, particularly to widely used broad-spectrum antibiotics such as Nalidixic Acid, Cefuroxime, Aztreonam, Cefotaxime, Ceftriaxone, Ceftazidime, Cefixime, and Cefdinir. There were significantly higher levels of IFNγ among the diabetic patients with UTI, but there were no significant changes in the levels of IL1β, IL6, IL10, IL17 and TNF-α cytokines among the diabetes patients with or without uropathogens.

***Conclusion:*** Our findings suggest that patients with diabetes have frequent UTIs, and the isolated uropathogens were highly resistant to antibiotics. Again, there were higher levels of pro-inflammatory cytokine IFNγ in diabetic patients with UTI. Our findings suggest that patients with diabetes experience frequent UTIs, and the isolated uropathogens show high levels of resistance to antibiotics. Additionally, we observed higher levels of the pro-inflammatory cytokine IFN-γ in diabetic patients with UTI. This elevated cytokine level could play a role in the immune response to infections and may serve as a potential biomarker for identifying UTIs in type 2 diabetic patients. The combination of frequent UTIs and antibiotic resistance highlights the need for improved management strategies and targeted therapies in this population.

**Keywords:** Antibiotics, cytokines, diabetes, uropathogens, prevalence

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## INTRODUCTION

Diabetes mellitus (DM) is a condition characterised by persistent hyperglycemia, resulting from either insulin deficiency or poor cellular response to insulin [1,2]. According to the International Diabetes Federation (IDF), an estimated 537 million adults aged 20 – 79 years worldwide, representing 10.5% of all adults in this age group, are living with DM. By 2030, this number is projected to rise to 643 million [3]. The increase in DM cases is expected to be predominantly in low and middle-

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income countries, with 94% of the growth occurrin by 2045 [3]. Uncontrolled DM can lead to life-threatening complications such as stroke, nephropathy, neuropathy, and retinopathy [4,5]. Moreover, uncontrolled DM can be accompanied by common uropathogens and other UTIs [6,7,8], which, if not properly managed, may often lead to complications such as disability and, in severe cases, premature death. DM has been found to be associated with reduced immunity and bladder dysfunction, which makes a diabetic individual more vulnerable to UTI [9].

Studies have shown that immunological deficiencies in diabetic patients, including impaired neutrophil migration, intracellular killing, phagocytosis, and abnormal levels of cytokines like interleukin (IL)-1β, IL-2, IL-6, IL-12, tumour necrosis factor (TNF)-α, and interferon-gamma (IFN)-γ [10,11], can contribute to bacterial colonisation and infection [12,13]. Also, pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, have been shown to significantly influence the pathophysiology of diabetic peripheral neuropathy (DPN) [14], which is a debilitating complication of diabetes mellitus.

Researchers have argued that the irrational use of antibiotics in diabetic patients has contributed to the increase in antibiotic-resistant uropathogens [15,16]. This improper or overuse of antibiotics can promote the development of resistance, making infections harder to treat and further complicating the management of UTIs in diabetic individuals. The etiologic agents responsible for UTIs and the varying resistance and susceptibility rates to commonly prescribed antibiotics can lead to longer hospital stays and increased treatment costs [17]. Moreover, antibiotic resistance to newer and more potent antimicrobials is reducing treatment options for UTIs, particularly affecting DM patients who are already more vulnerable to infections [18]. Unfortunately, there has been limited research in Ghana focused on identifying common uropathogens in DM patients, their antibiotic susceptibility profiles, and the levels of pro-inflammatory cytokines in the peripheral blood of these patients. This gap in research hinders a deeper understanding of UTIs in DM individuals and the effectiveness of treatment options. The purpose of the current study is to evaluate the peripheral blood immune environment (cytokine profiles of Th1, Th2, and Th17), identify common uropathogens, and assess their antibiotic resistance and susceptibility patterns in diabetic patients visiting Cape Coast Teaching Hospital. This research aims to provide valuable insights into the immunological and microbiological aspects of UTIs in diabetic individuals, ultimately contributing to more effective management and treatment strategies for these patients.

## MATERIALS AND METHODS

### Study design and sites

The study was a cross-sectional design conducted from October 2020 to December 2020 at the diabetic unit of the CCTH, a tertiary hospital with about 400-bed capacity within the Cape Coast Metropolitan District in the Central Region of Ghana. The patients were selected from those receiving treatment and glucose level monitoring at the diabetic unit, using a convenient sampling method. Medical records of participants were reviewed to obtain additional relevant information on demographic and clinical data.

### Recruitment of study participants

From a study population of approximately 412 type 2 diabetic patients who visited the CCTH daily for check-ups, a total of 202 patients aged between 18 and 83 years were recruited for the study using a convenience sampling technique.

The formula $n = \frac{\frac{Z^2 \, x \, P(1-P)}{E^2}}{1+\left(\frac{Z^2 \, x \, P(1-P)}{E^2 N}\right)}$

Where E = 0.05, N = 412, Z = 1.96 and P = 0.5 was used to evaluate and determine the required minimum sample size [19].

N = Population size
Z = z-score
E = margin of error
P = standard of deviation

$$n = \frac{\frac{1.96^2 \, x \, 0.5(1-0.5)}{0.05^2}}{1+\left(\frac{1.96^2 \, x \, 0.5(1-0.5)}{0.05^2 X 412}\right)} = \frac{\frac{3.8416x \, 0.25}{0.0025}}{1+\left(\frac{3.8416 \, x \, 0.25}{1.03}\right)} = \frac{\frac{0.9604}{0.0025}}{1+\left(\frac{0.9604}{1.03}\right)} = \frac{384.16}{1.932} = 199$$

### Inclusion criteria

Study participants were known type 2 diabetics for at least 3 years prior to the study and were actively receiving treatment in the diabetes clinic of CCTH. They had individually consented before being included in this research.

### Exclusion criteria

Patients were excluded from the study if they were known type 1 diabetics, were on antibiotic therapy or had a malaria infection within 14 days prior to recruitment. Individuals who were known as HIV-positive, pregnant, with gynaecological/urological disorders, undergone a kidney transplant, or using a catheter were all excluded from this study. Additionally, exclusion criteria included recent type 2 diabetics who had any of the following conditions: genitourinary surgery, urinary incontinence, urinary retention, psychiatric disorders or age above 83 years were excluded from this study. Furthermore, urine cultures that showed Candida growth were not included in the analysis of uropathogens.

### Sample collection and processing

#### Sociodemographic data and clinical history

Information on age, gender, duration of diabetes, complications, previous infections, medications, and laboratory findings upon admission were extracted from the patient's folder and electronic medical records. This was

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done through an open-loop interview and a structured questionnaire.

**Fasting Plasma Glucose (FPG) measurement.**
Fasting Plasma Glucose (FPG) levels of the study participants, including both known type 2 diabetics and non-diabetics, were measured using a glucometer (Morepen Gluco One Blood Glucose Monitor, Model BG 03) prior to the collection of their urine samples.

**Specimen collection**
All participants were carefully instructed to collect midstream urine samples using a sterile, graduated, wide-open plastic container. Female participants were also provided with sterile gauze to perform a front-to-back cleaning before urination. The urine samples were stored in the refrigerator after collection. Further microbiological investigations were conducted at the Microbiology Laboratory Department of the CCTH.

**Microbiological analysis**
Bacterial isolation and identification: Urine specimens were directly inoculated onto cysteine lactose electrolyte deficient (CLED) agar using a standard graduated wire loop. After 24 hours of aerobic incubation at 37◦C, the plates were examined macroscopically for morphological appearance as presumptive identification. The growth of bacterial colonies on the media was defined as a positive urine culture which was greater than 105 CFU/ml. Examination of the morphological appearance of the colonies was investigated. Gram staining was used for the identification of the bacteria. Citrate tests, indole tests, urease tests, and triple sugar iron (TSI) agar were the biochemical tests that were used to confirm the presence and isolation of the bacteria.

**Antimicrobial susceptibility testing**
The antimicrobial susceptibility test (AST) was done for each of the Uropathogens isolated, using the modified Kirby-Bauer disc diffusion method to identify resistant and sensitive isolates. A uniform lawn over the entire surface of Mueller-Hinton agar, using a sterile cotton swab, was dipped into the peptone water. Norfloxacin (NOR/10 µg), Aztreonam (AT/30 µg), Cefotaxime (CTX/30 µg), Nalidixic acid (NA/30 µg), Nitrofurantoin (NI/300 µg), Cefuroxime (XM/30 µg), Gentamycin (GM/10 µg), Amikacin (AK/30 µg), Ciprofloxacin (CI/5 µg), Ofloxacin (OF/5 µg), Cefixime (FIX/5 µg), Cefdinir (CD/5 µg), Ceftazidime (CAZ/30 µg), Levofloxacin (LEV), Ceftriaxone (CTR), Cotrimoxazole (COT), Chloramphenicol (CHL), Tetracycline (TET), Ampicillin (AMP), a total of 12 antibiotics were used on the bacteria isolates.

**Quality control**
The sterility and performance of the culture media were tested prior to using the culture media. Standard reference strains of E. coli (ATCC 25922) and S. aureus (ATCC 25923) were used as controls for culture and sensitivity testing.

**Cytokine measurement**
About 5 mL of venous blood was collected from each participant and placed into the EDTA tubes to obtain plasma. The plasma was then collected and stored in cryovials at −80 °C until ready to be used for the cytokine assays. Plasma concentrations of interleukin-6, interleukin-1β, interleukin-17, interleukin-10, interferon-gamma, and tumour necrotic factor-alpha were assessed using sandwich ELISA kits from CUSABIO Bihmmnn;otech (Wuhan, China). Strict manufacturer's protocols were followed. Cytokines in stored plasma were analysed using the Mindray MR-96A ELISA plate reader (Shenzhen, China).

**Statistical analysis**
All statistical analyses were performed using the GraphPad Prism version 8.0.1 (244) software. The results were expressed as means and standard deviations (SDs). For comparisons within groups, Analysis of Variance (ANOVA) was used. Continuous and categorical variables were summarised as counts and percentages. Univariable and multivariate logistic regression models were performed. Correlation analysis was performed by using the Pearson Correlation Coefficient. $P < 0.05$ was considered statistically significant in all analyses.

## RESULTS

As shown in Table 1, 87 out of 202 diabetic patients were found to have UTI, resulting in a prevalence of 43.1%. The percentage of female participants with positive urine cultures (50%) was significantly higher than that of their male counterparts ($p = 0.0001$). Moreover, there was a significant difference in UTI prevalence among the age groups ($p < 0.0001$). The 60 - 79 years age group had the highest prevalence of UTI at 49.6%, followed by the 20 - 39 years age group with 41.7%, and the 80 - 83 years age group had the lowest prevalence at 25%.

Married participants had the highest UTI prevalence at 47%, compared to divorced participants ($p = 0.009$) and widowed participants ($p = 0.025$), though the difference was not significant when compared to single participants ($P = 0.114$). There was no significant difference between single and divorced participants, single and widowed participants, or divorced and widowed participants. Most participants with high Fasting Plasma Glucose (FPG). (FBS ≥ 7.00) had a higher UTI prevalence (46.5%) compared to those with FBS < 5.6 ($p = 0.0007$). The prevalence of uropathogens was significantly higher in patients with diabetes for at least 5 years compared to those with diabetes for less than 5 years ($p = \leq 0.0005$). However, there was no significant difference between patients with diabetes for 5-20 years and those with diabetes for more than 20 years ($P = 0.6842$). Participants with tertiary and secondary education levels had the lowest prevalence of uropathogens, at 33.3% and 38.5%, respectively ($p > 0.05$), compared to those with no or primary level education, who had the highest prevalence of uropathogens at 50%. The findings on the common uropathogens isolated from the

Table 1. Demographic and clinical characteristic of study participants

| Variable | Frequency (%) N=202 | Frequency Positive for UTI (%) N=87 | P value |
|---|---|---|---|
| Gender | | | |
| Male | 46 (22.8%) | 9 (19.6%) | 0.0001 |
| Female | 156 (77.2%) | 78 (50%) | |
| Age | | | |
| 20-39 | 46 (22.8%) | 5 (41.7%) | < 0.0001 |
| 40-59 | 156 (77.2%) | 25 (34.3%) | |
| 60-79 | 12 (5.9%) | 56 (49.6%) | |
| 80-83 | 73 (36.1%) | 1 (25%) | |
| Marital status | | | |
| Single | 15 (7.4%) | 6 (40%) | 0.0063 |
| Married | 115 (56.9%) | 54 (47%) | |
| Divorced | 22 (10.9%) | 8 (36.4%) | |
| Widowed | 50 (24.8%) | 19 (38%) | |
| FPG mmol/L | | | 0.0007 |
| <5.6 | 45 (22.3%) | 14 (31.1%) | |
| ≥7 | 157 (77.7%) | 73 (46.5%) | |
| Duration of diabetes | | | |
| <5 years | 43 (21.3%) | 14 (32.6%) | 0.0002 |
| 5-20 years | 110 (54.4%) | 50 (45.5%) | |
| ≥20 years | 49 (24.3%) | 23 (46.9%) | |
| Level of education | | | |
| None | 44 (21.8%) | 22 (50%) | 0.0009 |
| Primary | 50 (24.7%) | 25 (50%) | |
| Secondary | 78 (38.6%) | 30 (38.5%) | |
| Tertiary | 30 (14.8%) | 10 (33.3%) | |

FPG: Fasting Plasma Glucose.

Table 2. Prevalence of common uropathogens and other UTI infections amongst Diabetic Patients

| Isolates | Frequency | Prevalence (%) |
|---|---|---|
| Escherichia coli | 38 | 18.8 |
| Citrobacter *spp* | 23 | 11.4 |
| Enterobacter *spp* | 11 | 5.4 |
| Candida albicans | 5 | 2.5 |
| Salmonella typhi | 5 | 2.5 |
| Shigella *spp* | 3 | 1.5 |
| Proteus vulgaris | 1 | 0.5 |
| Pseudomonas *spp* | 1 | 0.5 |

diabetic patients with UTI (Table 3) show that Escherichia coli was dominant with frequency of 38 cases (18.8%). This was followed by Citrobacter *spp* with 23 cases (11.4%) and Enterobacter spp with 11 cases (5.4%). Other pathogens identified included Candida and Salmonella typhi, each with 5 cases (2.5%), Shigella *spp* with 3 cases (1.5%) and Proteus *spp* and pseudomonas *spp*, each with 1 case (0.5%). The findings on the susceptibility patterns of uropathogen isolates from diabetic patients to antibiotics (Figure 1) reveal that Amikacin demonstrated the highest activity, with 89.2% of bacterial strains being susceptible. It was followed by Gentamycin, with 70.7% susceptibility (Figure 1A). All six bacterial strains were sensitive to both Amikacin and Ofloxacin.

Amikacin was particularly effective against nearly all gram-negative bacterial strains (Figures 1B, 1C, 1D, 1E, 1F, and 1G). With the exception of Pseudomonas, all five other isolates were sensitive to Nitrofurantoin, Ciprofloxacin, and Gentamycin. All isolates, except Pseudomonas and Shigella, were also sensitive to Norfloxacin. Three of the six isolates were sensitive to Nalidixic acid. Resistance patterns revealed that four isolates were resistant to Cefotaxime, while five isolates were resistant to Aztreonam, Ceftriaxone, Ceftazidime, and Cefixime. All isolates were resistant to Cefuroxime and Cefdinir. Shigella was found to be the most sensitive isolate, as it was susceptible to 11 out of the 14 antibiotics tested (Figure 1F). On the other hand, Pseudomonas was the most resistant isolate, being resistant to all antibiotics except Amikacin and Ofloxacin (Figure 1E).

There was a significantly higher level of pro-inflammatory cytokine IFNγ in diabetes patients with uropathogens

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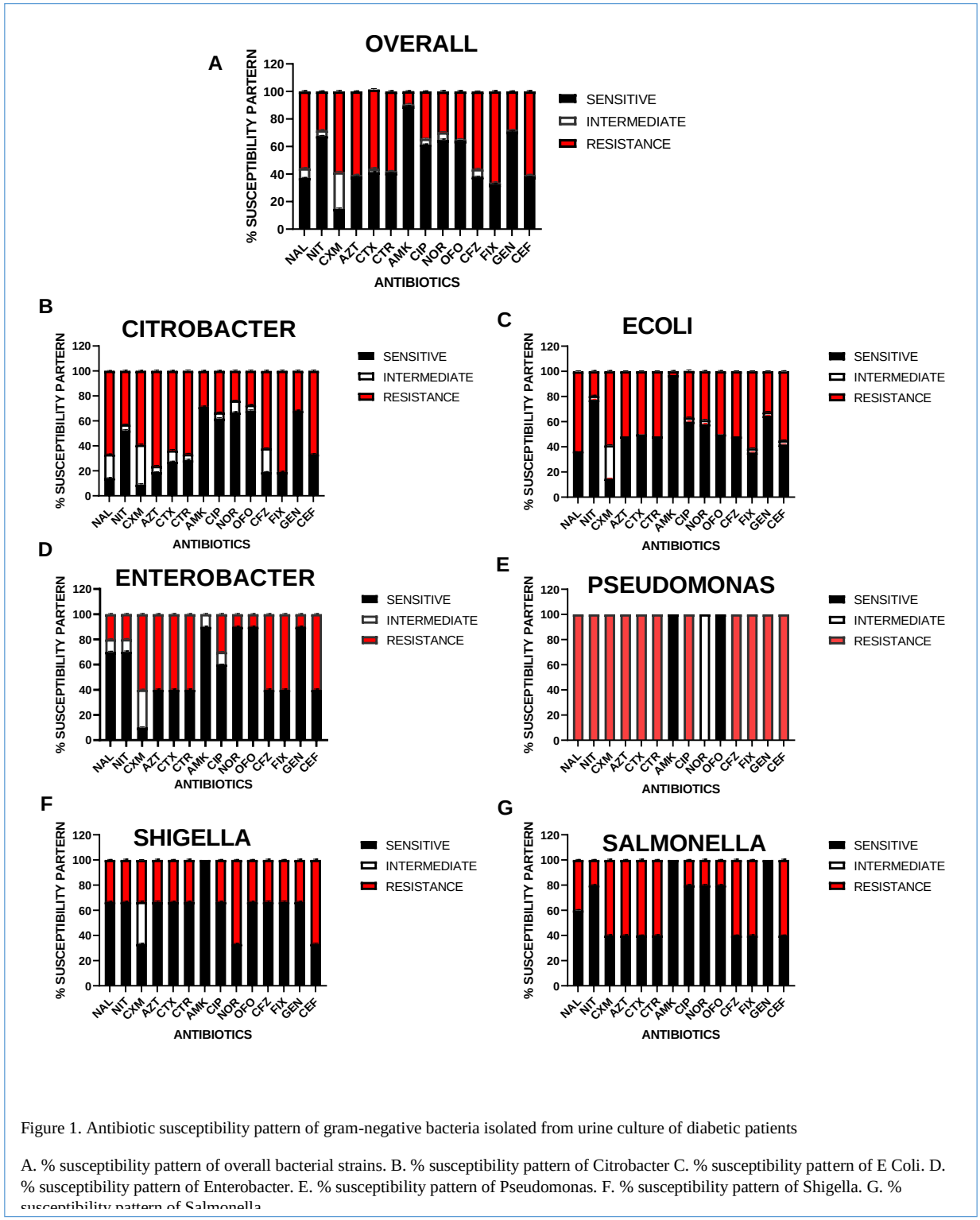


Figure 1. Antibiotic susceptibility pattern of gram-negative bacteria isolated from urine culture of diabetic patients

A. % susceptibility pattern of overall bacterial strains. B. % susceptibility pattern of Citrobacter C. % susceptibility pattern of E Coli. D. % susceptibility pattern of Enterobacter. E. % susceptibility pattern of Pseudomonas. F. % susceptibility pattern of Shigella. G. % susceptibility pattern of Salmonella

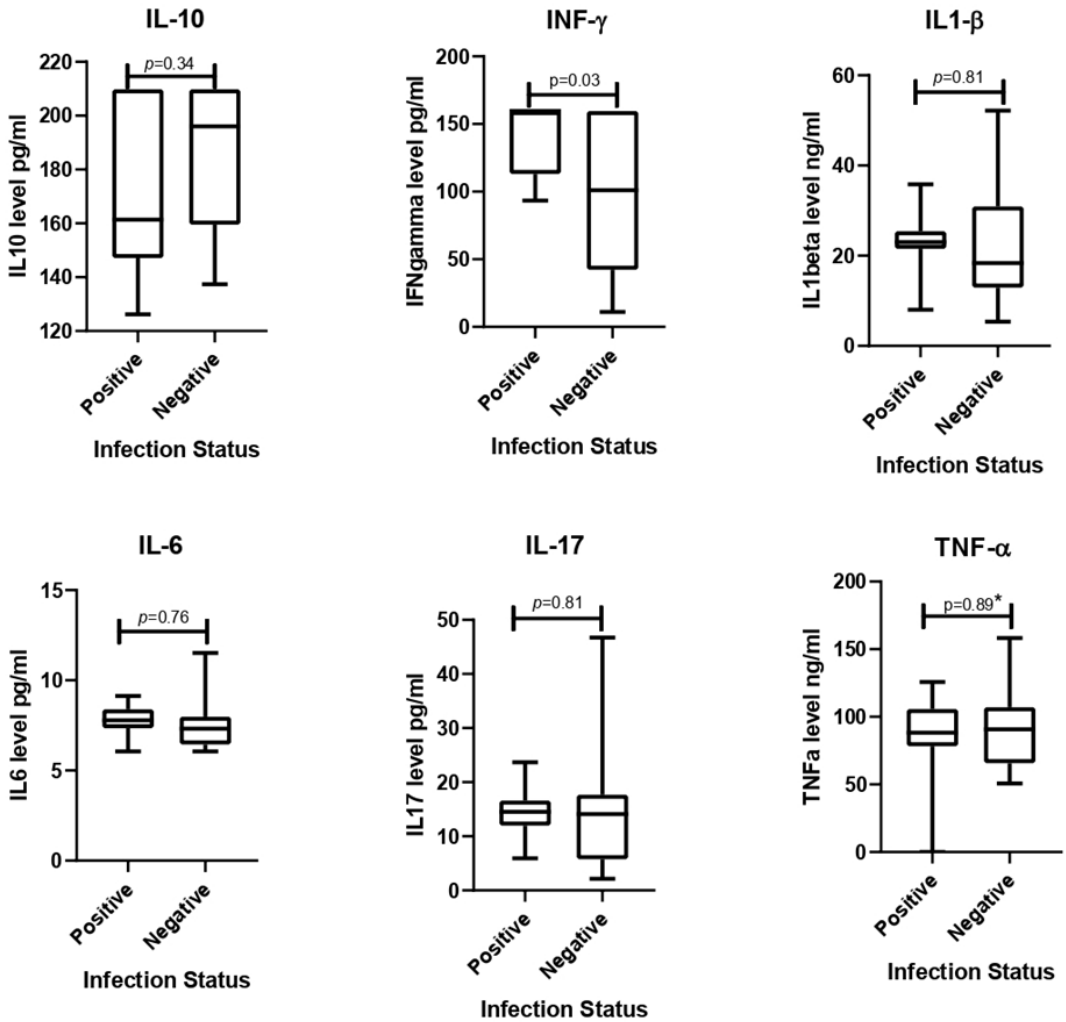


Figure 2. Mean plasma cytokine levels among diabetes patients with or without uropathogens. Number of diabetes patients with uropathogens (positive; n = 20) and without uropathogens (negative; n = 20). A significant difference between the two groups was assessed using an independent t-test. P values < 0.05 were considered statistically significant. The error bar represents the standard error of the mean. TNFα; tumor necrosis factor alpha, IFNγ; interferon gamma.

compared to diabetic patients without uropathogens (p = 0.03) (Figure 2). However, there were no significant changes in the levels of IL-1β, IL-6, IL-10, IL-17 and TNF-α cytokines among the diabetes patients with or without uropathogens (Figure 2).

## DISCUSSION

This study focused exclusively on type 2 diabetic patients to explore the immunological and microbiological aspects of UTIs and assess factors associated with UTI within this group, building on existing studies that compare diabetics and non-diabetics [20]. Our present study revealed that diabetes was associated with the incidence of UTI (Table 3.1). The total prevalence of UTI among the diabetic patients in this study was 43.1%, which was relatively high compared to other studies: 39.3% in Saudi Arabia [21], 31.1% in Uganda [22], 22.6% and 11.6% in Ethiopia [18,23], 19.5% in Sudan [24] and 8.08% in Pakistan [25]. The relatively high prevalence in this study could be attributed to factors such as poor diabetes management, duration of diabetes, sociodemographic variables, poor personal hygiene and lifestyle factors that may make diabetic individuals more susceptible to developing UTIs [26,27].

In this study, female diabetic patients were found to be more prone to developing UTIs, with a prevalence of 78 out

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of 156 (50%), compared to male diabetic patients, with a prevalence of 9 out of 46 (19.6%). This finding is supported by several studies [18,28-31] and could be due to the anatomical proximity of the female urethra to the anus, which increases the risk of bacterial movement into the bladder, especially if proper hygiene is not maintained. However, this finding contradicts some studies conducted in Ghana [32] and Sudan [24], where the prevalence of UTI did not show an association with sex. The differences in findings may be attributed to other factors, such as prostatic hypertrophy in males, biological or immunological changes, or potentially higher levels of personal hygiene among females in those studies.

The study found that the incidence of UTIs increased with age, particularly among the 60 - 79 years age group, where the prevalence was 49.6%. This aligns with previous studies [28,33-35], suggesting that age-related immune system decline [36], especially in uncontrolled diabetes, could contribute to the higher UTI incidence in this age group. However, other studies have shown varying UTI incidences across age groups [37], which may be due to differences in study methodologies, expertise of investigators, geographical factors, and screening practices [38]. Additionally, the study indicated that patients with diabetes for more than five years had a higher frequency of bacterial isolates compared to those with diabetes for less than five years. This may be due to prolonged diabetes impairing the immune system and complicating bladder emptying, which increases the risk of UTIs, particularly when blood sugar levels are not well controlled [9]. The study found that a higher bacterial count (46.5%) was associated with diabetic patients who had an FPG level of 7 mmol/l or higher. In contrast, only 31% of diabetic patients with FPG levels below 5.6 mmol/l had a high bacterial count. This suggests that controlling blood glucose levels could help reduce the risk of UTIs in diabetic patients, as glucose in the urinary tract provides a nutrient source for bacteria, potentially leading to infections.

The study found that married couples had the highest incidence of UTIs, likely due to the transmission of uropathogens during sexual intercourse [34]. As a result, it is recommended that patients with UTIs avoid sexual contact until the infection is fully treated to prevent the introduction of additional bacteria, which could worsen the infection and slow healing. Additionally, the study highlighted an association between education level and UTI prevalence in diabetic patients. Those with tertiary or secondary education had a lower prevalence of UTIs compared to those with only primary education or no education. This suggests that individuals with higher education may be better at managing their diabetes, which could reduce the risk of developing UTIs [39,40]. The study revealed, based on medical records, that 72% of the participants were on metformin (500 mg or 1000 mg taken twice daily), while the remaining 28% were on glibenclamide (15 mg daily). Studies have shown that type 2 diabetic patients who use metformin have a lower risk of UTI compared with those who do not use metformin [41,42]. Metformin stimulation has been shown to enhance the innate immune response of uroepithelial cells, resulting in increased extracellular and intracellular bacterial killing [43]. This suggests a beneficial role of metformin in supporting host defence mechanisms against urinary tract infections. On the other hand, glibenclamide is known to cause severe hypoglycaemia [44], and therefore, its use in diabetic patients requires careful monitoring during infections, as the combined effects can significantly increase the risk and severity of hypoglycaemic episodes, potentially complicating disease management and patient outcomes [45].

This study identified the prevalence of common uropathogens and other infections in diabetic patients (Table 3.2). The least isolated uropathogens were Proteus vulgaris and Pseudomonas *spp*., both with a prevalence of 0.5%, followed by Shigella *spp*. (1.5%), Candida (2.5%), and Salmonella typhi (2.5%). E. coli was the most common uropathogen, with a prevalence of 18.8%, followed by Citrobacter *spp*. (11.4%) and Enterobacter *spp*. (5.4%), consistent with findings from previous studies [23,38,46-50]. E. coli was noted as the most virulent uropathogen, likely due to its various virulence factors (toxins, adhesins, fimbriae, lipopolysaccharide capsules, and invasions), which help it to invade and attach to its host. Given the rise in antibiotic resistance, especially the multidrug resistance of E. coli, effective management of UTIs is crucial [51].

Interestingly, no gram-positive organisms, such as Staphylococcus *spp*., were isolated, which contrasts with other studies where these organisms were found [22,33,46]. This could be due to differences in diagnostic methods, geographic variations, expertise, sample sizes, and diabetic blood glucose control. Additionally, Candida *spp*., Pseudomonas, and Proteus were isolated only from female diabetic patients, aligning with findings from other studies [18,52]. The study examined the antibiotic susceptibility patterns of bacterial isolates (Figure 1) and found that all six bacterial isolates were sensitive to Amikacin and Ofloxacin. These two antibiotics were the only ones effective against Pseudomonas. Additionally, five isolates (except Pseudomonas) were sensitive to Nitrofurantoin, Ciprofloxacin, and Gentamycin, while four isolates (except Pseudomonas and Shigella) were sensitive to Norfloxacin. The higher susceptibility rates for these antibiotics could be due to their limited availability and higher cost compared to more commonly used antibiotics. As a result, Amikacin, Ofloxacin, Nitrofurantoin, Ciprofloxacin, Gentamycin, and Norfloxacin may be considered therapeutic alternatives for treating and managing UTIs in diabetic patients.

The study observed a high level of resistance to several antibiotics, including Nalidixic Acid, Cefuroxime, Aztreonam, Cefotaxime, Ceftriaxone, Ceftazidime, Cefixime, and Cefdinir, with Cefuroxime and Cefdinir being inactive against all the bacterial isolates. This resistance could be attributed to factors such as the low cost,

widespread availability, and the frequent broad-spectrum use of these antibiotics without proper medical prescriptions [18, 38]. Additionally, while individual antibiotics showed sensitivity to certain specific organisms, they were resistant to others, highlighting the need for careful selection of antibiotics based on the specific pathogens involved.

In this study, Amikacin emerged as the most active antibiotic, as was shown in other studies [53], with 89.2% of bacterial strains showing susceptibility, followed by Gentamycin, which was effective against 70.7% of strains. This result aligns with studies showing Gentamycin's effectiveness against S. aureus and MRSA, particularly among HIV-infected individuals in Cape Coast [54]. Both Amikacin and Gentamycin are aminoglycosides, which work by binding irreversibly to the 30S and 50S units of the bacterial ribosome, disrupting protein synthesis. Aminoglycoside-inactivating enzymes are known to be the primary cause of resistance to these antibiotics [55]. However, Amikacin has an advantage over Gentamycin because it is less susceptible to these inactivating enzymes due to structural differences between the two antibiotics.
The study also found that Nitrofurantoin, the only nitrofuran antibiotic included, exhibited a susceptibility rate of 67.6%, which was comparable to the fluoroquinolones. Ciprofloxacin (61.4%), Norfloxacin (64.8%), and Ofloxacin (64.0%) all had similar susceptibility rates, while Nalidixic Acid was found to be inactive against the bacterial strains.

On the other hand, all the cephalosporins tested (Cefuroxime, Cefotaxime, Ceftriaxone, Ceftazidime, Cefixime, and Cefdinir) were inactive against the bacterial strains. Aztreonam, the sole beta-lactam antibiotic tested, was also found to be inactive. These findings suggest that while Amikacin and Gentamycin remain highly effective, many commonly used antibiotics, including cephalosporins and beta-lactams, showed little to no activity against the bacterial strains, highlighting the importance of proper antibiotic selection in the treatment of UTIs in diabetic patients. In this study, Amikacin showed the highest activity against most of the gram-negative bacteria, with the predominant isolate E. coli exhibiting a high sensitivity rate of 97.1% to Amikacin. This was compared to other antibiotics, such as Nitrofurantoin (77.4%), Gentamycin (64.7%), Ciprofloxacin (60.0%), Norfloxacin (58.1%), Ofloxacin (50.0%), and Cefotaxime (50.0%). In terms of specific uropathogens, Citrobacter *spp*. showed high sensitivity to Amikacin (71.4%), Gentamycin (68.2%), Ofloxacin (68.2%), Norfloxacin (66.7%), Ciprofloxacin (61.9%), and Nitrofurantoin (52.4%). Enterobacter *spp*. showed high sensitivity to Amikacin (90%), Gentamycin (90%), Norfloxacin (90%), Ofloxacin (90%), Nalidixic Acid (70%), Nitrofurantoin (70%), and Ciprofloxacin (60%), while showing resistance to Aztreonam, Cefotaxime, Ceftriaxone, Ceftazidime, Cefixime, Cefdinir, and Cefuroxime. Pseudomonas *spp*. showed complete sensitivity (100%) to Amikacin and Ofloxacin, with no activity from the other antibiotics. Shigella *spp*. was highly sensitive to Amikacin, with the other antibiotics showing moderate sensitivity, except for Norfloxacin and Cefdinir, which were resistant. Salmonella typhi was highly sensitive to Amikacin, Gentamycin, Ciprofloxacin, Norfloxacin, Nitrofurantoin, Ofloxacin, and Nalidixic Acid.

These results highlight that Amikacin is the most effective antibiotic against a wide range of uropathogens, particularly for E. coli and other gram-negative bacteria, while other antibiotics showed varying levels of efficacy depending on the specific bacterial isolate. It is highly concerning that broad-spectrum antibiotics such as Nalidixic Acid, Cefuroxime, Cefdinir, Cefixime, Aztreonam, Ceftazidime, Ceftriaxone, and Cefotaxime showed a high rate of resistance among uropathogens in diabetic patients in this study. This contradicts other studies where Nalidixic Acid demonstrated high susceptibility to uropathogens [32]. In addition, studies from Nepal and Ethiopia also reported conflicting resistance patterns [23,37], which further underscores the variability in resistance across regions. The high resistance to these antibiotics could be attributed to their overuse and inappropriate application, particularly in treating complicated UTIs, which may lead to the development of resistance. The widespread and irrational use of these antibiotics is a known contributing factor to resistance in uropathogens, as highlighted by other studies [18].

In contrast, the antibiotics Amikacin, Gentamycin, Nitrofurantoin, Ofloxacin, Norfloxacin, and Ciprofloxacin have proven to be the most effective against almost all UTI infections in this study. Similar findings were reported by Addo et al., who also observed that Amikacin and Gentamycin were highly effective against uropathogens [32]. These results emphasise the importance of using targeted therapy rather than relying on a single antibiotic for all UTI infections. Thus, the study underlines the need for diagnostic testing to identify and isolate specific uropathogens before administering antibiotics. This approach ensures that the most appropriate and potent antibiotic is used, minimising the risk of resistance and improving treatment outcomes for diabetic patients suffering from UTIs. Asymptomatic UTI is common among diabetic patients [36], making its diagnosis challenging. Identifying specific biomarkers or profiles that can indicate the presence of UTI in diabetic patients would be valuable for early detection and effective management. In this study, cytokine levels were assessed to explore their potential as indicators of UTI in diabetic patients, and comparisons were made between those with uropathogens and those without, as shown in Figure 2.

A significant finding from this study was the higher level of the pro-inflammatory cytokine IFN-γ in diabetic patients with uropathogens compared to those without (p=0.03). IFN-γ plays a crucial role in mediating cellular immunity, particularly in the defence against infections. Several studies have highlighted the importance of IFN-γ in

enhancing antibacterial immune responses. For example, IFN-γ has been shown to protect epithelial monolayers from pathogen-mediated damage during Staphylococcus aureus infections [56]. It also contributes significantly to protection against Chlamydia and mycobacterial infections by activating effector cells and generating antibody-mediated responses [57]. Furthermore, IFN-γ is known for its role in combating viral and intracellular infections by activating macrophages' cellular immune responses. However, it's worth noting that excessive IFN-γ can also contribute to the pathogenesis of diabetes by promoting the expression of MHC class I and II molecules, as well as adhesion molecules on cells, including pancreatic β-islets. This leads to macrophage polarisation from an anti-inflammatory M2 to a pro-inflammatory M1 phenotype [58,59]. These findings may explain the elevated IFN-γ levels observed in diabetic patients with uropathogens in this study.

No significant differences were observed in the levels of other cytokines, including IL-1β, IL-6, IL-10, IL-17, and TNF-α, between diabetic patients with and without uropathogens. However, there was a slight increase in IL-1β and IL-6 among those with uropathogens, while IL-17 and TNF-α showed a slight increase in diabetic patients without uropathogens. In summary, this study suggests that cytokine profiling could serve as a potential surrogate tool for diagnosing UTIs in asymptomatic diabetes patients. Elevated IFN-γ levels may act as important markers to differentiate between diabetic patients with and without uropathogens. Further studies and larger sample sizes are needed to fully understand the role of cytokines in UTI pathogenesis in diabetes and to refine this marker for clinical use.

### Conclusion

This study reported higher incidences of UTIs among diabetic patients, with a significant presence of antibiotic-resistant uropathogens. The findings highlighted that common uropathogens in diabetic patients showed resistance to frequently prescribed antibiotics. Based on the high susceptibility rates observed, this study recommends Amikacin, Gentamycin, Nitrofurantoin, Ofloxacin, Norfloxacin, and Ciprofloxacin as potent antibiotics for managing UTIs in diabetic patients. Furthermore, a strong association between elevated levels of IFN-γ and the presence of UTIs in diabetic patients was observed. This suggests that IFN-γ may play a crucial role in the immune response to UTIs in this population.

The findings support the potential for using cytokine profiling, specifically IFN-γ levels, as a proxy for diagnosing UTIs in asymptomatic diabetic patients and guiding more effective treatment strategies. In conclusion, the study emphasises the importance of targeted antibiotic therapy and the potential role of immune markers like IFN-γ in improving the diagnosis and management of UTIs in diabetic patients.

## DECLARATIONS

### Ethical consideration

The research protocol was approved by the Cape Coast Teaching Hospital Ethical Review Committee (Ref: CCTHERC/EC/2020/086). Consent was obtained from the participants before their inclusion in the study.

### Consent to publish

All authors agreed on the content of the final manuscript.

### Funding

None

### Competing Interest

The authors declare no conflict of interest

### Author contribution

PAB conceived the idea of the study. PAB, RK and BA designed the study. PAB, RK, BA, DB, SAK, CAA, JKT, SM and EKA collected data. PAB, RK, BA, DB, SAK, CAA, JKT, SM and EKA did data analysis and interpretation. PAB and DB prepared the first draft of the manuscript with input from all co-authors. All co-authors edited the manuscript and endorsed the final version before submission.

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### Availability of data

Data is available upon request to the corresponding author

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# Sedative-analgesics use in Intensive Care: A Critical analysis of prescribed analgo-sedatives, treatment outcomes, and adverse drug events in adult patients at Komfo Anokye Teaching Hospital

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**Abstract**

***Background:*** Studies on the use of sedative-analgesics are limited in Africa and developing countries despite their high usage, benefits, and side effects among patients. Recent evidence on analgo-sedation suggests that protocols considering up-to-date scientific evidence and individual patient characteristics can improve treatment outcomes.

***Objective:*** This study aimed to analyse the prescribed analgo-sedatives, protocols, outcomes and adverse events of sedative-analgesics in the ICU in a teaching hospital in Ghana.

***Methods:*** This retrospective study reviewed data from adult patients admitted to the ICU of KATH from January 2017 to December 2019. Patient characteristics such as socio-demography, sedative-analgesic prescribed, and respondents' outcomes, including length of stay, survival and associated adverse drug events (ADE), were collected for analysis. The chi-square test was used to analyse associations between analgo-sedative usage, speciality and ICU stay, with $p < 0.05$ considered statistically significant.

***Results:*** The most prescribed analgo-sedatives were Morphine+Midazolam (53.24%), Morphine (16.19%) and Midazolam (6.47%). The relative risk of developing an ADE with analgo-sedation use was 2.1 ($p < 0.001$). The median duration of stay was longer in sedated patients (3 days, IQR: 2-9) compared to non-sedated ones (1 day, IQR: 1-3, $p < 0.001$). Analgo-sedation also significantly increased the occurrence of adverse events (RR 2.1; $p < 0.001$). Patients who experienced ADEs had 98% decreased odds of survival compared to those without ADEs (aOR: 0.02, 95% CI: 0.01 - 0.05, $p < 0.001$). Critically ill patients had 73% lower odds of survival than severely ill patients (aOR: 0.27, 95% CI: 0.15 - 0.48, $p < 0.001$).

***Conclusion:*** Analgo-sedation use is associated with prolonged ICU stays due to a significantly higher risk of adverse drug events, and treatment outcomes are associated with sedation protocols and patients' pre-existing medical conditions.

**Keywords:** Adverse drug events, analgo-sedation, critical care, intensive care, Teaching Hospitals, treatment outcomes

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## INTRODUCTION

Critically ill patients may require invasive and life-saving procedures such as mechanical ventilation, dialysis, tracheostomy, and central venous catheters for survival [1]. Besides the benefit of anxiolysis and antinociception, sedative-analgesic medicines support the smooth administration of these critical procedures, enhance care delivery and improve patient safety [2]. These medications may predispose patients to increased morbidity [3,4]. Further, the choice of sedative-analgesic medicine

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can significantly affect patient outcome and the cost of treatment, as such inappropriate and excessive use may result in agitation, self-removal of devices and post-traumatic stress disorder, neuromuscular abnormalities, lung injury, and death [5]. However, it is believed that critically ill adult patients show good treatment outcomes when guideline-based management approaches for pain, agitation, and delirium (PAD) are used [6,7]. Thus, it is prudent to implement assessment-driven and standardised pain management protocols as these are shown to improve ICU outcomes and clinical practice [6,8]. Variations exist in the choice of analgo-sedation prescribed because of the patient's condition, intensivist preference, cost, and availability in resource-constrained settings [9]. More importantly, genetic variation [10] and environmental influences [11] can significantly impact therapeutic outcomes, making it imperative for every ICU to develop analgo-sedation protocols that take into account up-to-date scientific evidence that supports best clinical practice [12].

The recent SARS-CoV-2 pandemic prompted the urgent need for significant improvement in global ICU practices. The practice, particularly in sub-Saharan Africa, has been a greater focus and investment in primary healthcare, with almost a complete neglect of specialised care such as critical care. Evidence is still being compiled about the choice, efficacy, and safety of sedative-analgesic medicines in critically ill patients. Additionally, studies on sedative-analgesic usage are limited in Africa and developing countries despite the high usage, benefits, and side effects associated with them among patients [13]. To improve care for the critically ill, this study analysed retrospectively the choices (protocols), outcomes and adverse drug events of sedative-analgesic medicines used for analgo-sedation in critically ill patients at Komfo Anokye Teaching Hospital, which is a major referral centre serving the northern and middle belt of Ghana.

## MATERIALS AND METHODS

### Study design and sites

Komfo Anokye Teaching Hospital (KATH) is in the Greater Kumasi Metropolitan Area of the Ashanti Region of Ghana. It is the only referral hospital in the middle belt of Ghana with a total bed capacity of 1200 and serves over 75% of the administrative regions in Ghana as well as some other neighbouring countries. The adult ICU is a level 3 ICU with an 8-bed capacity under the Directorate of Anaesthesia and Intensive Care. KATH has the following category of staff strength: Consultant Anaesthesiologist (1), Specialists Anaesthesiologists (10), Physicians (14), Pharmacists (2), Critical Care Nurses (7), General Nurses (24) and without a Specialist Intensivist.

### Study design and data collection

This study was a retrospective review of ICU patients' medical records (paper charts) from January 2017 to December 2019 on the use of sedative-analgesic medicines. Records were entered into a Microsoft Excel sheet for data cleaning and protected using codes. The participants' records were accessed for research purposes within a period of 4 months (December 2019 to March 2020). For uniformity and simplicity, patients with different medical cases were all grouped under the "Medical" speciality of care. Similarly, surgical, obstetrics and gynaecology (O&G) and trauma cases were respectively grouped as "Surgical"," O&G", and "Trauma" specialities of care. Patient characteristics collected and analysed include socio-demographic data, continuous/ intermittent sedative-analgesics used, patient's length of stay, survival and associated adverse drug events (ADE). The doses of analgesics/sedatives used and the procedure for evaluating and monitoring sedation and pain in the KATH adult ICU are presented in tables.

Records of all critically ill adult patients (16 years or above) admitted to the ICU between 1st January 2017 and 31st December 2019 were included in the study. Prospective participants whose records were not complete were excluded from the study.

### Data analysis

The data collected were analysed using IBM SPSS (version 25.0) and presented as mean ± standard deviation, frequencies and percentages where appropriate. Socio-demographic characteristics, reason/diagnosis for ICU admission, analgo-sedation status, the use of analgesics/sedative medicines, adverse events occurrence and duration of ICU stay among patients were presented using descriptive statistics. Mean and standard deviation were used to describe continuous variables with a normal distribution. Frequencies were used to describe categorical variables. Chi-square tests were used for inferential analysis to determine the associations between analgo-sedation and the diagnosis for ICU admission, analgo-sedation and ADE, analgo-sedation and duration of ICU stay, and analgo-sedation and survival of admitted patients, with $p < 0.05$ considered as statistically significant. Survival times and duration of ICU were analysed using Kaplan-Meier's curves. To minimise the effect of confounding factors on survival, disease severity (Quick Sequential Organ Failure Assessment, qSOFA score was used since the parameters were not complete to use the Sequential Organ Failure Assessment, SOFA score, diagnosis, age, and the presence of adverse events were adjusted using regression analysis. Contingency analysis using Fisher's exact test was used to determine the association between ADE and analgo-sedation.

## RESULTS

A total of 355 patients were recruited for this study. Documentation on all 355 adult patients was complete, and therefore all were included, with females comprising 45.4% (n = 161) and males 54.6% (n = 194). The median age was 42 years (IQR: 30 – 59). Ninety-two (25.9%) of the patients were aged ≤ 30 years, and 12.4% (n = 44) were aged 51 to 60 years. Approximately half the patients were diagnosed

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as surgical cases (50.7%, n = 180), and trauma cases were 13.2% (n = 47). The majority of the patients (73.2%, n = 260) had an adverse event, while 51.0% (n = 181) represented mortality. The median age among patients with no analgo-sedation was 43.5 years (IQR: 28.5 - 63), and among patients who survived was 39.5 years (IQR: 29 - 53) (Table 1).

Twenty-three (23) different types of analgo-sedation protocols were used. These protocols were obtained through a combination of five sedative-analgesic medicines. There was a significant relationship between analgo-sedation and the speciality for ICU admission (p = 0.021). Overall, analgo-sedation was used mostly on surgical patients (55.76%, n = 155), followed by medical, trauma, and O&G patients. The most preferred combination protocol for all types of patients was morphine plus midazolam. Several other protocols were used, but at lower frequencies. On the use of individual medicines, 84.2% of the patients received analgo-sedation protocols that contained morphine. Similarly, midazolam, ketamine, and propofol-based protocols were administered to 72.8%, 11.5%, and 6.8% of respondents, respectively. Morphine was the most preferred mono-sedative-analgesic medicine in O&G, whereas midazolam was preferred in surgery, trauma, and medical patients (Table 2).

There was a significant statistical relationship between diagnosis and analgo-sedation ($\chi 2$ = 28.06; p < 0.001). More so, 50.0% (n = 38) of the patients who had no analgo-sedation were medically diagnosed, and 55.9% (n = 156) of the patients who were sedated were surgically diagnosed (Table 3). The median duration of stay was longer in sedated patients (3 days, IQR: 2 - 9) compared to non-sedated ones (1 day, IQR: 1 - 3), with a statistically significant difference (p < 0.001). Patients who died had a longer stay if sedated (4 days, IQR: 2 - 10). Similarly, among survivors, sedated patients had longer stays (3 days, IQR: 2 - 8.5) (Table 4). Relative to patients with O&G diagnoses, those with medical conditions had 73% decreased odds of survival (aOR: 0.27, 95% CI: 0.08 - 0.92, p = 0.037). Patients who experienced adverse events had 98% decreased odds of survival compared to those with uneventful cases (aOR: 0.02, 95% CI: 0.01-0.05, p < 0.001). Critically ill patients had 73% lower odds of survival than those classified as severe (aOR: 0.27, 95% CI: 0.15 - 0.48, p < 0.001) (Table 5).

Overall, cardiovascular-related ADE were most frequent. Approximately 74.65% of cardiovascular ADE occurred in patients who received analgo-sedation. Hypotension was the highest occurring cardiovascular ADE amongst analgo-sedated patients (20.42%, n = 103, RR = 1.41; p = 0.1564). However, there was a higher relative risk of hypertension among analgo-sedated patients 2.53 (n = 55; 12.91%, p = 0.0159). Similarly, the relative risk of tachycardia within the analgo-sedated patients was 2.48 (n = 72;16.90%; p = 0.0033). Tachypnoea or abnormally rapid but shallow

Table 1: Socio-demographic Characteristics of adult Respondents admitted from January 2017 to December 2019 at the ICU of KATH

| Variable | Female (n=161) | Male (n=194) | Total (n=355) |
|---|---|---|---|
| Median age (IQR) | 45 (31 - 63) | 42 (30 - 56) | 42 (30 - 59) |
| Age | | | |
| ≤30 | 39 (24.2) | 53 (27.3) | 92 (25.9) |
| 31-40 | 33 (20.5) | 41 (21.1) | 74 (20.8) |
| 41-50 | 26 (16.1) | 35 (18.0) | 61 (17.2) |
| 51-60 | 19 (11.8) | 25 (12.9) | 44 (12.4) |
| 61+ | 44 (27.3) | 40 (20.6) | 84 (23.7) |
| Diagnosis | | | |
| Medical | 58 (36.0) | 45 (23.2) | 103 (29.0) |
| O & G | 25 (15.5) | 0 (0.0) | 25 (7.0) |
| Surgical | 68 (42.2) | 112 (57.7) | 180 (50.7) |
| Trauma | 10 (6.2) | 37 (19.1) | 47 (13.2) |
| Adverse event | | | |
| Eventful | 122 (75.8) | 138 (71.1) | 260 (73.2) |
| Uneventful | 39 (24.2) | 56 (28.9) | 95 (26.8) |
| Final outcome | | | |
| Died | 88 (54.7) | 93 (47.9) | 181 (51.0) |
| Survived | 73 (45.3) | 101 (52.1) | 174 (49.0) |
| Clinical classification | | | |
| Critical | 104 (64.6) | 105 (54.1) | 209 (58.9) |
| Severe | 57 (35.4) | 89 (45.9) | 146 (41.1) |
| | 161 | 194 | |
| Analgo-sedation | | | |
| Median (IQR) | Yes | 42 (31 - 58) | |
| | No | 43.5(28.5 - 63) | |
| Final Outcome | | | |
| Median (IQR) | Died | 45 (32 - 65) | |
| | Survived | 39.5(29 - 53) | |

breathing was the most significant adverse effect amongst analgo-sedated patients with a relative risk of 9.94 (n = 36; 8.45%, p = 0.0013). The relative risk of pyrexia was also statistically significant at 2.52 (n = 49; 11.50%; p = 0.0485) in Table 6.

There was a significant (p < 0.001) association between analgo-sedation protocol type and the occurrence of ADE. A very high occurrence (94.44%) of ADE was recorded in patients administered midazolam alone, but upon the addition of propofol or ketamine to midazolam, ADE occurrence reduced to 50.00% and 66.67%, respectively.

ADE occurrence versus diagnosis under the speciality of care, surgical ICU patients recorded the highest (47.59%), followed by medical patients (32.76%), trauma patients (14.64%) and then O&G patients (5.01%). Of a total of 170 medical patients who experienced ADE, 81.77% were cardiovascular-related. Comparing the occurrence of cardiovascular-related ADE, 30.23% of ADE in medical patients was hypotension, whereas 8.70% experienced hypertension. Among O & G patients, 20% recorded cardiovascular-related ADE. Surgical patients 25.67% versus 17.65%), and Trauma patients (16.67% versus 22.92%) (Table 5).

Table 2: Analgo-sedation protocols and preferences amongst ICU type of patients

| Analgo-sedation protocol | Type of patients (n = 278) | | | | | Significance |
|---|---|---|---|---|---|---|
| | Medical | O&G | Surgical | Trauma | Total (%) | |
| Ketamine | 4 | - | 2 | 2 | 8 (2.88) | Pearson |
| Midazolam | 12 | - | 5 | 1 | 18 (6.47) | Chi-Square |
| Midazolam, paracetamol | 0 | - | - | 1 | 1 (0.36) | Value = |
| Midazolam/Ketamine | 3 | - | - | - | 3 (1.08) | 130.84a |
| Midazolam/Ketamine/Paracetamol | - | - | 1 | - | 1 (0.36) | df = 100 |
| Midazolam/Propofol | 1 | - | 1 | - | 2 (0.72) | *P* = 0.021 |
| Midazolam/Propofol/Ketamine | 1 | - | - | - | 1 (0.36) | |
| Morphine | 4 | 2 | 35 | 4 | 45(16.19) | |
| Morphine/Ketamine | - | - | 5 | - | 5 (1.80) | |
| Morphine/Midazolam | 28 | 13 | 83 | 24 | 148 (53.24) | |
| Morphine/Midazolam/Ketamine/Propofol | - | - | - | 1 | 1 (0.36) | |
| Morphine/Midazolam/Ketamine | 3 | 1 | 4 | - | 8 (2.88) | |
| Morphine/Midazolam/Ketamine/Paracetamol | - | - | 2 | - | 2 (0.72) | |
| Morphine/Midazolam/Paracetamol | 1 | - | 5 | 2 | 8 (2.88) | |
| Morphine/Midazolam/Propofol | 2 | - | 5 | 2 | 9 (3.24) | |
| Morphine/Midazolam/Propofol/Paracetamol | - | - | - | 1 | 1 (0.36) | |
| Morphine/Paracetamol | 1 | - | 2 | 3 | 6 (2.16) | |
| Morphine/Propofol | - | - | 1 | - | 1 (0.36) | |
| Morphine/Propofol/Ketamine | 1 | - | - | - | 1 (0.36) | |
| Propofol | - | - | 1 | - | 1 (0.36) | |
| Propofol/Ketamine | 1 | - | - | - | 1 (0.36) | |
| Propofol/Ketamine/Paracetamol | 1 | - | - | - | 1 (0.36) | |
| Other | 2 | - | 3 | 1 | 6 (2.16) | |
| Total (%) | 65(23.38) | 16(5.76) | 155(55.76) | 42(15.10) | 278 (100) | |

Table 3: Diagnosis and analgo-sedation

| Variable | No Analgo-sedation | | Analgo-sedation | | χ2 (p-value) |
|---|---|---|---|---|---|
| | f | %(95% CI) | f | %(95% CI) | |
| Diagnosis | | | | | 28.06 (<0.001) |
| Medical | 38 | 50 (0.39-0.61) | 65 | 23.3 (0.19-0.29) | |
| O & G | 9 | 11.8 (0.06-0.21) | 16 | 5.7 (0.04-0.09) | |
| Surgical | 24 | 31.6 (0.22-0.43) | 156 | 55.9 (0.5-0.62) | |
| Trauma | 5 | 6.6 (0.03-0.15) | 42 | 15.1 (0.11-0.2) | |

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Table 4: Analgo-sedation use and duration of ICU stay of patients

| Variable | Duration of stay Median (IQR) | 95% CI | Rank sum | U; p-value |
|---|---|---|---|---|
| Analgo-sedation Status | | | | |
| No Analgo-sedation | 1 (1 - 3) | (1 - 1) | 8154 | -6.89; <0.001 |
| Analgo-sedation | 3 (2 - 9) | (3 - 4) | 55036 | |
| Outcome | | | | |
| Died | | | | |
| No Analgo-sedation | 1 (1 - 1) | (1 - 1) | | |
| Analgo-sedation | 4 (2 - 10) | (3 - 5) | | |
| Survive | | | | |
| No Analgo-sedation | 2 (1 - 3) | (1.2 - 3) | | |
| Analgo-sedation | 3 (2 - 8.5) | (3 - 4.3) | | |
| Diagnosis | | | | |
| Medical | | | | |
| No Analgo-sedation | 1 (1, - 3) | (1 - 2) | | |
| Analgo-sedation | 4 (2 - 10) | (3 - 6) | | |
| O & G | | | | |
| No Analgo-sedation | 1 (1 - 1) | (1 - 1.9) | | |
| Analgo-sedation | 3 (2.5 - 4.5) | (2.5 - 4.5) | | |
| Surgical | | | | |
| No Analgo-sedation | 1 (1 - 3) | (1 - 2.3) | | |
| Analgo-sedation | 3 (2 - 7) | (2 - 4) | | |
| Trauma | | | | |
| No sedation | 1 (1 - 1) | (1 - 3) | | |
| Analgo-sedation | 6 (2 - 13) | (2.1 - 11) | | |

Table 5: Risk factors and survival

| Variable | Died | Survived | χ2 (p-value) | cOR (95% CI), p-value | aOR (95% CI), p-value |
|---|---|---|---|---|---|
| age | | | 11.22 (0.024) | | |
| ≤30 | 40 (22.1) | 52 (29.9) | | 1 | 1 |
| 31-40 | 36 (19.9) | 38 (21.8) | | 0.81 (0.44-1.50), 0.507 | 0.62 (0.27-1.42), 0.260 |
| 41-50 | 26 (14.4) | 35 (20.1) | | 1.04 (0.54-1.99), 0.917 | 0.61 (0.25-1.47), 0.270 |
| 51-60 | 24 (13.3) | 20 (11.5) | | 0.64 (0.31-1.32), 0.228 | 1.19 (0.47-3.00), 0.709 |
| 61+ | 55 (30.4) | 29 (16.7) | | 0.41 (0.22-0.75), 0.004 | 0.54 (0.23-1.23), 0.142 |
| Gender | | | 1.59 (0.207) | | |
| Female | 88 (48.6) | 73 (42.0) | | | |
| Male | 93 (51.4) | 101 (58.0) | | | |
| Diagnosis | | | 21.12 (<0.001) | | |
| O & G | 12 (6.6) | 13 (7.5) | | 1 | 1 |
| Medical | 72 (39.8) | 31 (17.8) | | 0.40 (0.16-0.97), 0.042 | 0.27 (0.08-0.92), 0.037 |
| Surgical | 76 (42.0) | 104 (59.8) | | 1.26 (0.55-2.92), 0.585 | 1.19 (0.39-3.59), 0.764 |
| Trauma | 21 (11.6) | 26 (14.9) | | 1.14 (0.43-3.02), 0.788 | 1.56 (0.46-5.21), 0.473 |
| Analgo-Sedation Protocol | | | 3.52 (0.061) | | |
| No Analgo-sedation | 46 (25.4) | 30 (17.2) | | | |
| Analgo-sedation | 135 (74.6) | 144 (82.8) | | | |
| Adverse Event | | | 113.56 (<0.001) | | |
| Uneventful | 4 (2.2) | 91 (52.3) | | 1 | 1 |
| Eventful | 177 (97.8) | 83 (47.7) | | 0.02 (0.01-0.06), <0.001 | 0.02 (0.01-0.05), <0.001 |
| Clinical Classification | | | 46.02 (<0.001) | | |
| Severe | 43 (23.8) | 103 (59.2) | | 1 | 1 |
| Critical | 138 (76.2) | 71 (40.8) | | 0.21 (0.14-0.34), <0.001 | 0.27 (0.15-0.48), <0.001 |

Table 6: Frequency of adverse event occurrence with analgo-sedation

| Organ system | Adverse event | Total Respondents, n (%) | Analgo-sedated Respondents, n (%) | Significance (RR; p-value) |
|---|---|---|---|---|
| Cardiovascular | Hypotension | 104 (20.04) | 87 (20.42) | 1.41; 0.1564 |
| | Tachycardia | 80 (15.41) | 72 (16.90) | 2.48; 0.0033** |
| | Hypertension | 61 (11.75) | 55 (12.91) | 2.53; 0.0159* |
| | Bradycardia | 64 (12.33) | 46 (10.80) | 0.71;0.1805 |
| | Asystole | 60 (11.56) | 39 (9.15) | 0.98; 1.0000 |
| | Cardiac Arrest | 20 (3.85) | 14 (3.29) | 0.64; 0.4001 |
| | Unrecordable BP | 5 (0.96) | 3 (0.70) | - |
| | Ventricular Fibrillation | 4 (0.77) | 1 (0.24) | - |
| | Ventricular Tachycardia | 1 (0.19) | 1 (0.24) | - |
| Central nervous system | Seizures | 7 (1.35) | 6 (1.40) | 1.66; 1.0000 |
| | Agitation | 3 (0.58) | 3 (0.70) | - |
| | Insomnia | 1 (0.19) | 1 (0.24) | - |
| Respiratory | Tachypnea | 37 (7.13) | 36 (8.45) | 9.94; 0.0013** |
| | Hypoxemia | 10 (1.93) | 8 (1.88) | 1.10; 1.0000 |
| | Unrecordable $O_2$ Saturation | 1 (0.19) | 1 (0.24) | |
| Thermoregulatory | Pyrexia | 55 (10.60) | 49 (11.50) | 2.52; 0.0485* |
| | Hypothermia | 5 (0.96) | 3 (0.70) | - |
| Gastrointestinal | Constipation | 1 (0.19) | 1 (0.24) | |

## DISCUSSION

The emergence of the COVID-19 pandemic profoundly highlighted the urgent need for enhanced investment in critical care systems globally, particularly within Intensive Care Units (ICUs). One important area in ICU management is the use of sedative-analgesic (analgo-sedative) medications, which play a vital role in patient care. However, despite their benefits in managing pain and anxiety, these drugs have also be linked to adverse outcomes if not used optimally [1]. This study, therefore, explored the patterns of sedative-analgesic usage, treatment protocols, clinical outcomes, and adverse events in the ICU of a major teaching hospital in Ghana.

In this study, geriatric patients accounted for about 20% of all ICU admissions, with a higher proportion of male admissions compared to females. This finding is comparable with data from similar studies conducted in other regions, which also report a predominance of male patients in ICU settings [6,7,14]. The main reasons for ICU admission in this study were surgical and medical in nature. A substantial number of these patients were postoperative, with common complications such as pain and anxiety requiring critical care and the use of sedative-analgesics. In line with global best practice, ICU pain management strategies aim to minimise prolonged sedation to reduce the incidence of delirium, shorten ICU stays, and improve overall patient outcomes [15,16]. Many critically ill patients, particularly those with severe back and lower limb pain, also require sedation as part of their treatment [3,5]. These factors may explain the high proportion of surgical and medical admissions observed in this study. A concerning finding was the relatively high mortality rate of 50.84%, significantly higher than the 7 – 20% range typically reported in more developed nations [17,18]. This discrepancy could be attributed to systematic challenges involving limited healthcare resources, shortages in skilled ICU personnel, and the absence of specialised ICU sub-disciplines [19-21].

The study reported the use of 23 different analgo-sedative protocols involving five primary sedative-analgesic medications. Among these, morphine and midazolam were the most frequently prescribed drugs across all medical specialties. In low-income settings, cost and drug availability are major determinants of medication choice [19,20]. As such, advanced sedative-analgesics like dexmedetomidine, fentanyl, remifentanil, buprenorphine, and nalbuphine—despite their established efficacy—were not used during the study period. In addition to cost and availability, healthcare workers' familiarity with specific medications is also a critical factor in protocol selection [21]. The absence of an intensivist at the facility during the study period may have further influenced the preference for more familiar drugs like morphine and midazolam. In this study, although propofol and ketamine were used in some cases, their application was limited. This is because propofol is generally not recommended for long-term sedation, and ketamine use may be restricted due to its potential neuropsychiatric side effects [22,23]. Surgical patients, whether undergoing elective or emergency

procedures, were more likely to receive sedative-analgesia postoperatively. This is consistent with clinical standards, as adequate sedation and pain control are vital for postoperative recovery and patient safety in life-saving interventions [15,16].

Interestingly, approximately half of the patients who did not receive analgo-sedation were medical admissions. This may reflect varying approaches to sedation between medical and surgical specialties. However, the specific type of sedative-analgesic used did not significantly affect the duration of stay. These results are consistent with previous large-scale trials, such as MIDEX and PRODEX, which found midazolam to be associated with longer mechanical ventilation and ICU stays [24]. A major contributor to prolonged ICU stay could be knowledge gaps among health professionals regarding analgo-sedation management, including improper use of assessment tools, lack of clear protocols, and insufficient training [16]. Interestingly, age was not significantly associated with ICU mortality after adjusting for other variables. This contradicts findings from studies conducted in Malaysia and South Korea, which observed increased mortality with older age [25,26]. Furthermore, our study found that neither gender nor whether patients received analgo-sedation had a significant impact on mortality.

Nonetheless, the survival rate and median survival time were significantly higher for patients who received analgo-sedation, as similar presented in the findings of Wang et al. (2019), who reported improved ICU survival with the implementation of analgo-sedation [27]. These findings underscore the importance of optimising analgesic-sedative use in low-income settings to improve patient outcomes. Though not statistically significant, male patients exhibited better survival outcomes than females. Other studies have similarly suggested that, despite similar survival rates, men may have better functional outcomes, possibly due to age differences or underlying health conditions [28,29]. The study also found that medical diagnoses were associated with significantly lower survival odds (aOR: 0.27), comparable with findings from Abate et al. (2023) in Ethiopia [30]. Patients with adverse drug events (ADEs) also had significantly lower survival (aOR: 0.02), highlighting the importance of careful drug monitoring procedures. Higher disease severity was associated with worse outcomes, supporting the work of Oliveira et al. (2024), who linked higher severity with increased mortality during both early and late ICU phases [31].

Notably, patients who received analgo-sedation were 2.1 times more likely to experience an ADE. This finding is consistent with existing literature linking prolonged sedation to increased ADEs [32-34]. Cardiovascular-related events were most common, especially hypotension with compensatory tachycardia, likely due to frequent use of opioids and benzodiazepines [35,36]. Opioids reduce sympathetic tone and cause vasodilation, while benzodiazepines can result in hypotension, especially when co-administered [36]. Hypertension was also commonly reported, especially in trauma patients, possibly due to increased sympathetic activity [37]. This provides an indication that while sedative-analgesic use was associated with longer survival, it also carried a high risk of ADEs.

Despite the rigour of the statistical analysis and appropriate methodology employed, this study had a few limitations. The retrospective design and small sample size reduce generalizability. Grouping patients by diagnosis limited individualised analysis. Variables such as comorbidities, sepsis, and mechanical ventilation—which could influence ICU stay and survival—were not fully controlled. However, the strength of the study are captured in its detailed exploration of sedation protocols and associated outcomes. The findings can serve as a baseline for future prospective studies, particularly in low-resource settings where such data is scarce. Further research in sub-Saharan Africa is necessary to develop region-specific clinical guidelines.

### Conclusion

This study highlights the prevalent use of analgo-sedatives in the ICU, with Morphine and Midazolam being the most prescribed medications. While analgo-sedation is essential for patient management, its use is associated with prolonged ICU stays and a significantly higher risk of adverse drug events, which significantly reduces survival odds. The findings emphasise the need for carefully tailored sedation protocols that consider patient-specific factors to optimise outcomes and minimise risks. Future research should focus on developing evidence-based guidelines for sedation practices in resource-limited settings to enhance patient safety and treatment efficacy.

## DECLARATIONS

### Ethical consideration

Dual independent ethical clearance for the study was given by the Committee on Human Research, Publications and Ethics, Kwame Nkrumah University of Science and Technology, School of Medical Sciences (reference number CHRPE/AP/681/19); and the Research and Development Unit of Komfo Anokye Teaching Hospital, Kumasi (reference number RD/CR19/198). Individual permission and consent were not possible as medical records (paper charts) were the principal source of data. For confidentiality, patient names and addresses were not recorded.

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest.

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**Author contribution**

All the authors contributed to the drafting and preparation of the manuscript. JA, MSF, and KBM collected the data. AM, JA, PKTAG, CA and KBM planned the study design and carried out the data analysis. JA, KBM and AM drafted the manuscript. CA and KBM conceived the idea and carried out project management and supervision of the study. KBM revised the final manuscript, and all the authors approved the final manuscript.

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**Availability of data**

Data is available upon request to the corresponding author.

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# Increased levels of pre-treatment drug resistance of human immunodeficiency virus type 1 subtypes in people living with HIV in Ghana: A cross-sectional study

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**Abstract**

***Background:*** Antiretroviral therapy (ART) has significantly reduced the burden of human immunodeficiency virus (HIV-1) infection. However, the emergence of drug resistance (DR) during therapy and the transmission of resistant strains contribute to treatment failure and may compromise ART efficiency. Genotypic-DR testing guides the selection of drugs for initiation of therapy or a switch to new regimens. However, such precision medicine practice among persons living with HIV (PLWH) is not available in Ghana, thus creating a critical gap in knowledge of the contribution of pre-treatment drug resistance to treatment failure.

***Objective:*** The study aimed to determine the presence of drug-resistant HIV-1 strains in ART-naive people living with HIV (PLWH) in Ghana.

***Methods:*** Sixty-nine (69) ART-naive PLWH were enrolled from three hospitals in Accra. Demographics and clinical data were documented, and venous blood samples were collected. HIV-1 protease and reverse transcriptase genes were amplified by conventional polymerase chain reaction (PCR) and directly sequenced. Sequences were assembled and edited and submitted to the Stanford HIV Drug Resistance Database (HIVdb) for subtyping and DR analyses.

***Results:*** The mean viral load and CD4+ counts were 1.38 x $10^5$ copies/ml and 409 cells/µl, respectively. We found 10.8% resistance (K103N, V179I, A98G, E138A) against non-nucleoside reverse transcriptase inhibitors, three accessory protease inhibitors mutations (V32L, V11L, L10LF) in nine participants, but no NRTI mutations. Sixty-four percent (64%) of participants carried HIV-1 subtype CRF02_AG, 26% carried subtype B, and the remaining were subtypes CRF06_cpx, A, C and G.

***Conclusion:*** Our data confirmed CRF02_AG as the predominant HIV-1 subtype in Ghana, with increasing occurrence of subtype B. These findings indicate the need for continuous monitoring of subtype dynamics and drug resistance to guide the national ART program and enhance the clinical management of PLWH.

**Keywords:** ART, HIV-1, pre-treatment drug resistance, NNRTI, PI, CRF

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## INTRODUCTION

Human immunodeficiency virus (HIV) type-1 (HIV-1) infection occurs globally, with an estimated 37.9 million people living with the virus [1]. About 25.8 million people living with HIV-1 (PLWH) reside in sub-Saharan Africa [2-5]. Globally, HIV-1 infections have declined, and the UNAIDS has projected that by 2030, effective antiretroviral therapy (ART) should be available for all infected people in all HIV-1-endemic regions [3,6]. Antiretroviral therapy (ART) has effectively transformed HIV-1 into a manageable chronic illness by

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reducing HIV-1 replication. Many antiretroviral drugs belonging to different drug classes have been licensed, but the most widely used drugs in sub-Saharan Africa target protease, reverse-transcriptase (RT) and recently, integrase proteins of HIV [7,8]. Most patients on combination ART experience virologic suppression, delayed progression to Acquired Immune Deficiency Syndrome (AIDS), and increased life expectancy [9].

However, the emergence of drug resistance poses a major challenge to the effective management of HIV-1 with ART [10-12]. Studies conducted in HIV-1-endemic but well-resourced regions globally have identified and established drug resistance as a leading cause of treatment failures [10,11,13]. Recent studies have observed an increasing trend in the prevalence of transmitted HIV-1 drug resistance, ranging between 3% and 7% in some African countries and at about 10% globally [13-16].

In Ghana, previous studies have documented HIV drug resistance mutations in both ART-naive and ART-experienced PLWH [17-20]. However, due to the increasing trends of transmitted drug resistance reports in other parts of the world [13-16], it is imperative to regularly profile pre-treatment HIV-1 drug resistance mutations, particularly among PLWH and those naive to ART, to inform the choice of antiretrovirals in the first-line regimen. HIV-1 genotypic testing is done in developed countries prior to the initiation of ART to guide physicians in prescribing the appropriate drugs for each patient [13,21] and reduce treatment failure. However, in most African countries, including Ghana, pre-treatment resistance testing is not performed for PLWH prior to ART initiation. This situation could lead to the emergence and spread of drug-resistant mutations and compromise the effectiveness of ART [21,22]. Previous studies have documented a high prevalence of resistance mutations in HIV patients on ART in Ghana. However, the contribution of pre-treatment drug resistance to this is unknown [2,19,23,24].

This study, therefore, determined circulating HIV-1 subtypes and protease-inhibitor and/or reverse transcriptase-inhibitor resistance mutations in ART-naive PLWH in Ghana.

## MATERIALS AND METHODS

A cross-sectional design with a purposive sampling strategy was used to enrol sixty-nine (69) ART-naive HIV-1 seropositive participants. The study participants were enrolled from the Korle-Bu Teaching Hospital (KBTH), the Greater Accra Regional Hospital (GARH), and the La General Hospital (LGH), Accra, Ghana. These hospitals have well-structured HIV clinics that provide ART and care for PLWH. Sample and data collection were done from May 2017 to December 2019. We obtained consent and enrolled people living with HIV who had not yet initiated antiretroviral therapy (ART) from three hospitals during the study period, prior to the start of their treatment. All participants already on ART or who had prior initiated and discontinued ART were not enrolled in the study. Only participants who signed the informed consent form were recruited for the study. Socio-demographic and clinical data were accessed from clinical records and interviews with the aid of a semi-structured questionnaire. Data collected included age, gender, date of HIV-1 diagnosis and risk behaviours.

About 5 ml of venous blood was collected in EDTA tube by phlebotomy, from which an aliquot of 50 µl was used for CD4+ T cell count estimation by fluorescence-activated cell sorter (FACS) Count equipment from Becton Dickinson (BD) Biosciences (San Jose, CA, USA). The remaining sample was spun in a microcentrifuge at 1,500 rpm for 10 minutes to obtain plasma. Aliquots of the plasma were used to measure viral load using the Cobas Amplicor HIV-1 MonitorTM Test from Roche (Indianapolis, IN, USA). To determine circulating HIV-1 subtypes, HIV-1 RNA was purified from plasma using nucleic acid purification reagent (Quick-RNA Viral Kit-R1034) from Zymo Research (Irvine, California, USA). The viral RNA was converted into complementary DNA (cDNA) using ProtoScript II First Strand cDNA Synthesis Kit (New England Biolabs Inc.) and stored at -20 ℃ until use. HIV-1 protease and reverse transcriptase genes were amplified from the viral cDNA using a nested polymerase chain reaction (PCR) protocol adopted from the HIV Genotyping Laboratory at the Noguchi Memorial Institute for Medical Research, University of Ghana.

HIV-1 protease was amplified using primer sets DRPR05: PR outer sense (AGACAGGTTAATTTTTTAGGGA), DRPRO2L; PR outer anti-sense (TATGGATTTTCAGGCCCAATTTTTGA), DRPRO1M; PR inner sense (AGAGCCAACAGCCCCACCAG) and DRPRO6; PR inner anti-sense (ACTTTTGGGCCATCCATTCC). HIV-1 reverse transcriptase was amplified in a nested reaction using primer sets DRRT1L: RT outer sense (ATGATAGGGGGAATTGGAGGTTT), DRRT4L; RT outer anti-sense (TACTTCTGTTAGTGCTTTGGTTCC), DRRT7L; RT inner sense (GACCTACACCTGTCAACATAATTGG) and DRRT6L; RT inner anti-sense (TAATCCCTGCATAAATCTGACTTGC) as previously described (18).

Phusion High-Fidelity PCR Master Mix with HF Buffer from New England Biolabs was used for the PCR reactions. Each reaction mixture consisted of 12.5 µl of the master mix, 1.25 µl of each primer (sense and anti-sense), 5 µl of nuclease-free water, and 5 µl of cDNA or first-round PCR product. The thermal cycling was done in a SimpliAmp Thermal Cycler (Applied Biosystems, ThermoFisher Scientific) with the following conditions: initial denaturation at 98 ℃ for 30 seconds, followed by 30 cycles of 98 ℃ for 10 seconds, 58 ℃ for 30 seconds, 72 ℃ for 90 seconds, and then a final extension at 72 ℃ for 10 minutes

for both first round and nested PCR runs. The nested PCR products were resolved on a 1.5% agarose gel electrophoresis and visualised under ultraviolet (UV) light in a UV imager (UVP BioDoc-It2 Imager, Analytina). The expected sizes of the nested PCR products were 463 bp for the protease and 887 bp for the reverse transcriptase genes and this was confirmed by agarose gel electrophoresis.

The PCR products with the right sizes were purified and directly sequenced using a Sanger sequencing platform. Primer sequences and methods used in generating the data were adopted from previous studies [25,26]. The raw sequences were assembled in Seqman Pro software version 13 (DNASTAR, USA) to generate a consensus sequence and edited for correction of base calling. The edited consensus sequences were exported into BioEdit version 7 software and aligned with the reference HIV-1 HXB2 sequence to verify that they were in the right frames and that any occurring frameshifts were corrected.

**Data analysis**

The consensus sequences were submitted to the Stanford University HIV Drug Resistance Database (Stanford HIVdb version 9.0) to identify HIV-1 drug-resistant mutants and determine a score of susceptibility of the respective class of antiretroviral drugs. Mutations were compared to the World Health Organisation (WHO) drug resistance surveillance list for monitoring local, national, and regional drug resistance [27,28]. The Context-based Modelling for Expeditious Typing (COMET HIV-1) platform from the Luxembourg Institute of Health was used to determine the HIV-1 subtypes of the sequences. Statistical computations for each data set were applied, where necessary, in GraphPad Prism version 8, and descriptive statistics were used to analyse the demographic and clinical history data of the participants.

## RESULTS

Sixty-nine patients were enrolled, comprising 19 males and 47 females, representing 27.5% and 68.1%, respectively. Three participants (4.4%) did not indicate their gender. The demographic and clinical characteristics of the participants have been summarised in Tables 1 and 2, respectively.

**HIV-1 Drug Resistance Mutations and HIV-1 Subtype Distribution**

Out of the 69 samples, 62% (n = 43) and 54% (n = 37) were successfully sequenced for protease and reverse transcriptase coding regions, respectively, and submitted to the Stanford HIVdb for drug resistance mutation analysis. We found HIV-1 drug resistance mutations to NNRTIs and PIs (Table 3), some of which are on the WHO's drug resistance surveillance list [27,29]. However, no NRTI mutations were observed in this study (Table 3). Out of the 37 RT sequences obtained, four (10.8%) had NNRTI drug resistance mutations, K103N, E138A, V179I and A98G. The K103N is a major resistance and induces high-level resistance to Nevirapine and Efavirenz, the two NNRTIs used in Ghana at the time of the study. The A98G mutation induces low-level resistance. A polymorphic mutation E138A was observed in two different individuals with CRF02_AG subtypes. A minor NNRTI mutation V179I, selected in patients receiving etravirine and rilpivirine but with little effect on susceptibility, was also found in one individual. We also detected three protease inhibitor accessory mutations (V32L, V11L, L10LF). All drug resistance mutations found in this study have been summarised in Table 3. Out of the 9 patients with documented resistance mutations, 6 participants had HIV-1 subtype CRF02_AG while one each had subtypes G, A, C and B. Sixty nine percent of the circulating subtypes were CRF02_AG strains, followed by subtypes B and G being 26% and 4%, respectively. The minority populations were subtypes A, C and CRF06_cpx, which accounted for 2% each (Figure 1).

Table 1. Demographic characteristics of the study participants

| Variables | n = 69 | Percent (%) |
|---|---|---|
| Age in years (Range 8-66) Mean = 38 years | | |
| <21 | 4 | 5.80 |
| 21 – 40 | 24 | 34.78 |
| >40 | 33 | 47.83 |
| Undisclosed | 8 | 11.59 |
| | | |
| Duration since HIV-1 diagnosis | | |
| <2years | 32 | 46.38 |
| 2 to 5 years | 4 | 5.80 |
| >5 years | 33 | 47.83 |
| | | |
| Risk behavior | | |
| Men who have sex with men | 5 | 7.25 |
| Others | 4 | 5.80 |
| Heterosexual contact | 30 | 43.48 |
| Unidentified | 22 | 31.88 |
| Unwilling to disclose | 8 | 11.59 |

Table 2. Clinical characteristics of the study participants

| CD4+ lymphocyte counts (cells/mm$^3$) | n = 69 | Percent (%) |
|---|---|---|
| <200 | 22 | 31.88 |
| 200 to 500 | 17 | 24.64 |
| >500 | 22 | 31.88 |
| Undetermined | 8 | 11.59 |
| | | |
| Viral load (copies/µl) | | |
| Target not detected | 4 | 5.80 |
| <50 | 3 | 4.35 |
| 51 to 999 | 10 | 14.49 |
| 1,000 to 99,000 | 36 | 52.17 |
| >100,000 | 16 | 23.19 |

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Table 3. HIV-1 drug resistance mutations observed in the study

| NNRTI Mutations (frequency of occurrence) | | PI Mutations (frequency of occurrence) | |
|---|---|---|---|
| K103N (1) | NVP/EFV | V32I (1) | (ATV/LPV/DRV) *r |
| V179I (1) | ETR/RPV | V11L (1) | DRV*r |
| A98G (1) | EFV/ETR/NVP/RPV | L10LF (2) | (ATV/LPV/DRV) *r |
| E138A (2) | ETR/RPV | | |

(N)– Frequency of the mutation, NVP – nevirapine, EFV- efavirenz, RPV – rilpivirine, ETR – etravirine, ATV – atazanavir, LPV – lopinavir, DRV – darunavir, *r – ritonavir-boosted

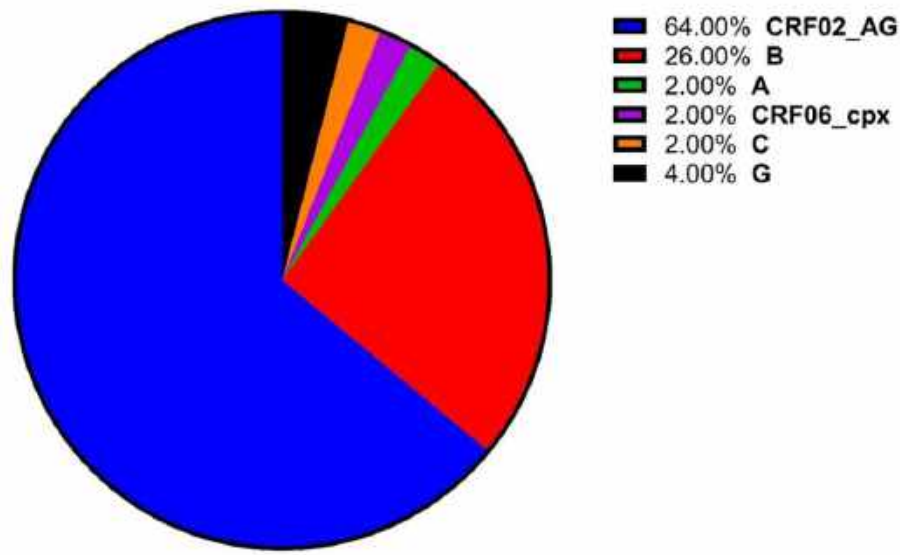


Figure 1. HIV-1 subtype distribution in the study population
A pie chart showing the percentages of the circulating HIV-1 subtypes CRF02_AG, B, A, CRF06_cpx, C and subtype G, respectively. CRF02_AG is dominant, followed by subtype B.

## DISCUSSION

Globally, HIV is still a pandemic, with infections higher in females than in males in sub-Saharan Africa [4,5,30,31], an observation which has also been reported in nearly all HIV-1 endemic populations in the West African sub-region, including Ghana. In this study, more females were recorded than males, which is consistent with Ghana's HIV-1 patient demographics, where the female-to-male ratio is about 2:1 [32]. While several reasons may explain this phenomenon, the most frequently attributed reason is that more than 90% of HIV-1 transmissions in the region are via heterosexual contact, and the female genitalia predisposes women to easier acquisition of sexually transmitted diseases from men [31,33].

Participants in this study were adults aged 18 to 66 years with a mean age of 38 years, suggesting a possible higher risk of transmission of HIV-1, including but not limited to transmission due to sexual contact. At least 30 participants indicated HIV infection was through sexual contact, and was mostly heterosexual. This finding is consistent with previous reports that HIV-1 is mainly transmitted through sexual contact and accounts for more than 90% of all new infections [33].

HIV-1 primarily infects CD4+ T lymphocytes, which also serve as a marker of immune activation. Consequently, untreated HIV-1 infection depletes CD4+ T lymphocyte count with a corresponding increase in viremia. These clinical events compromise the host immune response and increase the risks of acquiring other opportunistic infections [31,34]. All the participants enrolled in this study had not initiated ART at the time of sampling, and their enrollment criteria were confirmed with their clinical records. The participants were yet to initiate ART because they did not indicate their consent to initiation at the time of first diagnosis, suggesting that there remains a subpopulation of HIV-infected persons who are yet to initiate therapy despite the gains of the 'treat all infected persons' policy. The

immunological indicator (CD4+ T lymphocyte count), with a mean of 409 cells/mm3, was consistent with their clinical records, as all participants showed no symptoms of disease, suggesting a delayed progression from infection to disease. Considering that the participants were ART-naive and carried infection for at least two years, this observation was important, though in sharp contrast with expectations of a significant reduction in the CD4+ T cell population during untreated HIV-1 infection.

In HIV-1 infection, disease progression has been strongly linked with subtypes. HIV-1 subtype B has been shown to be more virulent and accounts for the most severe cases of morbidity reported [35-37]. Previous reports have shown that HIV-1 subtypes affect drug mutation patterns, and these differences are attributed to differences in codon calls [38,39]. A significant number (74%) of the participants in this study had non-B clades of HIV-1, and this could explain the delayed disease. While the delayed progression to disease of participants is good for the HIV situation in Ghana, the gradual increase in Subtype B (26%) compared to earlier reports is worthy of note and, hence, suggests enhanced surveillance.

Nearly all HIV-1 endemic countries have reported diverse CRFs from Group M due to the rapid replication and high mutation rate of the virus. Infection of host cells by one or two viral subtypes results in recombinant forms, which have stemmed mainly from Group M HIV-1. The development of these CRFs can have a selection advantage in the host, as noted in the CRF02_AG in West Africa, CRF01_AE in Central Africa, and CRF07_BC and CRF08_BC in China (40). Studies have shown that there may be recombinants between different HIV-1 groups but not between HIV-1 and HIV-2 [41]. The increasing frequency of HIV-1 subtype B in Ghana could be because of the observation of the year of return, during which many people from the global North visited Ghana, and the number of tourists to Ghana increased. The trend is of concern because subtype B, which drives the epidemic in Europe and North America, is more transmissible and virulent than some other subtypes [35–37]. In communities in which subtype B is the more prevalent circulating strain, it is known that the transmission and reports of new cases and drug resistance are relatively higher compared to areas where non-B subtypes are the majority strains in circulation [35,42-45]

Considering that the subtype B is associated with incidental increases in drug resistance and disease progression, it will be important to monitor the HIV-1 subtype dynamics in Ghana actively through the collection of geospatial data from multiple sites in order to understand the host and pathogen genomics of subtype B as well as other subtypes circulating the country. This will help to identify regions and communities that are lagging in each stage of the HIV care continuum and, hence, upscale efforts to consolidate the gains of antiretroviral therapy and sustain viral suppression. Our study found CRF02_AG as the predominant circulating subtype of HIV-1, followed by subtype B with minority populations of subtypes A, C, G and CRF06_cpx. Even though the majority of the global HIV population lives in sub-Saharan Africa, subtype B is not the dominant clade in this region (31,46,47). HIV-1 subtypes reported in African countries showed that newly infected individuals carry clades other than B (18,48,49). A study conducted in 2016 by Colleen et al. [41] in Cameroon found different subtypes and CRFs, with 64.9% CRF02_AG. Another study in Nigeria revealed a more diversified and prevalent HIV-1 epidemic with CRF06 cpx and CRF02_AG recombinant strains in circulation [50]. The findings from our study corroborate these previous findings. HIV-1 subtype B has accounted for the majority of newly diagnosed patients in Europe, North America, and Australia, scoring as high as 70-80% of newly diagnosed cases in Europe and in the USA [36,38,48], and has been the basis for most drug resistance analysis algorithms [22,38,51]. Even though drug resistance profiles between B and non-B subtypes may be different, the established reports of drug resistance in B subtypes are applicable to non-B subtypes due to resistance-related positions that are common to many of the HIV-1 strains [22,49]. Studies have shown that the non-B and CRF clades have mainly been associated with immigration and heterosexual transmission [48].

ART initiation in many resource-limited countries, including Ghana, is usually without prior genotypic testing [49]. In advanced and some developing countries, such precision medicine is common at the initiation of ART and could explain the sustained benefits of ART [52-54]. Generally, drug-resistant mutations are driven by the susceptibility or response to the drugs and occur at very different rates in different populations. The mutations are largely caused by factors including circulating subtypes, drug adherence, and random replication-driven mutations [39,55].

A limited number of studies have investigated pre-treatment drug resistance in Ghana [56,57]. An HIV-DR threshold survey that was conducted in 2009 reported low levels of transmitted drug resistance according to WHO guidelines for characterising transmitted drug resistance [57]. The study reported M184V and Y181C as major mutations in one person and A98G, K103R, K101Q and E138Q as minor mutations. It was recommended that the study be repeated every two years [56,57]. Contrary to the 2009 study, resistance to NNRTI mutations was observed in 4 of 37 people, representing 10.8%. A major NNRTI resistance mutation K103N was found in addition to A98G and E138A, which confer low resistance to NNRTIs [22,49].

This study found no major PI-associated mutations, but accessory PI resistance mutations (V32L, V11L and L10LF) were detected. This suggests the virus's susceptibility to protease inhibitors. This observation is expected because, at the time of the study, protease

inhibitors were not extensively used but were reserved as a second-line regimen. It is important to note that the PI accessory mutations found in our study only reduce susceptibility to protease inhibitors when present with other mutations [58]. Thus, investigating their occurrence and frequencies is strongly recommended in future studies. The K20I mutation, which confers resistance to PI in HIV-1 subtype B, was only seen in non-subtype B samples, in which it is the consensus amino acid and does not confer any drug resistance.

In HIV-endemic countries, including Botswana and Eswatini, the success of the ART program and achievement of the UNAIDS 95-95-95 targets reflect a strong comprehensive clinical management, including genotypic testing services, linkage to high-quality care, retention in care and a scale-up of periodic surveillance [54,59,60]. However, this is not the case in Ghana, and this may be the reason why Ghana is far behind in achieving its UNAIDS goals. Considering the emergence of drug resistance mutations in our population of PLWH, it will be imperative to incorporate genotypic drug resistance tests into the national response to HIV in order to monitor treatment with drug resistance testing and also conduct regular national surveys on HIV drug resistance. Introducing these objectives into the current HIV clinical management to monitor the 95-95-95 progress will consolidate the intended gains of ART and minimise the risks of treatment failure.

The limitations of our present study include the failure to enrol sufficient participants proportional to the sample population. This was due to the rollout of the treat-all policy, which made it difficult to easily identify PLWH, and we have yet to initiate therapy. To the best of our knowledge, the evolution of DR mutants is best studied in HIV infection acquired for at least a year and has yet to initiate ART. Secondly, the samples studied were collected between 2017 and 2019, all from HIV ART clinics within Accra. A larger sample size from a broader population, including all the HIV ART clinics, is therefore recommended in future studies to establish the pre-treatment HIV drug resistance situation in Ghana. Additionally, there is a need for periodic surveillance studies to establish a database comprising a stable trend of HIVDR information in Ghana, considering the relevance of longitudinal studies in providing quality health care [61,62].

### Conclusion

Low but increased levels of pre-treatment HIV-1 DR compared to the previous national threshold survey were observed in this study. We also found that HIV-1 subtype CRF02_AG is still dominant in Ghana, followed by subtypes B, A, C, G and CRF06_cpx. Surprisingly, we recorded a higher proportion of subtype B compared to previous studies. Although the level of PDR was low, the increasing trend strongly suggests that active monitoring of emergence of DR strains to guide the national ART program. It is therefore important to continually conduct active surveillance for subtype dynamics and drug resistance and integrate genotypic HIV drug resistance testing into routine monitoring of ART and public health campaigns. This will guide the national ART program, enhance the clinical management of PLWH and thus enable Ghana to attain the third ‘95 (viral suppression) of the UNAIDS goals.

## DECLARATIONS

### Ethical consideration

The protocol for this study was approved by the Institutional Review Board of the University of Ghana’s Noguchi Memorial Institute for Medical Research (NMIMR), Study 030/16-17, and the Ghana Health Service (GHS) Ethics Review Board. All participants consented to participate in the study, with parents consenting for their underage children.

### Consent to publish

All authors agreed on the content of the final paper.

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### Competing Interest

The authors declare no conflict of interest

### Author contribution

DNKQ, PKQ, OQ, GBK and EYB designed the study. DNKQ, AAM, ATB, SA and EYB performed the laboratory experiments. DNKQ, AAM, PKQ and EYB analysed the data. DNKQ wrote the first draft. GBK and EYB edited the draft manuscript. All authors revised the manuscript, contributed to the final draft and consented to its submission for publication.

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### Availability of data

The datasets generated and analysed in this work are included in this published article. The sequence dataset(s) supporting the conclusions of this article have been deposited at the GenBank with Accession

numbers ON411805 to ON411840 in https://www.ncbi.nlm.nih.gov/Genbank

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# Neuropsychological assessment of non-fluent variant of primary progressive aphasia in a bilingual French-Arabic speaking patient: A case study

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**Abstract**

***Background:*** This case study presents a comprehensive assessment of a Moroccan patient diagnosed with a non-fluent/agrammatic variant of primary progressive aphasia (nfvPPA).

***Objective:*** The study aimed to investigate neuropsychological and neurolinguistic deficits associated with nfvPPA and the potential implications for intervention.

***Methods:*** A thorough neuropsychological exploration was conducted to assess various cognitive domains, including memory, attention, language, perceptual, attentional and executive functions. Regarding neurolinguistic assessment, the Mini-Linguistic State Examination (MLSE) was used to characterise the patterns of PPA.

***Results:*** Neurolinguistic analysis revealed a clear pattern associated with nfvPPA, which includes impairments in the production of speech sounds, articulation, and phonological processing, alongside a reduced use of grammatical structures. Additionally, the patient exhibits challenges in understanding complex sentences, although his overall comprehension abilities remain relatively intact.
The patient also presented a significant decline in executive functions, memory, attention, and visual-constructive abilities. Linguistic deficits included impaired lexical-semantic abilities, phonological alexia, and lexical agraphia. Despite these impairments, the patient maintained some preserved functions, such as autobiographical memory and visuospatial abilities.

***Conclusion:*** This case study highlights the progressive nature of nfvPPA and its impact on multiple cognitive domains. The patient's presentation aligns with an advanced stage of PPA, characterised by the presence of extralinguistic impairments. Further neuroimaging studies would be beneficial to confirm the underlying pathology and inform targeted interventions.

**Keywords:** PPA, Aphasia, Non-fluent, Bilingual, Neurocognitive, Agrammatic, nfvPPA

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## INTRODUCTION

Primary progressive aphasia (PPA), referred to as Mesulam syndrome, is defined by a gradual and distinct deterioration in language capabilities, primarily resulting from progressive focal atrophy in the left perisylvian regions of the dominant hemisphere [1]. Affected individuals do not exhibit the typical characteristics associated with post-stroke Wernicke's or Broca's aphasia, likely due to the multifocal, partial, or progressive nature of the lesions involved [2]. PPA may present as either fluent speech, where normal speech patterns are preserved, or non-fluent speech, and it can impact phonology, syntax, or semantics to varying extents. Due to its clinical and linguistic variability, classification has been established [3,4] to guide standardised clinical assessments. Neuroimaging methods, such as magnetic resonance imaging (MRI), are utilised to exclude specific causes of aphasia, including stroke or tumours, and may reveal atrophy indicative of the degenerative process. Furthermore, functional imaging techniques like positron emission tomography (PET) may demonstrate localised hypometabolism, which can occur before any noticeable atrophy is detected on MRI [3].

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Table 1. A summary of the four main clinical variants of PPA

| Variant | Core Features | Associated Neuropathology (Often, but not always) | Other Common Features |
|---|---|---|---|
| Nonfluent/Agrammatic PPA (nfvPPA) | * Agrammatism (difficulty with grammar)<br>* Effortful, halting speech<br>* Speech sound distortions (apraxia of speech) | Tau-related pathology (e.g., progressive supranuclear palsy, corticobasal degeneration) | * Relatively preserved comprehension<br>* Motor deficits (e.g., rigidity, bradykinesia) may develop |
| Semantic PPA (svPPA) | * Anomia (difficulty finding words)<br>* Impaired comprehension of single words<br>* Surface dyslexia (difficulty reading irregular words) | TDP-43 pathology (often associated with frontotemporal lobar degeneration) | * Relatively preserved grammar and speech production<br>* Prosopagnosia (difficulty recognizing faces) may be present |
| Logopenic PPA (lvPPA) | * Word-finding difficulties (pauses, circumlocutions)<br>* Impaired sentence repetition<br>* Phonological working memory deficits | Alzheimer's disease pathology (amyloid plaques and neurofibrillary tangles) | * Relatively preserved single-word comprehension and grammar<br>* Slower rate of progression compared to other variants |
| Mixed/Unclassifiable PPA | Presents with features of more than one PPA variant but doesn't clearly fit into one of the other categories. | Variable, reflecting the mixed clinical presentation | Varies depending on the combination of features present. |

The classification system introduced by Mesulam et al. [4] delineates PPA as a spectrum that includes several distinct variants: the non-fluent and agrammatic variant (nfvPPA), the semantic variant (sv-PPA), the logopenic variant (lv-PPA), which may present with or without challenges in sentence repetition and the mixed variant (mv-PPA), which encompasses any combination of the above-mentioned types (Table 1). Moreover, additional taxonomies have emerged, emphasising narrative discourse and writing as potential early markers of pre-linguistic impairments in PPA [5-7]. Given these insights, it is crucial to reevaluate PPA to adequately address the linguistic, cognitive, neuroanatomical, and biological intricacies and variabilities that characterise each variant while integrating specific screening assessment tools [8]. Our study focused on illustrating the linguistic and neuropsychological profile of a bilingual Arabic-French-speaking patient who has been diagnosed with the non-fluent and agrammatic variant of PPA.

## CASE

The neuroimaging showed a fronto-parietal atrophy with a slight hippocampal atrophy (Figure 1). A thorough neuropsychological assessment was conducted over the course of two days every week throughout January 2020 to evaluate the cognitive condition of the patient. Each segment of the testing lasted one hour and utilised neuropsychological evaluations in either Arabic or French, depending on the patient's linguistic proficiency and preferences.

During the neuropsychological assessments, the patient reported experiencing difficulties with recent event recall, reading comprehension, and dressing. The patient demonstrated nosognosia and was informative about his

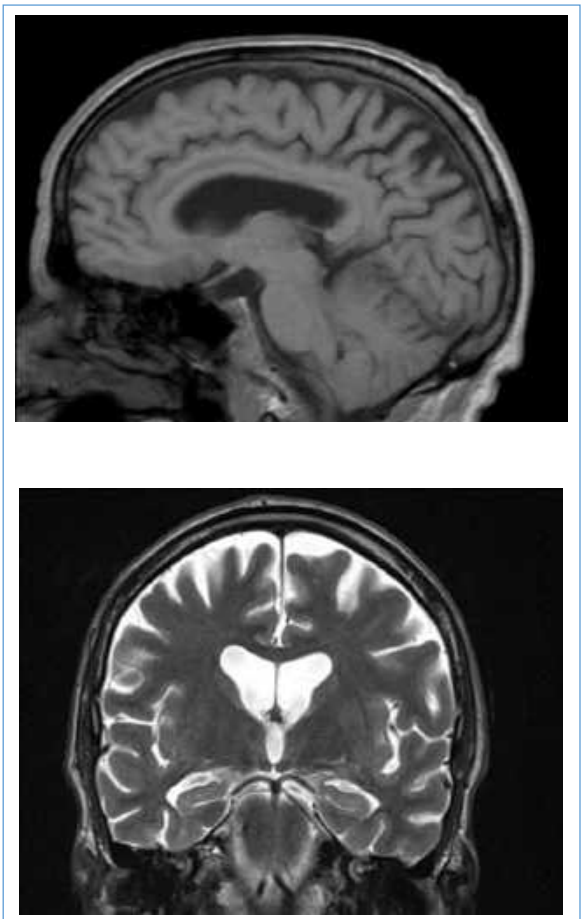

Figure 1. MRI – a) Sagittal cut highlighting a fronto-parietal atrophy b) Coronal cut showing a slight hippocampal atrophy

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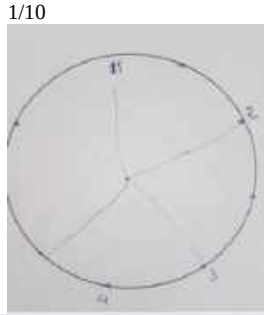
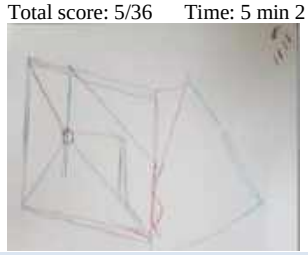
complaint. He expressed significant concern regarding his memory deficits, word-finding difficulties, and occasional fluctuations in cognitive performance throughout the day. He also exhibits reduced autonomy (IADL: 6/8). An interview with the patient's spouse provided more detailed information about the memory complaint. She reported that her husband's forgetfulness began in 2015. More specifically, while they were on pilgrimage in 2017, the deficit intensified, resulting in the patient becoming disoriented for three days, which caused prolonged distress. Subsequently, a topography study office opened by the patient was closed after three years due to forgetfulness and apprehension about committing errors (plans, distance estimations). The patient had a keen interest in Arabic music and played the Arabic guitar (wtar). He possessed extensive knowledge of oriental musical repertoire and demonstrated a clear and harmonious singing voice.

Regarding leisure activities, he had been cycling regularly for 10 years, participating in group rides in the vicinity of Rabat. However, forgetting bicycle repair procedures and losing basic mechanical knowledge were the initial signs that alerted the patient and his friends during cycling events. The patient exhibited high compliance and engagement in conversation, reporting partial details of his daily routine, distant and professional experiences (studies, hobbies, work, and autobiographical information). His speech was well-adapted, and his mood and behaviour did not exhibit any anxiety, depression or apathy signs (apathy scale: score 3/42). He actively participated in cooking therapy and music sessions conducted at the Alzheimer Centre of Rabat.

## RESULTS

Three years after the onset of the initial progressive memory disorders (Table 2) the neuropsychological assessment revealed, a severe executive dysfunction that interferes with memory performance (in working and long-term memory), attentional, and visual-constructive abilities within the context of significantly impaired intellectual efficiency and dysfunctional linguistic and lexico-semantic abilities (parallel impairment of spoken language marked by lack of words and a suspicion of phonological alexia associated with lexical agraphia). It should be noted that the processes of encoding and retrieving information require increased cognitive effort compared to previous functioning. Visuo-perceptual abilities remained intact; however, praxis abilities were impaired (presence of gestural apraxia and suspicion of mild dressing apraxia). Visuo-constructional abilities were severely impaired, which is consistent with a left parietal profile (quasi-compliance with the global plan but absence of details). The patient's performance on the Clock Drawing Test (CDT), scoring 1 out of 10, revealed a profound deficiency in visuospatial abilities, executive functioning, and motor coordination. This outcome indicates challenges in understanding the layout of the clock face, organising

Table 2. Neuropsychological assessment of Mr R.

| Tests | Initial Assessment in 2020 |
|---|---|
| Montreal Cognitive Assessment (MoCA) | Total score 10/30<br>Visuospatial/Executive 1/5<br>Naming 3/3<br>Attention 2/5<br>Language 2/3<br>Abstraction 1/2<br>Delayed Recall 0/5 and Orientation 1/6 |
| Mini-Mental State Examination (MMSE= | Total score: 15/30<br>Orientation to time and place 4/10<br>Immediate recall 3/3,<br>short-term verbal memory 1/3<br>calculation 0/5,<br>language 7/8, and construct ability 0/1 |
| FAB (Frontal assessment battery) | Total score: 11/18<br>Conceptualization 3/3<br>Mental flexibility 2/3<br>Motor programming 1/3<br>Sensitivity to interference 1/3,<br>Inhibitory control 1/3<br>Environmental autonomy 3/3 |
| TMT -Trail Making test | TMT A ( 6 Errors / 3 min 57 sec)<br>TMT B ( 11 Errors / 3 min 20 s) |
| Clock Drawing Test | 1/10<br>  |
| Categorical and literal verbal fluency | Letter Fluency P(9) (3 intrusions) / R (10) (9 intrusions)<br>Semantic category fluency<br>- Animals (9) 0 repetitions /3 intrusions<br>- Fruits (5) 2 intrusion / 0 repetitions |
| MIS (Memory impairment screen) | Immediate recall: 3/4<br>Free recall 8/8 cued recall 0/8<br>Delayed Free recall : 0/8 delayed cued recall 1/8 (5 intrusions) |
| Digit span task | Digit span forwards (4)<br>Digit span backwards (2) |
| PEGV (visual perception) | Intertwined figures: 32/36<br>Identical figures: 7/10<br>Categorical matching : 10/12<br>Functional matching: 9/12 |
| Praxis examination | Symbolic gestures 5/5<br>Pantomines 8/10<br>Abstract gestures 5/8 |
| Rey-Osterrieth Complex Figure (ROCF) Test | Total score: 5/36 Time: 5 min 2 s<br>  |
| IADL | 6/8 |

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spatial elements, and executing the drawing task effectively (Table 2).

Regarding episodic memory, the patient exhibited significant executive dysfunction in retrieval mechanisms. No learning effect was observed. Cueing did not normalise or improve performance. Furthermore, there was a substantial deficit in storage (a delayed recall deficit reflecting dysfunction of the hippocampal regions). However, the slight deficit in encoding was more appropriately attributed to the underlying executive deficit (lack of effective memory strategy in immediate recall). Severe executive dysfunction was observed in central executive processes, including inhibition, dual-task processing, flexibility, planning, and maintaining an isolated strategy. Semantic memory demonstrated dysfunction in the retrieval mechanisms of naming and word generation, while perseverative intrusion errors were dysexecutive in nature. Visuo-perceptual abilities did not exhibit difficulties at the level of asemantic or associative agnosia. However, the Rey-Osterrieth Complex Figure (ROCF) Test, which assessed visual-attentional, visuospatial, and constructional functions, revealed significant difficulties in visuospatial perception, constructional abilities, and visual memory. This score suggested that the patient struggled to accurately interpret and replicate a complex visual image, pointing to potential issues with attention, planning, the integration of visual and motor functions and the exploration of space, both at the level of apprehension of spatial relations between the different elements of a figure and at the level of executive processes (organisation and arrangement of details) (table 2).

In terms of spontaneous language, it exhibited reduced categorical and literal fluency (Table 2), accompanied by anomia and certain features of paragrammatism. At the levels of motor speech and oro-practo-motor function, there were no indications of speech apraxia, dysarthria, or oro-linguo-facial apraxia. Neurolinguistic analysis utilising Mini-Linguistic Status Examination (MLSE) [9] (Table 3) demonstrated a distinct pattern of nfvPPA, encompassing mild deficits in in sequencing (phonological processing),

Table 3. MLSE results of Mr R by subtests and main subdomains

| Subtests | Patient's results |
|---|---|
| 1-Picture naming (n=6) | 6 |
| 2- Repetition of mono and multi-syllabic words (n=3) | 3 |
| 3- Single word comprehension (n=3) | 2 |
| 4- Repetition (n=3) | 3 |
| 5- Semantic association (n=4) | 2 |
| 6- Oral comprehension of sentences 1 (n=4) | 3 |
| 7- Oral comprehension of sentences 2 (n=4) | 2 |
| 8- Sentence repetition (n=4) | 3 |
| 9- Reading (n=10) | 7 |
| 10- Writing (n=6) | 2 |
| 11- Picture description (n=5) | 3 |
| MLSE subdomains | Patient's results |
| Motor speech (n=30) | 30 |
| Semantics (n=30) | 21 |
| Phonology (n=30) | 26 |
| Syntax (n=10) | 5 |
| Global score (n=100) | 82 |

Table 2. MLSE results of Mr R. H by subtests and main subdomains

| Subtests | Patient's results |
|---|---|
| 1-Picture naming (n=6) | 6 |
| 2- Repetition of mono and multi-syllabic words (n=3) | 3 |
| 3- Single word comprehension (n=3) | 2 |
| 4- Repetition (n=3) | 3 |
| 5- Semantic association (n=4) | 2 |
| 6- Oral comprehension of sentences 1 (n=4) | 3 |
| 7- Oral comprehension of sentences 2 (n=4) | 2 |
| 8- Sentence repetition (n=4) | 3 |
| 9- Reading (n=10) | 7 |
| 10- Writing (n=6) | 2 |
| 11- Picture description (n=5) | 3 |
| MLSE subdomains | Patient's results |
| Motor speech (n=30) | 30 |
| Semantics (n=30) | 21 |
| Phonology (n=30) | 26 |
| Syntax (n=10) | 5 |
| Global score (n=100) | 82 |

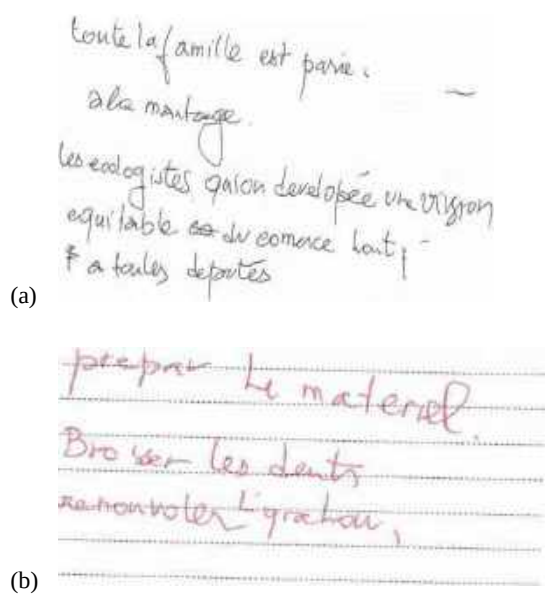


Figure 2. Mr R writing performance in French – a) Writing to dictation b) spontaneous writing sample

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diminished utilisation of grammatical structures (agrammatic speech) and difficulties comprehending complex sentences (although comprehension skills may be relatively preserved). Furthermore, the patient did not exhibit reduced speech rate, effortful articulation or apraxia of speech which are indicative of motor speech impairment. However, working memory deficits were observable, affecting the capacity to maintain information in short-term memory. Reading aloud was impaired for both regular and irregular words, with particular difficulty in the latter. Paralexic and phonologically plausible errors were produced on pseudo-words and non-words. Lexico-semantic and syntactic comprehension was partially preserved. Generally, the grapho-motor function was coherent, characterised by regular strokes, and performance was maintained over time. At the allographic level, few errors were present; however, at the graphemic level, omission errors were more prevalent than substitutions (Figure 2).

Nevertheless, the fact that Mr. R predominantly employs French in his daily life, despite his inclination towards spoken French infused with the Moroccan Arabic dialect, indicates that the cognitive requirements of written language, especially in formal settings, may differ from those associated with spoken language. Moreover, the partial impairment of L1 (Arabic) alongside relatively better retention of L2 (French) may be elucidated by the distinct linguistic patterns linked to the non-fluent/agrammatic variant of PPA as displayed by MLSE performance.

## DISCUSSION

Mr. R demonstrated a distinct pattern of nfvPPA, encompassing deficits in phonological processing, grammatical structures and difficulties comprehending complex sentences in French and Arabic. Furthermore, the patient did not exhibit reduced speech rate, effortful articulation or apraxia of speech, which are indicative of motor speech impairment. Nosognosia is consistently experienced by the patient, who spontaneously expressed these complaints while maintaining some activities of daily living. This clinical presentation suggests a progression towards an advanced stage of nfvPPA. It may also evolve into a mixed variant of PPA while some features of logopenic variant were present or towards a PPA-plus syndrome with more extended cognitive impairments, including episodic memory, gestures and executive functions.

Neurolinguistic assessment of nfvPPA involves assessing various language and cognitive domains. Patients typically present with agrammatism in language production and effortful speech [10]. Key features include phonological and semantic paraphasias, impairment in repetition, writing of non-words, and sentence comprehension difficulties [11]. A comprehensive assessment should include both language and non-language testing to aid in diagnosis and subtyping [12]. Language evaluations often involve connected speech analysis, which is crucial for identifying agrammatism, a core feature of nfvPPA [13]. Simultaneously, non-language cognitive impairments in nfvPPA may include executive function deficits, with relative preservation of memory and visuospatial functions [12]. This contrasts with other PPA variants, such as the logopenic variant, which exhibits impairments in phonological working memory, acalculia, and mild difficulties with memory and visuospatial functions [12]. Notably, some cases of nfvPPA may present with atypical features, such as generalised auditory agnosia, as reported in a case study where the patient was unable to identify verbal sounds, environmental sounds, or familiar songs [14]. Unlike nf-vPPA in our case study, it can evolve into a more complex clinical syndrome known as PPA-plus, which includes additional cognitive and motor symptoms. The evolution of the neuropsychological profile in this progression is characterised by several key features. The neuroimaging profile typically shows initial involvement of the premotor/motor cortex, with subsequent spread into the prefrontal cortex over time [15,16].

The issue of differential language preservation among bilingual individuals diagnosed with PPA presents a multifaceted challenge [17,18], exemplified by the case of Mr. R, who speaks both Arabic and French. Although the emphasis on his bilingualism is noteworthy, a more thorough examination of which language—Arabic or French—remains relatively intact would enhance the understanding of the targeted language in rehabilitation. It is essential to take into account not only the language dominance observed during assessments but also Mr. R's stated language preferences and the typical environments in which he utilises each language throughout his daily activities. His inclination to converse in French, occasionally incorporating the Moroccan Arabic dialect, while predominantly communicating in French through writing, indicates cross-linguistic factors that contribute to the dynamics of language retention and attrition [19].

Several theories may account for this observed linguistic pattern. One potential explanation is that Mr. R's language usage habits prior to the onset of PPA have shaped the progression of his language decline [20]. As long as French served as his primary language for professional or written communication, its more frequent engagement could have offered a cognitive buffer, thereby postponing the disease's effects on this particular language system [21]. In contrast, while Arabic, including the Moroccan dialect, may be more prevalent in social interactions, the informal and potentially less cognitively taxing nature of these exchanges might not afford the same degree of protective benefit. Additionally, the age at which each language was acquired could play a significant role; if French was learned later in life (as a second language which not the case of our patient), it may be more vulnerable to the impacts of neurodegeneration, especially if the disease predominantly affects the brain regions responsible for the acquisition and processing of a

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second language. However, the observation that Mr R primarily uses French in writing, despite his preference for spoken French in Moroccan Arabic dialect, suggests that other factors beyond the simple frequency of use are at play. The cognitive demands of written language, particularly in a formal context, might be different from those involved in spoken language [22,23]. It is possible that the cognitive resources required for written French are relatively preserved compared to those needed for spoken Arabic or that the specific neural networks supporting written French are less affected by the disease process [24]. Furthermore, the quasi-impairment of L1 (Arabic) with relatively better preservation of L2 (French) could be explained by the specific patterns of brain atrophy associated with the non-fluent/agrammatic variant of PPA. Research suggests that this variant often affects frontal brain regions crucial for grammatical processing, and these regions might be more critical for Arabic [25,26], a language with a more complex grammatical structure compared to French. Further investigation into the specific linguistic features affected in each language, along with neuroimaging data, would be needed to explore these possibilities further.

Individualised treatment is paramount, as it underscores the necessity of customising interventions to align with the unique profile of each patient, taking into account their specific strengths, weaknesses, and communication objectives [27]. Though they could be adapted to Mr R, it is worth mentioning that his assessment has not been followed by specific neuro-cognitive interventions. However, the identification of specific neuropsychological and linguistic deficits, such as agrammatism, apraxia of speech, and word-finding difficulties, is crucial for developing targeted intervention strategies. For instance, the presence of significant agrammatism indicates that interventions aimed at enhancing grammatical production, including techniques like sentence structure training and mapping therapy [28], may prove advantageous. To proactively prevent the installation of apraxia of speech, it is essential to implement approaches that focus on motor speech planning and articulation, utilising methods such as Combined Aphasia and Apraxia of Speech Treatment (CAAST) [29].

Furthermore, addressing observed anomia can be effectively achieved through interventions designed to enhance lexical retrieval, employing strategies like semantic feature analysis and cueing hierarchies [30]. Neuropsychological rehabilitation and interventions for nfvPPA focus primarily on language deficits but also address associated cognitive impairments. Research indicates that patients with nfvPPA exhibit deficits in executive, working memory functions and praxis in addition to their core language impairments [31]. These disorders may be present in nfvPPA, even in the early stages, suggesting the need for targeted executive function training [32,33]. Therefore, the complex nature of nfvPPA, with its primary language deficits and associated cognitive impairments, underscores the importance of individualised, multimodal interventions tailored to each patient's specific profile of strengths and weaknesses [34].

Simultaneously, involving caregivers in the intervention process is essential, as providing them with education and support can significantly enhance communication between the patient and their caregivers. Future clinical studies should investigate the effectiveness of specific treatment approaches for nfvPPA and explore innovative intervention techniques such as neuromodulation [35,36]. It is also important to set realistic expectations, recognise the progressive nature of PPA, and emphasise that interventions should aim to maintain communication abilities and improve quality of life rather than attempting to reverse the underlying condition [37]. A multidisciplinary approach is also vital, as it highlights the collaborative roles of various professionals, including speech-language pathologists (SLP), occupational therapists, behavioural neurologists and neuropsychologists, in the intervention process. Additionally, exploring communication strategies, particularly the use of augmentative and alternative communication (AAC) and e-health devices, becomes increasingly important in the later stages of the disease [38,39].

A comprehensive neuropsychological and neurolinguistic assessment for nfvPPA should encompass an assessment of language production and comprehension, executive functions, and other cognitive domains. It is essential to note that the clinical presentation of nfvPPA can be complex, and there may be overlap with other PPA variants or neurodegenerative conditions, necessitating specific assessment and longitudinal follow-up for accurate diagnosis [8,40-42].

### Conclusion

The present case study highlighted the neuropsychological and cross-linguistic features of nfvPPA in bilingual Arabic-French-speaking patients. The clinical outcome and prognosis align with extralinguistic impairments as found in advanced stages of mixed variant or PPA plus syndrome, characterised by the emergence of gestural apraxia, significantly impaired constructive apraxia, and agraphia with surface dysorthographia. These findings elucidate the severity of this neurodegenerative condition and its potential progression over time. Further neuropsychological, neurolinguistic, and neuroimaging studies would be beneficial in confirming differential cross-linguistic impairment in French vs Arabic, as well as the underlying pathology, leading to tailoring specific clinical interventions.

## DECLARATIONS

### Ethical consideration

This study does not possess an ethics code; nonetheless, all ethical considerations were taken into account in the preparation of this article. The participant and his spouse

were informed about the research objectives and its diagnostic phases, and they were assured of the confidentiality of their personal information. Additionally, they were given the option to withdraw from the study at any time they desired.

**Consent to publish**
All authors agreed on the content of the final paper.

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None

**Competing Interest**
The authors declare no conflict of interest

**Author contribution**
MT contributed to the study's conceptualisation, design, data collection, analysis, drafting and finalisation of the manuscript.

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**Availability of data**
Data is available upon request to the corresponding author

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# Impact of plant-derived galactagogues on breast milk production and blood prolactin levels in early postpartum mothers of preterm infants: A double-blind randomised controlled trial.

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**Abstract**

***Background:*** Preterm infants require efficient care and provision of adequate nutrition to enhance their survival and minimise complications that may arise during growth and development. Breast milk represents the sole recommended source of nutrition for preterm infants until 6 months after birth.

***Objective:*** This study investigated the effect of plant-derived galactagogues on breast milk production and serum prolactin levels of early postpartum mothers, as well as on the weight of their preterm infants.

***Methods:*** A double-blinded, randomised and controlled study design was used to determine breast milk volume and serum prolactin levels on days 1 and 7 of early postpartum mothers of preterm infants given food products containing plant-derived galactagogues (granola or chocolate drink) or the corresponding placebo food products. The weight of the preterm infants fed on breast milk was also measured on days 1 and 7.

***Results:*** Mean breast milk volume was significantly increased in mothers who received the granola ($p < 0.0001$), chocolate drink ($p < 0.0001$), granola placebo ($p < 0.0001$) and chocolate drink placebo ($p = 0.0007$) by day 7. Serum prolactin levels of the mothers and the weight of the preterm infants were not significantly different on day 7 compared to the values obtained on day 1. There was no significant correlation between breast milk volume and either serum prolactin levels or infant weight on days 1 and 7 for the intervention and placebo groups.

***Conclusion:*** Plant-based galactagogues did not increase breast milk supply or affect serum prolactin levels in early postpartum mothers with hypogalactia. Further research is needed to elucidate the molecular mechanisms regulating breast milk production and composition in lactating women

**Keywords:** Preterm babies, galactagogues, breast milk, serum prolactin

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## INTRODUCTION

Breastfeeding is a crucial aspect of maternal and infant health, especially for preterm infants, due to their vulnerability to diverse health challenges. Breast milk provides essential nutrients, antibodies, and growth factors that promote optimal growth and development of preterm infants [1]. It is estimated that 13.4 million infants were born preterm in the year 2020 globally, and preterm births occurring from 32 to < 37 weeks of gestation were the most predominant [2]. In the largest tertiary hospital in Ghana, the preterm birth rate doubled from 9.3% to 18.9% over a

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decade [3]. Infants born before the recommended 37 weeks of gestation are at risk of developing complications that could lead to mortality or long-term adverse outcomes in those who survive beyond five years [4]. It is, therefore, essential to provide adequate breastfeeding and medical care to preterm infants to boost their survival, growth and development during the early stages of life.

Lactating mothers of preterm infants may experience challenges with producing adequate breast milk, which can affect compliance with the highly recommended exclusive breastfeeding of infants till six months after birth. A notable cause of ineffective breastfeeding of preterm infants is reduced production of breast milk in lactating mothers, even though other factors such as ill-health in mothers or infants, weak suckling by infants and lack of nipple stimulation can also affect optimal breast milk production and location of infants. Sub-optimal breast milk production in lactating mothers of preterm babies is also influenced by the emotional and psychological status of the mother, especially when they are temporarily separated from their babies receiving treatment at the neonatal intensive care unit of hospitals [5]. Lactating mothers of preterm infants affected by hypogalactia can boost breast milk production via galactagogues, which are available as medications or present in indigenous diets and commercial food products [6-8].

Pharmacological galactagogues such as metoclopramide, domperidone, chlorpromazine and sulpiride can boost breast milk production and prolactin secretion [9]. These synthetic galactagogues induce an increase in breast milk production by stimulating prolactin synthesis in lactotrophic cells of the anterior pituitary gland [9]. Pharmacological galactagogues can cause significant adverse effects in both lactating mothers and infants, including gastrointestinal disorders, extrapyramidal symptoms, amenorrhea, severe depression and seizures. Hence, their prescription to lactating mothers must be guided by the need to improve breast milk production and tolerance of the potential side effects. Notable galactagogues from herbs and other plant sources include fennel (*Foeniculum volgare*), fenugreek (*Trigonella foenumgraecum*), moringa (*Moringa oleifera*), alfalfa (*Medicago sativa*), milk thistle (*Silybum marianum*), and ginger, even though their precise mechanism of action for enhancing breast milk production is currently unknown [10-12].

In Ghana, the use of galactagogues is reported as 67.7% in the northern and southern parts, and the most common lactogogues used by mothers include groundnut/peanut soup prepared with Bra leaves (Hibiscus sabdariffa), hot black tea, Werewere/Agushi (Citrulus colocynthis) prepared with Bra leaves, and Abemudro (a polyherbal formulation) [13]. Hormones such as oxytocin, progesterone, cortisol and oestrogen are also vital in stimulating breast milk production in lactating mothers [9]. The severe adverse effects that might be associated with synthetic galactagogues render plant-derived galactagogues the preferred agents for boosting breast milk production, especially in lactating mothers having a history of non-tolerance of these adverse effects from the synthetic agents. Moreover, several lactating mothers would avoid synthetic galactagogues when they are enlightened on the potential to cause side effects in neonates. Hence, plant-derived galactagogues represent a suitable agent for boosting breast milk production and efficient lactation of preterm infants in mothers that produced inadequate volumes of breast milk.

In Ghana, commercial food products containing plant-derived galactagogues are usually recommended as intervention products for early postpartum mothers of preterm infants producing insufficient breast milk after child delivery. This practice necessitates continual investigations of the effect of these lactation products on breast milk production in early postpartum mothers. The present study investigated the impact of food products containing plant-derived galactagogues on breast milk production and serum prolactin levels of early postpartum mothers and the weight of the preterm infants. The data from this study provide evidence-based insights that healthcare professionals can use to offer informed guidance and support to lactating mothers of preterm infants.

## MATERIALS AND METHODS

### Study design and participants

This was a double-blinded, randomised and controlled study, which involved early postpartum mothers of preterm infants at the neonatal intensive care unit of the 37 Military Hospital in Accra, Ghana. The participants who met the inclusion criteria were recruited over six months, as they reported to the study site. The study had four arms: two intervention groups and two placebo (control) groups, each comprising 6 participants (Fig. S1). The inclusion criteria were mothers (18 - 45 years old) of preterm infants (born before or on the 37th week of gestation) from 1st to 10th day of postpartum with daily breast milk volume below 300ml and mechanically pumping breastmilk throughout the days before the onset of the study (at least four times per day). Lactating mothers of full-term infants were excluded from the study.

Other exclusion criteria were lactating mothers with breast engorgement, mothers on medications for inducing breast milk production, mothers who were ill, mothers taking diuretics, pseudoephedrine, anticholinergics, warfarin or any anticoagulant or oestrogen-containing birth control pill, mothers who had undergone surgery that could affect their ability to produce breast milk or mothers diagnosed with polycystic ovary syndrome, asthma or atopic diseases. Mothers who are allergic to peanuts, mothers of infants with congenital anomalies or acute conditions and mothers with obstetrical evaluations recommending exclusion were also not recruited for the study.

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**Lactation products**

The lactation products used for the study are indicated below:

i) Chocolate drink (FDA/Dk 21-1461): cocoa powder, chia seeds, flax seeds, cinnamon, fenugreek, fennel, brewers' yeast.
ii) Chocolate drink placebo (FDA/Ce 21-1461A): cocoa powder, chia seeds, flax seeds, cinnamon.
iii) Granola (FDA/Dk 21-1047): rolled oats, raisins, almonds, honey, pumpkin seeds, flax seeds, chia seeds, brewer's yeasts, fennel, and fenugreek.
iv) Granola placebo (FDA/Ce 21-1047A): rolled oats, raisins, brewers' yeasts, almonds, honey, pumpkin seeds, flax seeds and chia seeds.

**Determination of the effect of lactation products on breast milk volume, serum prolactin levels and infant weight**

Participants were randomly allocated to the intervention and placebo groups via a secret ballot procedure. The study design was also aligned with the requirements of the per protocol analysis. Participants in the intervention groups received a lactation product (granola or chocolate drink) containing plant-derived galactagogues for 7 days, along with lactation guidance on how to enhance breast milk production. They consented to physically pump breast milk 4-6 times daily at intervals of at least 3 hours. The participants in the control groups received lactation products (granola placebo or chocolate drink placebo) without the plant-derived galactagogues, and lactation advice was provided for both groups. They were also required to physically pump breast milk four to six times daily at intervals of at least three hours. All lactating mothers recruited for the study received training and supervision on best practices for optimal breast milk pumping. The breast milk volume of all early postpartum mothers and the weight of the preterm infants were measured on day 1, before administering the intervention and placebo products (baseline measurements), and at 24-hour intervals until day 7.

Two (2) millilitres (ml) of whole blood were collected via venipuncture for the measurement of serum prolactin levels of the mothers, which were measured on day 1 prior to administering the intervention and placebo products (baseline measurements) and on the 7th day of the study. The whole blood samples were centrifuged at 2,000 x g for 10 minutes at 4ºC, and the serum obtained was used to measure prolactin levels via the chemiluminometric method using the Advia Centaur XP device (Siemens).

**Data Analysis**

All data were stored using Microsoft Excel 2013, and the statistical analysis was done using IBM SPSS version 25 software. Demographic and clinical information (age, marital status, educational level, mode of delivery, employment status, gravidity, parity and gestational age of infants) was analysed for all the study participants in each group (intervention or placebo). The Kolmogorov-Smirnov Test of Normality was used for the assessment of conformity with a normal distribution of the data on breast milk volume, serum prolactin levels and infant weight. The mean, standard deviation and range for serum prolactin, breast milk volume and infant weight were also determined. An unpaired T-test was used to determine whether the mean breast milk volume, serum prolactin levels or infant weight measured on day 1 significantly differed from those on day 7 for each of the four groups. The unpaired T-test was also used to evaluate whether the mean breast milk volume, serum prolactin levels or infant weight measured for the placebo group was significantly different from the corresponding intervention group on days 1 and 7. The Pearson and Spearman's rank correlation coefficients were also determined to assess the correlation between breast milk volume and either serum prolactin levels or infant weight. A p-value of less than 0.01 was considered statistically significant.

## RESULTS

Thirty-two early postpartum mothers initially consented to participate in the study (Fig. S1). However, eight mothers were later excluded from the study due to the loss of their preterm infants (3 mothers), lack of interest in the study (2 mothers) and mothers citing personal reasons to discontinue the study (3 mothers). Hence, the total sample size used in this study was 24 mothers of preterm infants. The granola intervention group, chocolate drink group, granola placebo group and chocolate drink placebo group had 6 participants for each group (Table 1). Two mothers were between 40 and 49 years old, and eleven mothers were in the age range of 20 to 29 years, which was the highest frequency of participants. This was followed by the 30 to 39 years age range, which had 10 participants. More than half of the mothers (14 participants) were married, and the remaining were single. For educational background, tertiary education had ten mothers, followed by eight mothers with senior high school education and five with junior high school education.

Mothers who delivered their preterm infants through spontaneous vaginal delivery, which is a normal birth through the vagina requiring no surgical procedure, were 11 participants, and the mothers that delivered through a Caesarean Section (CS) were 13 participants. Analysis of the gestational age of the infants indicated that most infants were in the late preterm range (35 – 37 weeks; 14 infants) and was followed by the moderate preterm range (33 – 34 weeks; 6 infants), very preterm (28 – 32 weeks; 3 infants), and extreme preterm (< 28 weeks; 1 infant). The number of pregnancies (gravidity) had four categories: mothers in the first pregnancy had 8 participants, the second pregnancy had the highest number of participants (9), the third pregnancy had the least number of participants (2) and the fourth or more pregnancy had 5 participants. Parity, which is the number of successful deliveries, had the most participants (13) being non-first-time mothers and 11 participants being first-time mothers.

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Table 1. Demographic features of mother and babies of the study population

| | Granola (n = 6) | Chocolate drink (n = 6) | Granola placebo (n = 6) | Chocolate drink placebo (n = 6) |
|---|---|---|---|---|
| Age | | | | |
| 10 – 19 years | - | - | - | 1 |
| 20 – 29 years | 2 | 3 | 4 | 2 |
| 30 – 39 years | 4 | 2 | 1 | 3 |
| 40 – 49 years | - | 1 | 1 | 0 |
| Marital status | | | | |
| Single | 2 | 2 | 4 | 2 |
| Married | 4 | 4 | 2 | 4 |
| Educational level | | | | |
| No level | - | - | - | 1 |
| Junior High | 1 | 3 | - | 1 |
| Senior High | 2 | 1 | 2 | 3 |
| Tertiary | 3 | 2 | 4 | 1 |
| Mode of Delivery | | | | |
| Vaginal | 2 | 3 | 4 | 2 |
| C.S. | 4 | 3 | 2 | 4 |
| Employment | | | | |
| Employed | 6 | 4 | 3 | 5 |
| Unemployed | - | 2 | 3 | 1 |
| Gravidity | | | | |
| 1st pregnancy | 1 | 1 | 3 | 3 |
| 2nd pregnancy | 4 | 2 | 2 | 1 |
| 3rd pregnancy | - | 2 | - | - |
| 4th pregnancy/more | 1 | 1 | 1 | 2 |
| Parity | | | | |
| Primiparous | 1 | 1 | 5 | 4 |
| Multiparous | 5 | 5 | 1 | 2 |
| Gestational Age | | | | |
| Extreme (< 28 weeks) | - | - | - | 1 |
| Very Preterm (28–32 weeks) | 1 | - | - | 2 |
| Moderate (33–34 weeks) | 1 | - | 4 | 1 |
| Late preterm (35–37 weeks) | 4 | 6 | 2 | 2 |

**Analysis of the effect of the intervention and placebo products on breast milk volume, serum prolactin and infant weight**

Breast milk volume, serum prolactin levels and infant weight were measured on day 1 (baseline) and on day 7 to ascertain the effect of the intervention and placebo products on these parameters. The values from the 6 participants were used to calculate each group's mean and standard deviation. Prior to administering the lactation products on day 1 (baseline), the breast milk volumes collected from the participants in the intervention (granola and chocolate drink) groups were not significantly different from those in the corresponding placebo groups (Table 2). A four-fold increase in the mean breast milk volume was recorded for the participants on granola treatment on the seventh day compared to the baseline, whereas a 3.63-fold increase was obtained for the participants on granola placebo (Fig. 1A). Moreover, a 3.88-fold increase in mean breast milk volume was obtained on day seven compared to the baseline for the participants on chocolate drink and a 2.87-fold increase was obtained for participants on chocolate drink placebo. The highest difference in mean breast milk volume from day 1 to day 7 was obtained for participants on the granola treatment. It was followed by participants on the granola placebo and the chocolate drink. Participants on the chocolate drink placebo recorded the lowest difference in mean breast milk volume. The mothers given the granola or chocolate drink products containing galactagogues produced significantly higher mean breast milk volume on day seven compared to the mean volume reported on day 1 ($p < 0.0001$ for granola and $p < 0.0001$ for chocolate drink).

The mean breast milk volumes of the mothers on placebo products were also significantly different on days 1 and 7 ($p < 0.0001$ for granola placebo and $p = 0.0007$ for chocolate drink placebo). Collectively, these data demonstrate that the placebo products caused statistically significant improvement in breast milk production in the early postpartum mothers of preterm infants within the 7-day study duration. The inclusion of the natural galactagogues in granola and chocolate drink also caused an additional modest increase in breast milk volume on day 7 relative to the corresponding placebo products, even though the difference in breast milk volumes was not statistically significant (Table 2). The mothers on granola placebo and chocolate drink placebo recorded modest increases in mean prolactin levels on day 7 compared to day 1 (14.5 ug/ml and 13.8 ng/ml, respectively, Figure 1B). The inclusion of galactagogues in the granola and chocolate

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drink did not cause statistically significant increase in the mean prolactin levels on the 7th day compared to day 1 (p = 0.2422 for granola and p = 0.0993 for chocolate drink). The data also indicated that the mean prolactin level for the participants in the chocolate drink group was significantly lower relative to the chocolate drink placebo group on both day 1 and day 7 (Table 3). It can be inferred that the relatively low mean prolactin levels in the chocolate drink group is not dependent on the effect of the lactation product and might reflect the physiological states of the participants on day 1. Further analysis demonstrated there was no statistically significant correlation between breast milk volume and serum prolactin levels on days 1 and 7 for each treatment group (Table 4).

The preterm infants of the 24 mothers were weighed on day 1 (baseline) and day 7 to ascertain the effect of the lactation products consumed by their mothers on the weight of the infants. The difference in mean weight of the infants whose mothers consumed the granola product was equivalent to the infants whose mothers consumed the granola placebo product, indicating that consumption of these products by the mothers had no detectable effect on the weight of their infants on day 7 (Figure 1C). Moreover, the difference in the mean weight of the infants whose mothers consumed the chocolate drink was similar to the infants whose mothers consumed the placebo chocolate drink. Statistical analysis also indicated no significant difference in the mean infant weight reported on day 7 compared to the baseline weight for all four groups in the study. Moreover, the low

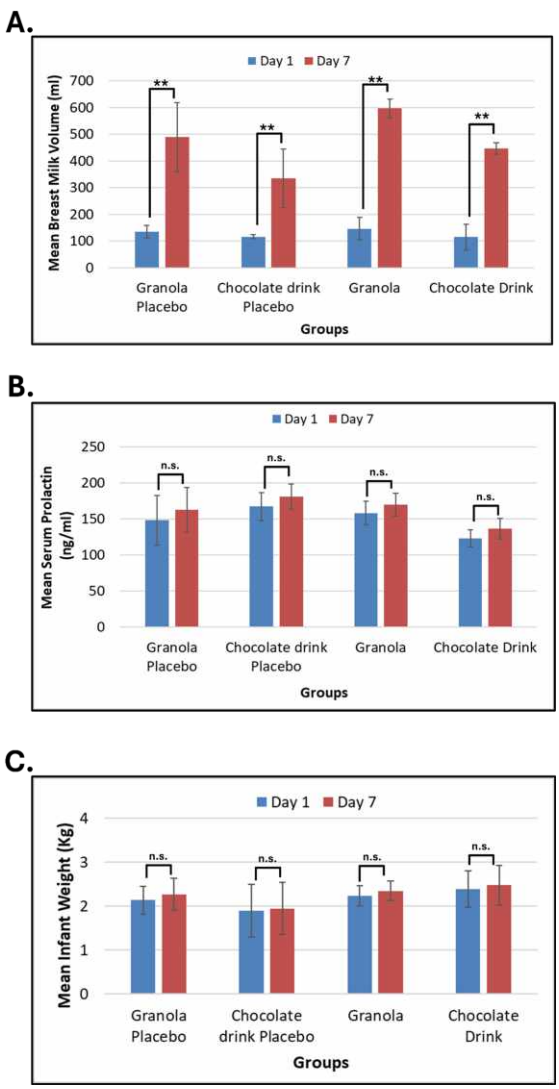


Figure 1. Effect of lactation products on breast milk production, serum prolactin levels and infant weight.

Table 2. Statistical analysis of breast milk volumes from the control and intervention groups on days 1 and 7

| Comparison of control and intervention groups | p-value |
|---|---|
| Day 1 | |
| Granola Placebo vs. Granola | 0.5608 |
| Chocolate drink placebo vs. Chocolate drink | 0.9355 |
| Day 7 | |
| Granola Placebo vs. Granola | 0.0780 |
| Chocolate drink placebo vs. Chocolate drink | 0.0351 |

Table 3. Statistical analysis of serum prolactin levels from the control and intervention groups on days 1 and 7

| Comparison of control and intervention groups | p-value |
|---|---|
| Day 1 | |
| Granola Placebo vs. Granola | 0.5270 |
| Chocolate drink placebo vs. chocolate drink | 0.0008 |
| Day 7 | |
| Granola Placebo vs. Granola | 0.6199 |
| Chocolate drink placebo vs. Chocolate drink | 0.0007 |

Table 4: Correlation analysis between breast milk volumes and serum prolactin levels for the control and intervention groups on days 1 and 7

| Groups | Pearson correlation coefficient | p-value |
|---|---|---|
| Granola placebo | | |
| Day 1 | -0.3846 | 0.451 |
| Day 7 | 0.8122 | 0.050 |
| Chocolate drink placebo | | |
| Day 1 | -0.2454 | 0.639 |
| Day 7 | 0.1504 | 0.776 |
| Granola | | |
| Day 1 | -0.001 | 0.99 |
| Day 7 | -0.094 | 0.859 |
| Chocolate drink | | |
| Day 1 | 0.6467 | 0.165 |
| Day 7 | 0.4992 | 0.313 |

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infant weights recorded by the chocolate drink placebo group relative to the chocolate drink group on days 1 and 7 were not statistically significant (Table 5). Furthermore, no statistically significant correlation was obtained between breast milk volume and infant weight on days 1 and 7 for each treatment group (Table 6). Hence, it can be inferred that the consumption of products containing galactagogues by the mothers did not lead to a significant increase in the weight of the infants on the seventh day of the study.

**Local diets consumed by the participants were believed to boost breast milk production**

Lactating mothers producing inadequate breast milk after childbirth are usually encouraged to consume indigenous diets believed to boost breast milk production. The participants in this study were not restricted from consuming these diets during the duration of the study. On the seventh day of the study, the participants were interviewed to obtain information on diets they consumed during the study, which are believed to boost breast milk production.

Seven of the 12 participants in the placebo groups indicated they consumed hot millet porridge, whereas 4 participants from the intervention (granola & chocolate drink) groups consumed hot diets containing galactagogue (Table S1). Three participants from the intervention and placebo groups consumed groundnut-containing foods, which are believed to boost breast milk production. One participant from the placebo group consumed soup made from jute (ayoyo) leaves, which is also believed to boost breast milk production in lactating mothers. We infer that consumption of these indigenous foods might have contributed to boosting breast milk production in participants from both the intervention and placebo groups.

## DISCUSSION

The present study assessed the effect of two food products containing plant-derived galactagogues on breast milk production and serum prolactin levels in early postpartum mothers of preterm infants. We also evaluated the impact of the mothers' consumption of these galactagogues-containing food products on the weight of preterm infants. The intervention and placebo products investigated by this study caused a significant increase in mean breast milk volume in the early postpartum mothers by day 7. However, mean serum prolactin levels of the mothers and mean infant weight were not significantly different on days 1 and 7. Moreover, the study identified no correlation between breast milk volume and either serum prolactin or infant weight.

Fennel and fenugreek are derived from the seeds of Foeniculum *volgare* and *Trigonella foenumgraecum*, respectively, and are notable for enhancing breast milk production in lactating mothers [5,18]. A previous study has reported that consumption of herbal tea containing fenugreek led to a significant increase in breast milk volumes in the first few days after childbirth [19]. *Moringa oleifera* also boosts breast milk production in early

Table 5. Statistical analysis of infant weights from the control and intervention groups on days 1 and 7

| Comparison of control and intervention groups | p-value |
|---|---|
| Day 1 | |
| Granola Placebo vs. Granola | 0.5844 |
| Chocolate drink placebo vs. Chocolate drink | 0.1270 |
| Day 7 | |
| Granola Placebo vs. Granola | 0.6725 |
| Chocolate drink placebo vs. Chocolate drink | 0.1153 |

p-value < 0.01 was considered statistically significant

Table 6. Correlation analysis between breast milk volumes and infant weights for the control and intervention groups on days 1 and

| Groups | Pearson correlation coefficient | p-value |
|---|---|---|
| Granola placebo | | |
| Day 1 | 0.3312 | 0.521 |
| Day 7 | -0.2705 | 0.604 |
| Chocolate drink placebo | | |
| Day 1 | 0.5743 | 0.233 |
| Day 7 | -0.6167 | 0.192 |
| Granola | | |
| Day 1 | -0.6104 | 0.198 |
| Day 7 | 0.5399 | 0.269 |
| Chocolate drink | | |
| Day 1 | 0.08204 | 0.877 |
| Day 7 | 0.5254 | 0.284 |

p-value < 0.01 was considered statistically significant

postpartum mothers of preterm infants [20]. Our data demonstrate that both the intervention and placebo food products used in this study caused a significant improvement in breast milk production in lactating mothers of preterm infants. The data also highlight the crucial role of these lactation products in minimising undernutrition in preterm infants caused by insufficient breast milk production. We also demonstrated that the increase in breast milk production was not due to increased serum prolactin levels after administering the food products containing galactagogues. Even though higher levels of serum prolactin in lactating mothers have been associated with increased breast milk production [21], our data indicate that the basal threshold of prolactin necessary for stimulating the production of breast milk is sufficient to attain breast fullness in mothers of preterm infants consuming food products containing galactagogues [10].

The events leading to childbirth can be stressful and may result in a concomitant delay in breast fullness and a reduction in lactose concentration in breast milk [14,15]. Breastmilk is predominantly carbohydrates, fats, proteins, and water; hence, lactating mothers are usually advised to eat well and consume foods containing agents known to boost breast milk production, especially when the volume of milk produced daily is insufficient for the nutritional needs of the neonate. The fulfilment of the dietary needs of preterm infants is vital for facilitating their survival and proper growth and development during the first weeks after birth. Breastfeeding also enhances the immunity of neonates against infectious diseases, highlighting the vital role of breast milk in ensuring well-being and good health in infants [16,17]. Preterm infants typically have birth weight below 2.5kg, necessitating adequate nutrition using breast milk to facilitate holistic growth and development. Continuous monitoring of the weight of preterm infants after birth also enables pediatric healthcare professionals to evaluate the health status and well-being of the infant [22].

We demonstrated that there was no difference in the weights of preterm infants who received galactagogues-containing food products during the 7-day study period and those who received the placebo. This observation may be attributed to the study's short duration. A longer duration for monitoring the weight of preterm infants whose mothers are continuously receiving galactagogues-containing food products would provide comprehensive insight into the plant-derived galactagogues' effect on the infant weight. Assessment of the effect of the plant-derived galactagogues on lactose concentration and other nutrients in breast milk would also provide useful data for an in-depth evaluation of the nutritional benefits of galactagogues-stimulated breast milk for preterm infants. Psychological well-being, stress, diet, and the environment of lactating mothers are potential confounding factors that may affect breast milk production in the study participants. Hence, a potential limitation of this study is the absence of the measurement of cortisol levels in the study participants who received either the intervention or placebo lactation products.

### Conclusion
Plant-based galactagogues had no effect on serum prolactin levels or the amount of breast milk produced in early postpartum mothers with hypogalactia. The molecular processes that control the bioavailability of prolactin, composition and production of breast milk in nursing mothers require further investigation.

## DECLARATIONS

### Ethical consideration
Both the Ethical and Protocol Review Committee of the College of Health Sciences at the University of Ghana (Protocol Identification Number: CHS-Et/M:8-p4.12014-2015) and the Institutional Review Board of the 37 Military Hospital (Protocol Identification Number: 37MH-IRB/MP/IPN/684/2023) gave their approval to the study protocol. A consent form was signed by each participant after they had been provided with all of the required information regarding the study.

### Consent to publish
All authors agreed on the content of the final paper.

### Funding
None

### Competing Interest
The authors declare no conflict of interest

### Author contribution
WAM conceptualised the study, designed the study, and provided overall supervision. ESA and NG collected data, conducted initial analyses, and drafted the manuscript. VA performed critical revisions and the submission process. EO, MAA, EPA, and IO contributed scientific guidance, data interpretation, and manuscript refinement.

### Acknowledgement
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### Availability of data
Data is available upon request to the corresponding author

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## Supplementary

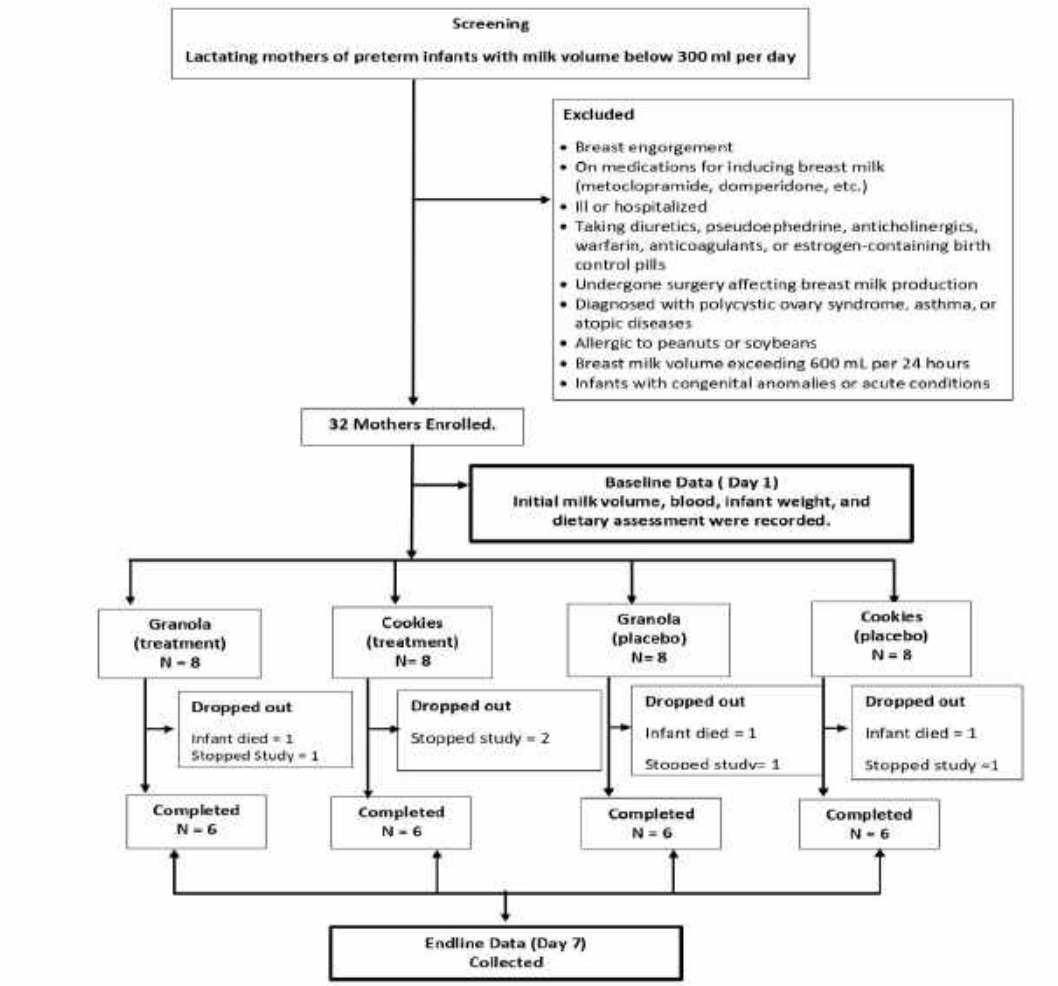


Figure S1. Flow chart for recruitment of participants for the study. Cookies in the flow chart represent chocolate drink.

Table S1. Number of participants that consumed local diets believed to boost breast milk production in lactating mothers.

| Galactogogues-containing diets | Intervention groups (n = 12) | Placebo groups (n = 12) |
|---|---|---|
| Herbs-related galactogogues | - | 1 participant (soup containing jute leaves) |
| Hot diets containing galactogogues | 4 participants (hot millet porridge, hot corn porridge) | 7 participants (hot millet porridge) |
| groundnuts | 3 participants (groundnuts & maize, groundnut soup, mashed kenkey & groundnuts ) | 3 participants (mashed kenkey & groundnuts) |
| Non-galactogenic foods | 4 participants (apples, watermelon, rice) | 2 participants (coconut, tom brown porridge) |

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# Mapping herbal medicine cancer research in Africa: A bibliometric analysis

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**Abstract**

Herbal medicines have long been a part of the traditional healthcare systems across Africa, and their integration into modern medical practices has been significantly impactful in recent years. In Africa, the potential of herbal medicine as an alternative therapy is increasingly being explored. This is even more relevant to cancer, which remains a significant public health challenge worldwide. Cancer leads to high morbidity and mortality rates globally. This study offers a bibliometric analysis of research on herbal medicines for use in cancer therapy care in Africa. This is relevant for knowledge mapping to inform research policy regarding herbal medicines in cancer treatment. Using 1,134 datasets from Scopus (Elsevier) up to 2023, the study employed MS Excel, Harzing's Publish or Perish, and VOSviewer for analysis and visualisation. The results reveal a growing trend in publications on this topic, with the Journal of Ethnopharmacology (JEP) being the most active source, contributing 116 articles (10.23%). South Africa emerged at the forefront in this research area, accounting for 166 publications (9.05%). The most prolific author was Efferth, T., with 31 documents, while the University of Dschang, Cameroon, was the most influential institution, with 36 publications (2.75%). The National Research Foundation was the top funder, supporting 42 publications (3.26%). The most cited article was Chang and Adami (2006), which received 1,097 citations. Keyword analysis revealed that "article", "human", and "medicinal plant" were the most frequently used terms. The co-occurrence analysis identified five thematic clusters centred on "article", "human", "human cell", "in vitro study" and "drug effect". This study provides valuable insights for policymakers, researchers, and medical professionals by identifying key research areas, emerging trends, and influential contributors to herbal medicine in cancer management in Africa. These results are expected to inform future research and funding strategies to support the advancement of cancer care across the continent.

**Keywords:** Herbal medicine, cancer, Africa, bibliometric analysis, citation analysis, research impact

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## INTRODUCTION

Cancer remains one of the leading causes of death globally, with developing nations bearing a particularly heavy burden [1,2]. The global cancer burden increased to an estimated 20 million new cancer cases, including 9.7 million deaths in 2022 [2]. In Africa, the incidence of cancer is expected to rise steadily in less than a decade, with millions of new cases predicted [3,4]. For instance, the projections for 2030 indicate a significant rise to an estimated 1.27 million cases and 0.97 million deaths, largely driven by population growth and ageing in Africa [4]. Limited access to conventional cancer treatment across much of the continent due to economic constraints, inadequate healthcare infrastructure, and a shortage of medical professionals accounts for the patronage of poorly-researched traditional and alternative therapies, particularly herbal remedies, which are deeply rooted in African cultural practices [5,6].

Herbal medicine has long been an integral part of Africa's traditional healthcare systems, treating various ailments, including cancer [7-9]. Recently, the integration of these herbal remedies into modern medical practices has significantly increased as researchers and healthcare providers explore complementary and alternative

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treatments for cancer [10]. In resource-limited settings where access to chemotherapy and radiotherapy is often scarce, herbal medicines offer a cost-effective option for managing cancer. Despite the growing interest, research on herbal medicines in Africa faces numerous challenges, including insufficient funding, weak research infrastructure (facilities, equipment, resources, and services that support herbal medical cancer research), and disparities in research output [11,12]. While countries such as South Africa and Nigeria have established research capabilities in this field, many other nations lag [13,14], thus hindering progress in validating the efficacy of herbal medicines for cancer treatment [15].

The rising burden of cancer in Africa, coupled with limited access to conventional treatments, underscores the urgency of exploring alternative therapies in this respect [3]. The research landscape remains fragmented across the continent. While some African countries have made notable contributions, overall research output in cancer studies is limited when compared to other global regions [16-18]. A clearer understanding of the research productivity and impact of African scholars and institutions is needed to harness herbal medicine research effectively in addressing the continent's healthcare challenges. Without this understanding, it will be difficult to successfully develop policies or allocate resources that will support the rapid integration of herbal medicine into cancer care. Bibliometrics, the quantitative analysis of academic literature, provides a powerful tool for assessing research productivity, impact, and collaboration within a specific field [19]. By examining publication trends, citation metrics, and keyword co-occurrence, bibliometric studies can reveal influential researchers, institutions, and topics shaping the discourse in herbal medicine for cancer management in Africa. This approach can help identify which countries, institutions, and researchers are leading the field and where research gaps exist.

Other analyses could highlight the role of international collaborations and funding bodies in supporting African research. By using bibliometric tools such as VOSviewer and Harzing's Publish or Perish, researchers can thus visualise the structure of research networks and access the impact of individual studies through citation analysis [20,21]. Such methodical findings provide crucial information for policymakers, funding agencies, researchers, and research institutions to enhance the visibility and effectiveness of herbal medicine research across Africa. Understanding the current research landscape enables stakeholders to make informed decisions about where to allocate resources and how to foster greater collaboration and innovation in this vital area of healthcare.

**Benefits of bibliometric studies on herbal medicines used in the treatment of cancer**

This study is aligned with key global and continental development frameworks, particularly the United Nations Sustainable Development Goals (SDGs) and the African Union's Agenda 2063. The SDGs highlight the importance of promoting good health and well-being for all ages (Goal 3) [22]. By focusing on herbal medicines used in cancer management, this research contributes directly to SDG Target 3.4, which aims to reduce premature mortality from non-communicable diseases, including cancer, through prevention, treatment, and the promotion of mental health and well-being. Moreover, this study supports SDG 9, which advocates for building resilient infrastructure, promoting inclusive and sustainable industrialisation, and fostering innovation. By identifying gaps and opportunities for African research on herbal medicine, this study encourages healthcare innovation and the development of locally appropriate solutions to pressing health challenges. The African Union Agenda 2063's Aspiration 1 emphasises the importance of a healthy and well-nourished population [23]. In alignment, this study supports the aspiration for a prosperous Africa that is rooted in inclusive growth and sustainable development. This study also contributes to the integration of traditional knowledge with modern healthcare systems, thereby improving the well-being of African populations. Additionally, the study encourages collaboration across African research institutions, promoting pan-African cooperation in line with Agenda 2063's vision of a people-driven development that harnesses the potential of Africa's youth and scientific community.

As researchers affiliated with the University of Ghana, this study also contributes directly to the achievement of the institution's strategic goals for 2024-2029 [23] by addressing one of Africa's most critical health issues, "cancers" [24] and exploring the potential of indigenous knowledge in providing cost-effective treatment alternatives. The focus on cancer aligns with the University's commitment to producing research that has a lasting impact on society, particularly within the context of African healthcare. The focus on cancer aligns with the University's commitment to producing research that has a lasting impact on society, particularly within the context of African healthcare. The primary purpose of this study is to conduct a comprehensive bibliometric analysis of the research on herbal medicines in cancer management in Africa. The aim is to map out the research landscape, identify leading contributors, and highlight emerging trends and gaps in the literature. By analysing research productivity, collaboration networks, and citation impact in the field of herbal medicine, the study generates insights that can inform policy, guide future research and investments, and ultimately improve cancer care across the continent.

The findings are also expected to inform researchers, funders and healthcare professionals about the current state of research in this field. Additionally, the study aims to guide future initiatives to promote collaboration, knowledge sharing, and innovation in the use of herbal medicines for cancer treatment, ultimately improving healthcare outcomes across the continent.

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**Current bibliometric studies on herbal medicines used in the treatment of cancer**

A study conducted by Biglu in 2014, utilising the MEDLINE database (2000-2014), revealed that most Iranian breast cancer articles were published in journals from Thailand, followed by the USA and the UK [25]. Similarly, a study by Perez Santos and Anaya-Ruiz on Mexico's breast cancer research output (2003-2012) highlighted that the National Autonomous University of Mexico (22.3%), the National Institute of Cancerology (21.9%), and the Mexican Social Security Institute (20.3%) were the leading contributors based on 256 articles [25]. Cross-national assessments using Scopus and Web of Science databases consistently show that the US leads in cancer research output and impact [25]. Despite advancements in conventional cancer care, the use of herbal medicine remains widespread, particularly as it is the most common form of alternative and complementary medicine available [26]. Herbal treatments, rooted in indigenous knowledge (IK), are prevalent across African communities (8, 9). There is a growing need to foster dialogue between scholars and traditional health practitioners to promote best practices [26].

Globally, research on traditional herbal medicine has grown steadily since 1990, with China, Japan, and India being major contributors, and China leading in both publications and funding [27]. In Africa, health informatics research has also seen a notable increase in publication output. A study covering the period from 1987 to 2018 identified 2,332 publications, with South Africa emerging as the leading contributor [26]. The University of Cape Town was the top institution for health informatics research, and the PLoS One journal was identified as a primary publication platform. Funding from bodies like the Bill and Melinda Gates Foundation and the National Institutes of Health has been instrumental in supporting health informatics research in Africa [26]. Additionally, a bibliometric analysis of health-related research in Africa has revealed increasing productivity and collaboration. Stem cell research performance analysis shows the US, UK, and the Netherlands as top contributors, with English-language publications accounting for 88.52%, followed by Chinese (2.86%) and Japanese (0.94%) [28].

Another study examined the publishing patterns related to herbal medicine in cancer management in Africa from 1968 to 2023 using bibliometric methods and a dataset from Scopus. Previous studies by Koobotse et al. (2023) and Moodley et al. (2015) have explored herbal medicine and cancer research, focusing on individual countries. Therefore, this study assesses the visibility of African scholarly works and the disparity in research output, focusing on areas where their contributions are significant. Musa et al. (2023) revealed that the most cited article on herbal medicine for cancer treatment, TCMSP: A Database of Systems Pharmacology for Drug Discovery from Herbal Medicines, amassed 1,346 citations, averaging 149.56 citations annually. The second most cited article, Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene, received 774 citations, with an average of 36.86 citations per year.

## METHODOLOGY

The bibliometric analysis for this study involved data collection, analysis, and visualisation to systematically capture and examine relevant bibliographic data. For data collection, Scopus (Elsevier) was selected as the primary database due to its comprehensive coverage of peer-reviewed literature across multiple disciplines, including medicine, pharmacology, and the life sciences and its extensive citation data and indexes a wide range of African-based research outputs (31). A team of information specialists developed a tailored search strategy using keywords related to herbal medicine, cancer management, and geographical terms specific to Africa. The search covered publications from the inception of Scopus up to 2023 to ensure a comprehensive longitudinal analysis. This study included all document types (peer-reviewed journal articles, conference proceedings, etc.) indexed in Scopus without any language restriction. Only documents explicitly focusing on the use of herbal medicine in cancer treatment within the African context were included.

This resulted in the extraction of 1,134 datasets from Scopus, capturing information such as author names, article titles, source journals, publication years, institutional affiliations, and citation metrics. A combination of software tools was employed for the data analysis. MS Excel was used for initial data cleaning, sorting, and conducting basic statistical analysis. Harzing's Publish or Perish software was applied to gather citation metrics (the h-index, g-index and so on) and analyse the impact of authors and institutions. VOSviewer was utilised to visualise bibliometric networks (keyword co-occurrence networks). Descriptive statistics summarised the distribution of publications across different categories such as document and source types, language of documents, subject area and so on, while temporal trends in publication output were analysed to identify growth patterns. The study also identified the most prolific authors and their institutional affiliations, thus shedding light on key contributors to herbal medicine research used in cancer care in Africa.

Additionally, citation metrics were used to identify highly cited articles and influential authors. Keyword analysis revealed prominent themes and research focus areas through co-occurrence analysis, highlighting the specific areas of interest within the field of study. The visualisation of the data employed various tools and techniques to ensure a clear representation of the findings. Line charts were used to visualise temporal trends in the number of publications over the years, while geographical maps and charts illustrated the distribution of research outputs across the African countries, thus showcasing which nations are leading in this area of study. VOSviewer was crucial in generating network maps that depicted relationships

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between keywords. Keyword co-occurrence networks revealed thematic clusters within the research.

## RESULTS

### Document type and source type

Details of the distribution of the various document types in the dataset are displayed in Table 1. The distribution of the document types underlines the active participation of African scholars in a range of scholarly works, with a particular focus on articles and reviews. This pattern suggests a strong culture of research activities. Of the 1134 publications, articles accounted for 916 (80.78%) and were followed by reviews (15.34%) and book chapters (15.32%). Conference papers and letters accounted for 8 (0.71) of all publications. Less than 1% of the total publication types were also recorded by the following document types: books, notes, editorials and short surveys. Conference review was the document type with the lowest publishing rate (0.09%). The types of sources of the publications are shown in Table 2. Most of the articles were in journals, which accounted for 1109 (97.80%). Books came in second with 17 (1.50%), book series 6 (0.53%), trade journals 1 (0.09%), and conference proceedings 1 (0.09%).

### Year of publications/ evolution of published studies

Figure 1 presents the distribution of publications over the years from 1968 to 2023 and shows a fluctuating trend in publications over this period, with the most recent years having the highest number of publications. There was a significant increase in publications within the 13 years (2011-2023), with the highest records occurring in 2021 (8.82%), 2022 (8.02%), and 2023(8.02%).

### Languages of documents

Table 3 shows the various languages used for the publication of literature on herbal medicines employed in cancer therapy in Africa. The most predominant language used was English, accounting for approximately 1103 (96.92%) of the publications over the study period. There were 16 (1.41%) publications in French as the second predominant language. All the other languages recorded less than 1% of the total publications. They included German 6 (0.70%), Chinese 6 (0.53%), Russian 2 (0.18%), and 1 (0.09%) of the publications were in Portuguese, Spanish and Ukrainian.

### Subject area

Figure 2 displays the distribution of herbal medicine in cancer management across various subject areas. The table illustrates the highly interdisciplinary nature of the field in question. Medicine recorded the highest number of publications: 548 (26.20%), followed by Pharmacology, Toxicology, and Pharmaceutics with 539 (25.76%). Other notable fields include Agricultural and Biological Sciences with 199 (9.51%), Chemistry with 172 (8.22%), Immunology and Microbiology with 49 (2.34%), Environmental Science with 48 (2.29%), Chemical Engineering with 36 (1.72%), Multidisciplinary with 29 (1.39%), Biochemistry, Genetics and Molecular Biology

Table 1. Document Type

| Document Type | Total Publications (TP) | Percentage (%) |
|---|---|---|
| Article | 916 | 80.78 |
| Review | 174 | 15.34 |
| Book Chapter | 15 | 1.32 |
| Conference Paper | 8 | 0.71 |
| Letter | 8 | 0.71 |
| Short Survey | 4 | 0.35 |
| Editorial | 3 | 0.26 |
| Note | 3 | 0.26 |
| Book | 2 | 0.18 |
| Conference Review | 1 | 0.09 |
| Total | 1134 | 100.00 |

Table 2. Source Type

| Source Type | Total Publications (TP) | Percentage (%) |
|---|---|---|
| Journal | 1109 | 97.80 |
| Book | 17 | 1.50 |
| Book Series | 6 | 0.53 |
| Trade Journal | 1 | 0.09 |
| Conference Proceeding | 1 | 0.09 |
| Total | 1134 | 100.00 |

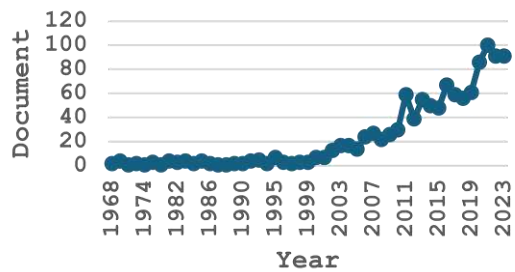


Figure 1: Document by Year

Table 3: Languages Used for Publications

| Language | Total Publications | Percentage (%) |
|---|---|---|
| English | 1103 | 96.92 |
| French | 16 | 1.41 |
| German | 8 | 0.70 |
| Chinese | 6 | 0.53 |
| Russian | 2 | 0.18 |
| Portuguese | 1 | 0.09 |
| Spanish | 1 | 0.09 |
| Ukrainian | 1 | 0.09 |
| Total | 1138 | 100.00 |

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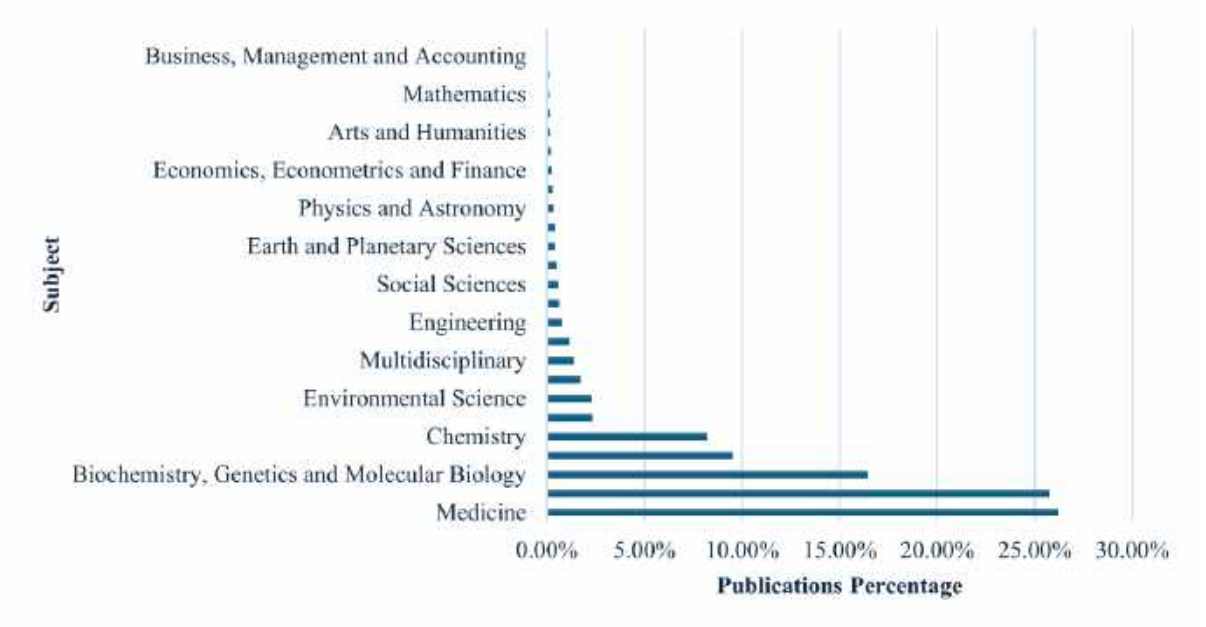


Figure 2: Subject Area

Table 4. Top 19 Most Active Source Title

| Source Title | Total Publications (n=1134) | Percentage (%) |
|---|---|---|
| Journal of Ethnopharmacology | 116 | 10.23 |
| Journal of Natural Products | 54 | 4.76 |
| South African Journal of Botany | 32 | 2.82 |
| Evidence-based Complementary and Alternative Medicine | 30 | 2.65 |
| BMC Complementary and Alternative Medicine | 25 | 2.20 |
| Fitoterapia | 17 | 1.50 |
| Molecules | 17 | 1.50 |
| Pharmaceutical Biology | 16 | 1.41 |
| Planta Medica | 16 | 1.41 |
| Natural Product Communications | 14 | 1.23 |
| African Journal of Traditional, Complementary and Alternative Medicines | 13 | 1.15 |
| Phytomedicine | 13 | 1.15 |
| Frontiers in Pharmacology | 12 | 1.06 |
| Natural Product Research | 12 | 1.06 |
| Tropical Journal of Natural Product Research | 12 | 1.06 |
| PLoS ONE | 11 | 0.97 |
| Tropical Journal of Pharmaceutical Research | 11 | 0.97 |
| Journal of Herbal Medicine | 10 | 0.88 |
| Phytochemistry | 10 | 0.88 |

Table 5. Top Keywords

| Keywords | Total Publications (n = 18824) | Percentage (%) |
|---|---|---|
| Article | 729 | 3.87 |
| Human | 703 | 3.73 |
| Medicinal Plant | 685 | 3.64 |
| Plant Extract | 559 | 2.97 |
| Unclassified Drug | 555 | 2.95 |
| Nonhuman | 501 | 2.66 |
| Controlled Study | 453 | 2.41 |
| Humans | 440 | 2.34 |
| Plant Extracts | 341 | 1.81 |
| Human Cell | 314 | 1.67 |
| Plants, Medicinal | 296 | 1.57 |
| Chemistry | 263 | 1.40 |
| Female | 262 | 1.39 |
| Cytotoxicity | 261 | 1.39 |
| Antineoplastic Agent | 254 | 1.35 |
| Antineoplastic Activity | 252 | 1.34 |
| Male | 238 | 1.26 |
| Plant Leaf | 216 | 1.15 |
| Phytotherapy | 211 | 1.12 |
| Traditional Medicine | 211 | 1.12 |

with 344 (16.44%), and Nursing with 24 (1.15%). Less prominent areas, each with fewer than 1% of the publications, included Engineering with 16 (0.76%); Materials Science with 13 (0.62%), Social Sciences with 12 (0.57%), Computer Science with 11 (0.53%), Earth and Planetary Sciences with 9 (0.43%), Health Professions with 9 (0.43), Physics and Astronomy with 7 (0.33%); Neuroscience with 6 (0.29%), Economics, Econometrics, and Finance with 5 (0.24), Energy with 4 (0.9%), Arts and Humanities with 3 (0.14%), Veterinary with 3 (0.14%), Mathematics with 2 (0.10%); Psychology with 2 (0.10%), Business, Management and Accounting with 1 (0.05%), and Dentistry with 1 (0.05%).

**Most active source titles**

Table 4 details journals with their respective publications on herbal medicine in cancer management in Africa. The Journal of Ethnopharmacology published the most articles, with a record of 116 (10.23%). Other journals with notable publications in this area were the Journal of Natural Products (4.76%, n = 54), the South African Journal of Botany (2.82%, n = 32), and Evidence-Based Complementary and Alternative Medicine (2.65%, n = 30). Journal of Herbal Medicine and Phytochemistry are among the journals that recorded the least publications, with 10 (0.88%) publications each.

**Keywords analysis**

Several important themes emerged from the keyword analysis of the field of herbal medicines in cancer management research conducted in Africa (Table 5). The term "Article" is widely used, indicating the reliance and engagement with existing literature in 729 (3.87%) of the publications. Specific mentions such as Medicinal Plant 685 (3.64%), Plant Extract 559 (2.97%), Plants, Medicinal 296 (1.57%), Plant Leaf 216 (1.15%) and Traditional Medicine 211 (1.12%) demonstrate that the focus was on herbal medicine. The societal influence is highlighted by the human-centred keywords like Human 703 (3.73%), Non-human 501(2.66%), Humans 440 (2.34%), Human Cell 314 (1.67%), Female 262 (1.39%) and Male 238 (1.26%).

**Geographical distribution of publications - most influential countries**

Figure 3 presents the top 20 countries that have also made significant contributions to this research field in Africa, with South Africa, the United States, Nigeria, and Germany leading the chat with contributions of 166 (9.05%), 141 (7.69%), 131 (7.14%) and 104 (5.67) respectively. India 99 (5.40%) and Egypt 95 (5.18%) were also countries that contributed notably. Also, Tunisia, Madagascar, and Ghana

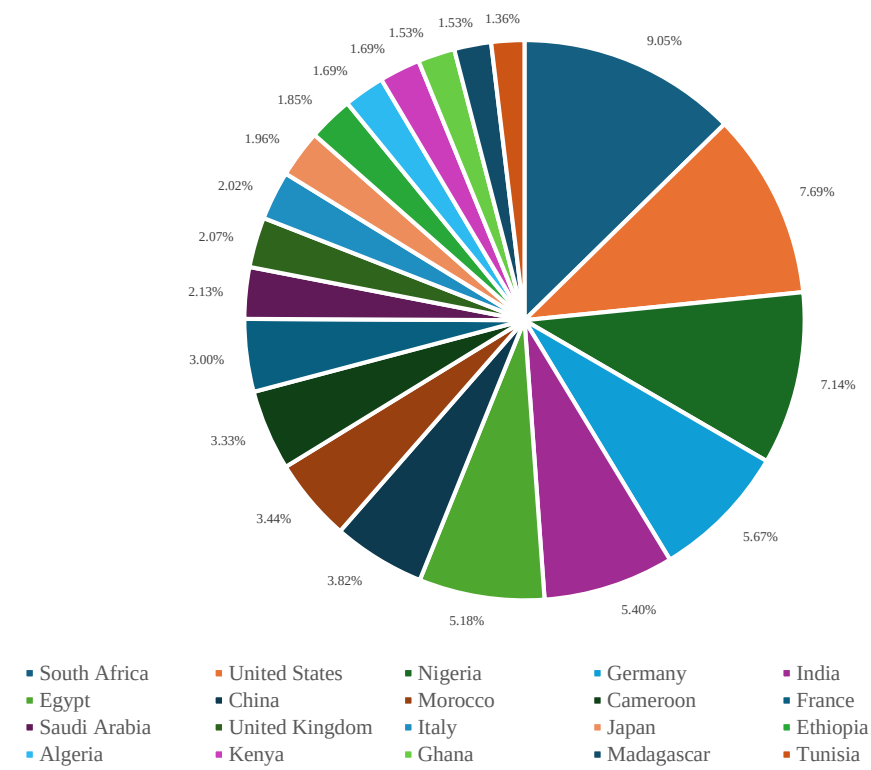


Figure 3. Top 20 Countries contributing to publications

made the least, with Ghana and Madagascar contributing 28 (1.53%) each and Tunisia 25 (1.36%).

**Authorship**

Table 6 lists the number of authors per document. Most publications, according to the findings, had few authors. The most published articles were those with four authors, 155 (13.67%), followed by articles with three authors, 153 (13.49%), and five authors, 147 (12.96%), respectively.

A total of 118 (10.41%) were co-authored and 73 (6.44%) were solely authored. Generally, articles with more than 13 authors accounted for 0.62% of the total publications. Table 7 presents the productivity of the authors as measured by their respective number of documents published on herbal medicines used in cancer management in Africa. Most of the authors published fewer than ten papers. Authors like Efferth, T., Kingston, D.G.I., Kuete, V., Rasamison, V.E. published 31 (4.06%), 27 (3.53%), 22 (2.88%), and 21 (2.75%) respectively, thus being the top four (4) most productive authors.

**Text analysis**

Figure 4 shows the network visualisation map, which comprehensively analyses the relationships between texts in the research areas of Herbal Medicines in Cancer Management research in Africa. This map aids in understanding the prevailing research trends by illustrating how frequently various texts co-occur in literature. The map encompasses 1000 texts, grouped into five (5) distinct clusters represented by different colours. These texts are interconnected by 184215 links, reflecting a total link strength of 608639 thematically organised around "article," "human," "human cell," "in vitro study," "drug effect," "female," "male", and "animals". This dense network indicates a robust interrelationship among the research topics in this field.

**Most influential institutions**

Figure 5 below shows institutions that have contributed substantially to publications within this field of study. With a total of 160 institutions, only institutions with a minimum of 13 publications were included. The University of Dschang emerged as the most productive institution, with 36 (2.75%) publications. The University of KwaZulu-Natal was the second highest with 34 (2.60%), followed by the National Research Centre and Johannes Gutenberg-Universität Mainz, which both had 32 (2.44%) publications.

**Funding sponsor**

Table 8 presents the top 20 sponsors of publications on herbal medicines in cancer care in Africa. The National Research Foundation led with 42 publications (3.26%), followed by the National Cancer Institute with 30 (2.33%), the Fogarty International Centre with 27 (2.10%), and the National Institutes of Health with 17 (1.32%). Styrelsen för Internationellt Utvecklingssamarbete and the Tertiary Education Trust Fund each supported the fewest publications, contributing 6 (0.47%) each.

Table 6. Number of author(s) per document

| Author Count | Total Publications | Percentage (%) |
|---|---|---|
| 0 | 3 | 0.26 |
| 1 | 73 | 6.44 |
| 2 | 118 | 10.41 |
| 3 | 153 | 13.49 |
| 4 | 155 | 13.67 |
| 5 | 147 | 12.96 |
| 6 | 130 | 11.46 |
| 7 | 95 | 8.38 |
| 8 | 92 | 8.11 |
| 9 | 56 | 4.94 |
| 10 | 40 | 3.53 |
| 11 | 20 | 1.76 |
| 12 | 22 | 1.94 |
| 13 | 11 | 0.97 |
| 14 | 7 | 0.62 |
| 15 | 4 | 0.35 |
| 16 | 2 | 0.18 |
| 17 | 2 | 0.18 |
| 19 | 2 | 0.18 |
| 21 | 1 | 0.09 |
| 46 | 1 | 0.09 |
| Total | 1134 | 100.00 |

Table 7. Most productive authors

| Author's Name | No. of Documents (n=764) | Percentage (%) |
|---|---|---|
| Efferth T. | 31 | 4.06% |
| Kingston D.G..I | 27 | 3.53% |
| Kuete V. | 22 | 2.88% |
| Rasamison V.E. | 21 | 2.75% |
| Brodie P.J. | 15 | 1.96% |
| Miller J.S. | 12 | 1.57% |
| Rakotobe E. | 11 | 1.44% |
| Andriantsiferana R. | 10 | 1.31% |
| Afolayan A.J. | 9 | 1.18% |
| Callmander M.W. | 9 | 1.18% |
| Cao S. | 9 | 1.18% |
| Bouyahya A. | 8 | 1.05% |
| Harinantenaina L. | 8 | 1.05% |
| Proksch P. | 8 | 1.05% |
| Randrianaivo R. | 8 | 1.05% |
| Shen Y. | 7 | 0.92% |
| Van Staden J. | 7 | 0.92% |
| Anywar G. | 6 | 0.79% |
| Awale S. | 6 | 0.79% |
| Birkinshaw C. | 6 | 0.79% |
| Dibwe D.F. | 6 | 0.79% |
| Grierson D.S. | 6 | 0.79% |
| Mbaveng A.T. | 6 | 0.79% |
| Rakotonandrasana S. | 6 | 0.79% |
| Spiteller M. | 6 | 0.79% |
| Suh E.M. | 6 | 0.79% |
| Wiench B. | 6 | 0.79% |
| Zengin G. | 6 | 0.79% |

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Table 8. Funding Sponsor

| Funding Sponsor | Total Publications (n = 1288) | Percentage (%) |
|---|---|---|
| National Research Foundation | 42 | 3.26 |
| National Cancer Institute | 30 | 2.33 |
| Fogarty International Center | 27 | 2.10 |
| National Institutes of Health | 17 | 1.32 |
| Deutscher Akademischer Austauschdienst | 16 | 1.24 |
| National Natural Science Foundation of China | 14 | 1.09 |
| Alexander von Humboldt-Stiftung | 12 | 0.93 |
| National Research Foundation of Korea | 11 | 0.85 |
| Council of Scientific and Industrial Research, India | 10 | 0.78 |
| Fundação para a Ciência e a Tecnologia | 9 | 0.70 |
| Inyuvesi Yakwazulu-Natali | 9 | 0.70 |
| Ministry of Education, Culture, Sports, Science and Technology | 9 | 0.70 |
| Bundesministerium für Bildung und Forschung | 8 | 0.62 |
| Fonds National de la Recherche Luxembourg | 8 | 0.62 |
| University of Johannesburg | 8 | 0.62 |
| Addis Ababa University | 7 | 0.54 |
| Department of Science and Technology, Ministry of Science and Technology, India | 7 | 0.54 |
| Japan Society for the Promotion of Science | 7 | 0.54 |
| Styrelsen för Internationellt Utvecklingssamarbete | 6 | 0.47 |
| Tertiary Education Trust Fund | 6 | 0.47 |

## Citation analysis

Table 9 shows an overview of research conducted on HMs in cancer management in Africa between 1968 and 2023. The citation metrics provide valuable insights into the impact and dissemination of research findings during this time frame. The dataset includes 1134 papers with 33,912 citations over a 56 years time period (1968 – 2024). This equals to an average of 605.57 citations annually. Additionally, the h-index and g-index values of 86 and 130, respectively, show the impact of the most influential papers within the dataset.

## Highly cited articles

Table 10 displays the leading publications on HMs in cancer management in Africa, thus showing how different studies have impacted this field. The most cited work on the list is "The enigmatic epidemiology of nasopharyngeal carcinoma" by Chang and Adami (2006), with 1097 citations and an average of 60.94 citations per year. Batiha et al. (2019) came in second with 483 citations and an average of 120.75 per year on "Chemical constituents and pharmacological activities of garlic (Allium sativum L.): A

Table 9. Citations Metrics

| Metrics | Data |
|---|---|
| Publication years | 1968-2023 |
| Citation years | 56 (1968-2024) |
| Papers | 1134 |
| Citations | 33912 |
| Citations/year | 605.57 |
| h-index | 86 |
| g-index | 130 |

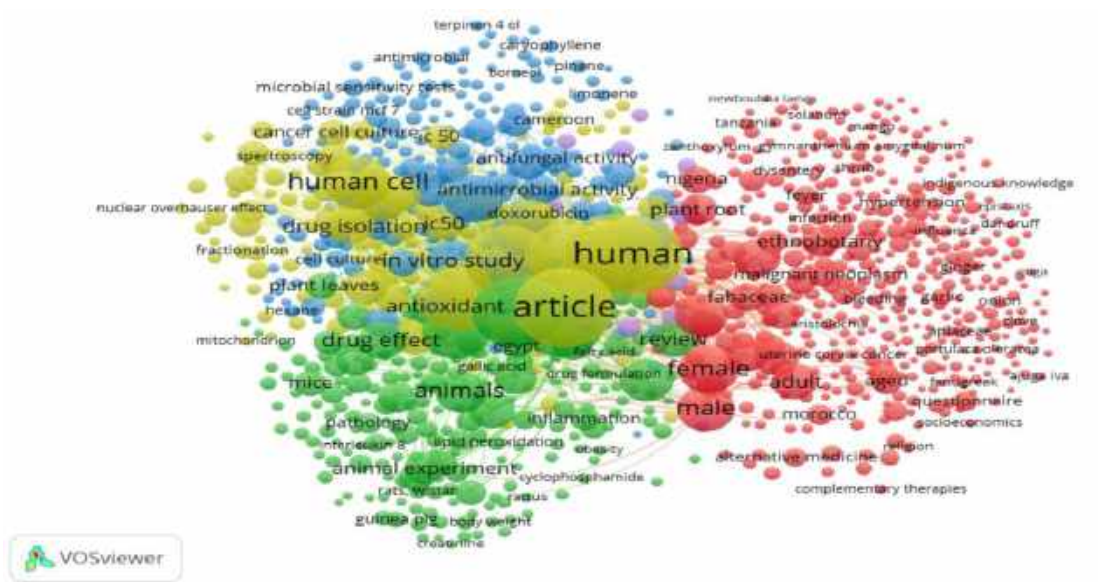


Figure 4: VOSviewer visualization of texts co-occurrence network based on title and abstract fields (Full Counting)

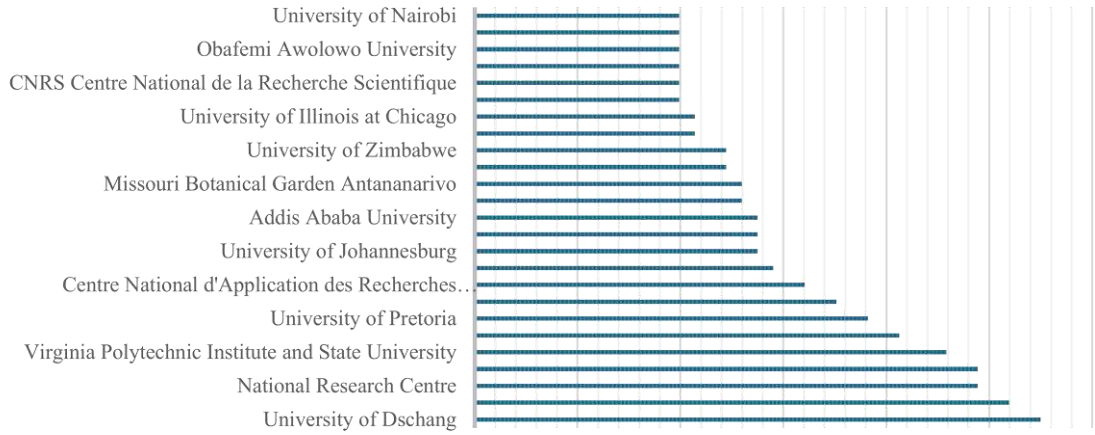


Figure 5. Most influential institutions

Table 10: Highly cited articles

| Authors | Title | Year | Cites | Cites Per Year |
|---|---|---|---|---|
| Chang E.T., Adami H-O | The enigmatic epidemiology of nasopharyngeal carcinoma | 2006 | 1097 | 60.94 |
| Batiha G.E.-S. *e.t al.* | Chemical constituents and pharmacological activities of garlic (*Allium sativum L.*): A review | 2020 | 483 | 120.75 |
| Kingston D.G.I. | Modern natural products drug discovery and its relevance to biodiversity conservation | 2011 | 407 | 31.31 |
| Russo E.B. | History of cannabis and its preparations in saga, science, and sobriquet | 2007 | 402 | 23.65 |
| Joseph B., Jini D. | Antidiabetic effects of *Momordica charantia* (bitter melon) and its medicinal potency | 2013 | 325 | 29.55 |
| Kupchan S.M. *et. al.* | Bruceantin, a New Potent Antileukemic Simaroubolide from Brucea antidysenterica | 1973 | 325 | 6.37 |
| Kamatou G.P.P. *et. al.* | South African Salvia species: A review of biological activities and phytochemistry | 2008 | 250 | 15.63 |
| Facchini P.J., De Luca V. | Opium poppy and Madagascar periwinkle: Model non-model systems to investigate alkaloid biosynthesis in plants | 2008 | 225 | 14.06 |
| Van Wyk B.-E. | The potential of South African plants in the development of new medicinal products | 2011 | 213 | 16.38 |
| Hsouna A.B. *et. al.* | Chemical composition, cytotoxicity effect and antimicrobial activity of Ceratonia siliqua essential oil with preservative effects against Listeria inoculated in minced beef meat | 2011 | 206 | 15.85 |
| Fouche G. *et. al.* | In vitro anticancer screening of South African plants | 2008 | 206 | 12.88 |
| Kuete V., Efferth T. | Cameroonian medicinal plants: Pharmacology and derived natural products | 2010 | 203 | 14.5 |
| Boukhatem MN *et. al.* | Lemon grass (*cymbopogon citratus*) essential oil as a potent anti-inflammatory and antifungal drugs | 2014 | 202 | 20.2 |
| Hostettmann K *et. al.* | The potential of African plants as a source of drugs | 2000 | 193 | 8.04 |
| Ochwang'i D.O. | Medicinal plants used in treatment and management of cancer in Kakamega County, Kenya | 2014 | 188 | 18.8 |
| Sargin S.A. *et. al.* | An ethnobotanical study of medicinal plants used by the local people of Alaşehir (Manisa) in Turkey | 2013 | 184 | 16.73 |
| Shen T. *et. al.* | The genus Commiphora: A review of its traditional uses, phytochemistry and pharmacology | 2012 | 183 | 15.25 |
| Atawodi S.E. *et. al.* | Evaluation of the polyphenol content and antioxidant properties of methanol extracts of the leaves, stem, and root barks of Moringa oleifera Lam. | 2010 | 183 | 13.07 |
| Mills E. *et. al.* | African herbal medicines in the treatment of HIV: Hypoxis and Sutherlandia. An overview of evidence and pharmacology | 2005 | 183 | 9.63 |
| Teklehaymanot T. | Ethnobotanical study of knowledge and medicinal plants use by the people in Dek Island in Ethiopia | 2009 | 174 | 11.6 |

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review". Kingston (2011) and Russo (2007) added a significant amount with 407 and 402 citations, respectively.

## DISCUSSION

The findings of this bibliometric analysis have provided a deeper understanding of the research landscape of herbal medicines in cancer management in Africa by building on trends outlined in the literature review. The global burden of cancer, particularly in low- and middle-income countries with limited access to conventional therapies, has driven interest in alternative treatment approaches such as herbal medicines. This analysis reinforces the growing role of herbal medicines as a complementary option and aligns with previous studies that highlight the persistent use of herbal treatments in cancer care across Africa [26]. A key insight from the results is the geographical concentration of research output. South Africa's prominence in herbal medicines research, as noted in this study, contrasts with the literature, which identifies China, India, and the USA as global leaders in this area [27]. While South Africa leads within Africa, there remains a significant disparity in research outputs between other African nations and top-performing countries worldwide. Nigeria, Egypt, and Cameroon contributed notably, but many other African countries remain underrepresented.

To the best of our knowledge, no similar bibliometric study has been conducted on this same topic, thus limiting direct comparisons with the current study. However, a study examining research trends globally and advancements in medicinal plant-synthesised nanoparticles for cancer treatment reported that India, China, Iran, Saudi Arabia, and the USA are the top contributors in this speciality, with India accounting for 27.7% of all the research outputs. The leading journals in this field included the International Journal of Nanomedicine, Molecules, and the Journal of Drug Delivery Science and Technology, which are very different from the leading African journals identified in this study, such as the Journal of Ethnopharmacology. This suggests that Africa's research focus and dissemination channels differ from those of global leaders, possibly due to funding limitations, institutional priorities, and regional research interests.

The role of funding and international collaboration in African research on herbal medicines is critical. This review noted that institutions like the Bill and Melinda Gates Foundation and the National Institutes of Health have supported health informatics research in Africa [26]. This analysis further identified key funding sponsors, such as the National Research Foundation and the National Cancer Institute, which play crucial roles in supporting African research on herbal medicines for cancer. However, funding disparities and institutional challenges remain significant barriers to research productivity in Africa. Many African countries allocated less than 0.5% of their GDP to research and development, with Kenya and South Africa being among the highest spenders, of 0.98% and 0.82%, respectively, albeit far below global averages [33]. This limited investment hinders the development of research infrastructure, access to cutting-edge technologies, and opportunities for collaboration. Consequently, African researchers face significant challenges in conducting long-term studies, accessing modern laboratory equipment, and engaging in international partnerships that could enhance research quality and impact. The inadequate funding also results in a scarcity of locally generated and shared knowledge, which impedes the development of context-specific healthcare solutions tailored towards African needs. Several other obstacles hinder research progress in Africa, including inadequate mentorship, language barriers, and brain drain [34]. To accelerate the translation of herbal medicine research into clinical practice, it is essential to address these challenges through increased funding, supportive policies, and strengthened regional collaborations, ultimately enhancing Africa's research impact in herbal medicine and cancer management.

### Conclusion

This study provides a comprehensive bibliometric analysis of research on herbal medicines in cancer management across Africa by analysing 1,134 publications from the Scopus database. The results reveal significant contributions from South Africa, Nigeria, and Egypt, with the Journal of Ethnopharmacology being the most active publication outlet. Through co-authorship, co-citation, and keyword co-occurrence analyses, this study has identified key research themes, influential authors, and institutions driving this field while also pointing to emerging trends and gaps in the research landscape. The findings of this study thus contribute to the growing body of literature on the use of herbal medicines in cancer treatment by mapping out the research landscape across Africa. This bibliometric analysis not only identified the most prolific researchers and institutions but also provided valuable insights into thematic clusters and trends, helping to guide future research directions. By highlighting the role of funding agencies and international collaborations, this study offers a framework for policymakers, researchers, and funding bodies to support and expand research efforts in this critical area of healthcare. Furthermore, this study underscores the need to strengthen research infrastructure and collaboration across African countries to enhance the integration of traditional medicine into modern cancer care.

While this study offers valuable insights, several limitations must be acknowledged. First, the analysis was restricted to data from the Scopus database, which may not capture all relevant publications, particularly those indexed in other databases like PubMed or Web of Science. Secondly, the focus on English-language publications, which constitute most of the dataset, may overlook significant research conducted in other languages, limiting the inclusivity of the analysis. Finally, the study primarily relied on citation metrics, which may not fully reflect the quality or real-world impact of the respective research.

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Future studies should aim to expand the scope of bibliometric analyses by incorporating data from multiple databases to ensure a more comprehensive understanding of the research landscape. There is also a need for more patient-centred studies to validate the efficacy of herbal medicines in cancer management. Additionally, efforts should be made to increase the visibility of research conducted in non-English languages to ensure that all relevant contributions are recognised. Finally, further exploration of funding trends and their impact on research output would help guide resource allocation to herbal medicine research across Africa.

## DECLARATIONS

**Ethical consideration**
Not Applicable

**Consent to publish**
All authors agreed on the content of the final paper.

**Funding**
None

**Competing Interest**
The authors declare no conflict of interest

**Author contribution**
All authors contributed equally to the study's conceptualisation, design, data collection, analysis, drafting and finalisation of the manuscript.

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**Availability of data**
Data is available upon request to the corresponding author

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# Integrating mental health and socioeconomic strategies during the post-COVID-19 era: Lessons for future pandemics

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**Abstract**

The COVID-19 pandemic had profound and unprecedented effects on global health, with an intricate interplay between socioeconomic factors and mental health outcomes. The pandemic exacerbated existing mental health conditions and introduced new stressors, including economic instability, job loss, and social isolation, disproportionately affecting vulnerable populations. Effective interventions that integrate mental health considerations into socioeconomic policies are crucial for coping with future pandemics. This paper employs a dual approach, combining a literature review and a case study, to apply Tayyib's five strategic points for community mental health action and delineate strategies for mitigating these impacts. A conceptual model frames socioeconomic disparities as critical leverage points for improving mental health outcomes. Key findings emphasise the importance of integrated strategies that address economic and psychological well-being, particularly for vulnerable populations. Recommendations include expanding social support networks, enhancing community engagement, and integrating economic support with mental health services to foster inclusive and resilient communities in the post-pandemic era.

**Keywords:** COVID-19, mental health, socioeconomic

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## INTRODUCTION

The COVID-19 pandemic exerted a profound and unprecedented impact on global health, economies, and societies, highlighting and exacerbating the intricate links between socioeconomic factors and mental health outcomes. Its effects have been devastating infection and mortality rates, and the mitigation measures implemented have long-term consequences on the global population [1]. The pandemic also exemplified the intertwined nature of socioeconomic factors and mental health outcomes. The WHO reported a significant rise in anxiety and depression, with mental health challenges affecting 40% of adults in the United States [2]. Over 1.6 billion students faced school closures, heightening stress and learning disparities [3]. Socioeconomic effects included a surge of 33 million unemployed globally, with 22 million jobs lost in the U.S. and unemployment peaking at 14.8% [4]. These interconnected crises underscore the urgent need for integrated strategies addressing mental health and socioeconomic challenges.

The health impacts of COVID-19 included millions of confirmed cases and deaths worldwide, exerting immense pressure on healthcare systems and exposing vulnerabilities and deficiencies in public health infrastructures [5]. In addition, the pandemic indirectly affected health outcomes through delayed or inaccessible healthcare services for non-COVID-19 conditions, leading to worse outcomes for

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chronic diseases, mental health issues, and emergency conditions [6,7].

The global economy experienced a significant recession due to lockdowns, travel restrictions, and decreased consumer spending [8–10]. Industries such as tourism, hospitality, and retail were particularly repressed, leading to massive job losses/unemployment and financial instability [11–13]. The economic downturn disproportionately affected lower-income groups and exacerbated pre-existing income inequalities [14]. Job losses and reduced work hours were more common among low-wage, less secure jobs, often engaged by marginalised communities [15]. Educational systems worldwide also faced closures and a sudden shift to online learning, highlighting and widening the digital divide. This disruption significantly impacted students' learning outcomes, particularly among those from lower socioeconomic backgrounds [16].

Furthermore, the pandemic also exacerbated social inequalities, as marginalised groups experienced higher susceptibility to COVID-19 infection, increased mortality rates, job losses, and barriers to accessing healthcare and essential support services [17] and aid [7]. Among the pandemic's effects were increased rates of anxiety, depression, stress, and substance use disorders, mainly driven by feelings of isolation, uncertainty, fear of infection, and economic instability [18-22]. A clear relationship was observed between socioeconomic factors and mental health outcomes [23]. Access to mental healthcare services was limited for lower-income populations due to systemic barriers, further worsening disparities. Economic hardship, job loss, and financial stress contributed to increased mental ill-health [24].

This study sought to espouse effective and sustainable pathways for addressing the broader impacts of the pandemic by strategically targeting the socioeconomic determinants of mental health. We posit that the intertwined nature of socioeconomic factors and mental health outcomes necessitate a holistic approach to pandemic response strategies.

**Conceptual Framework**

The conceptual model that linked socioeconomic factors, mental health impacts, and COVID-19 mitigation efforts involved interrelationships and feedback loops between these elements (Figure 1). This model underscores how socioeconomic disparities exacerbate mental health challenges and posits that addressing these disparities can be a strategic lever for broader public health mitigation.

**Theoretical basis of framework**

This study's conceptual framework is founded on theories that portray the complex interrelationships between socioeconomic factors, mental health impacts, and COVID-19 mitigation efforts as follows:

**Social determinants of health**

This framework postulates that health is profoundly affected by multiple social factors, including economic stability, education, social context, and access to healthcare

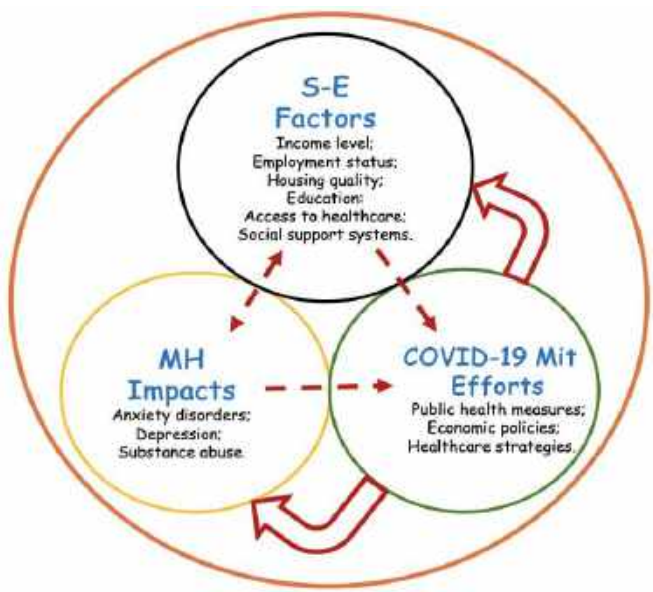


Figure 1. The model is represented as three interconnected circles, each representing one of the main components (Socioeconomic Factors, Mental Health Impacts, COVID-19 Mitigation Efforts). The arrows between the circles indicate the direction of influence, with bidirectional arrows between Socioeconomic Factors and Mental Health Impacts showing their reciprocal relationship. The larger surrounding circle represents the broader context of the COVID-19 pandemic, indicating that these interactions occur within the pandemic's overarching influence. MH – mental health; Mit – mitigation; S-E – socioeconomic.

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[29]. It supports our argument that socioeconomic disparities directly impacted mental health outcomes during the COVID-19 pandemic.

**Bronfenbrenner's ecological systems theory**

This theory provides a layered perspective on how individual experiences are influenced by interactions within various environmental systems, from immediate settings like family and school to broader societal and cultural contexts. It underscores the importance of considering multiple levels of influence when designing pandemic mitigation strategies [30].

**Maslow's hierarchy of needs**

Maslow's theory illustrates why addressing socioeconomic factors is essential for mental health. The pandemic's impact on economic and social security had direct consequences on individuals' ability to meet these needs, thereby affecting mental well-being [31]. Our conceptual framework integrates these theories to explain how improved socioeconomic conditions can lead to better mental health outcomes, which in turn enhance the efficacy of public health mitigation strategies.

**Underlying assumptions of the framework**

The strategic focus on mental health-related socioeconomic impacts for effective pandemic mitigation was predicated on several key assumptions:

a. Socioeconomic factors are major determinants of mental health. The model assumes that socioeconomic status significantly influences individuals' mental health and suggests that interventions aiming to improve socioeconomic conditions can directly enhance mental health outcomes.
b. Mental health impacts influence pandemic outcomes. It is assumed that mental health challenges can affect an individual's behaviour and capacity to adhere to pandemic mitigation measures. Poor mental health may lead to reduced compliance with public health guidelines, thereby influencing the overall effectiveness of pandemic response efforts.
c. Integrated approaches enhance mitigation efficacy. This assumption posits that pandemic mitigation strategies integrating mental health support with socioeconomic interventions were more effective than isolated approaches.
d. Disparities exacerbate pandemic impact. This model assumes that socioeconomic and health disparities — particularly those affecting marginalised and vulnerable populations intensify the pandemic's impact.

Building on these theoretical insights, this study employs a dual approach of literature review and case study to explore practical strategies for integrating mental health considerations into socioeconomic policies.

# MATERIALS AND METHODS

## Approach

We employed an approach that integrated a literature review with a case study, directly applying Tayyib's five key strategies for developing community mental health action plans. This provided a guide for the practical implementation of our theoretical framework. Tayyib's strategies were selected due to their strong alignment with the ecological models and theories of social support that underpin our study. The strategies have been substantiated by empirical research findings that demonstrate success in enhancing mental health outcomes across diverse settings.

**Case study application**

Individual interviews and group discussions were conducted, allowing participants and stakeholders involved in the case study to gather insights into the effectiveness and impact of the strategies. Feedback from these sessions was used to assess satisfaction, perceived benefits, and potential areas for improvement. Findings from the case study were synthesised with results from the literature review to provide an understanding of the effectiveness of the strategies. Practical recommendations for policymakers were formulated based on insights gained from both the case study and the literature review.

**Description of case study**

The case study examined the psychological support provided to Ghanaian students stranded in China during the early stages of the COVID-19 pandemic. On February 7, 2020, Ghana's Ministry of Foreign Affairs requested assistance for students experiencing severe distress in Wuhan, Enshi, and Shiyan. Challenges included isolation, lack of access to mental health services, and trauma from witnessing the pandemic's impact, particularly in Wuhan, the outbreak's epicentre. The intervention focused on tele-therapy and community support. Online group discussions were also held with various groups. These included psychological first aid, coping strategies, and the establishment of support networks. A WeChat counselling group provided ongoing assistance, fostering resilience and empowerment.

**Group and individual teletherapy sessions**

There were five interactive online group sessions, each lasting between two and three hours, that helped to establish community support networks in addition to training and discussions on mental health, psychological first aid, and signs and symptoms of mental health distress. These online sessions served as community outreach programs on effective, supportive, and coping skills, as well as accessing mental health resources and teletherapy. Over 70 hours of individual teletherapy sessions were done. The individual teletherapy sessions involved 34 participants, comprising Ghanaian students located in Wuhan, Enshi, and Shiyan. The participants were a diverse group of undergraduate and graduate students with a mix of genders and academic backgrounds, reflecting the varied demographics of the Ghanaian student community in China.

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These cities were selected due to their differing levels of exposure to the COVID-19 outbreak, with Wuhan being the epicentre. Participants were recruited through outreach efforts coordinated by Ghana's Mission in China and the Ghanaian student leadership in these cities. Selection criteria focused on identifying students facing significant psychosocial distress. The discussions revealed recurring themes, including feelings of isolation, fear of infection, and anxiety about evacuation delays. Participants highlighted the emotional strain of witnessing the pandemic's toll in their immediate environment, particularly medical students housed near hospitals. Feedback underscored the importance of the interventions, which included group therapy, coping strategies, and the establishment of support networks, in alleviating distress and fostering resilience.

**Literature search strategy**

The goal of the search was to identify evidence supporting the integration of mental health considerations into socioeconomic policies for effective pandemic mitigation. We searched several electronic databases, including PubMed, Web of Science, and Google Scholar. Additionally, reports from the Africa Centres for Disease Control and Prevention (Africa CDC), World Health Organisation (WHO), and the Centres for Disease Control (CDC) were reviewed. Searches were conducted using a combination of keywords and phrases related to three main themes: "COVID-19," "socioeconomic factors," and "mental health impacts." Specific search strings included combinations like "COVID-19 and mental health," "socioeconomic impacts of pandemics," and "public health interventions for COVID-19". The included materials comprised peer-reviewed articles, official reports, and relevant book chapters published between December 2019 and the present, focusing on studies that addressed both socioeconomic and mental health aspects of COVID-19. The literature review was limited to available and accessible English-language publications.

**Synthesis of findings**

Our findings were organised using a thematic analysis approach. Themes were derived from the study's objective, literature review, and case study. The findings were mapped against our conceptual framework to highlight how socioeconomic factors and mental health interventions interact and impact pandemic mitigation efforts.

## RESULTS

**Socioeconomic impact of the pandemic on mental health**

The significant pre-pandemic decline in mental health has been worsened by the COVID-19 pandemic and its containment measures. According to Prescott et al., "The unprecedented global rise in mental anguish is closely linked with the erosion of our social fabric, economic and political systems, and our natural environments. We are facing multiple new large-scale threats to health, safety, and security, with a growing lack of trust in others and in authorities. Pervasive stress, anxiety, depression, and uncertainty are of a nature and scale we have never seen before—manifesting in surging violence, community breakdown, domestic abuse, opioid and other drug overdoses, social isolation, and suicides—with alarming new mental health trends in children and young people. This has been made worse by the COVID-19 pandemic and amplified by an exponential increase in the amount and immediacy of information propagated through electronic media, often negative, with manipulative intent aimed at dividing opinions through anger and fear. At the same time, there has been a progressive erosion of kindness, civility, compassion, and social supports" [27].

Infectious disease outbreaks disrupt every aspect of human life and have serious implications for the psychological well-being of affected individuals, families, and communities. Infectious disease outbreaks are often accompanied by increases in anxiety, depression, acute stress, posttraumatic stress disorder (PTSD), substance use disorders, domestic violence, and child abuse[32,33]. In addition, studies of the psychological impact of infection containment measures such as lockdowns, social distancing, and quarantine show that people experience anger, confusion, and posttraumatic stress symptoms, which worsen as the length of time practising such measures increases [28]. COVID-19, its containment measures and post-COVID impact caused a huge disruption in lives and livelihoods, with dire consequences for well-being and mental health, especially for the vulnerable. In response to this, the United Nations has called for the protection of mental health as a policy priority [34].

**Pandemic-related stressors**

Four key pandemic-related stressors led to deterioration in mental health: economic shock because of income or job loss and employment insecurity; isolation and loss of social support where individuals are alone and without access to their usual social support or network; restriction of movement and inability to access essential services like education and healthcare; and fear of getting infected with COVID-19 with the possibility of severe or critical disease and death [24]. Lockdown measures also had a direct impact on mental health deterioration because of the economic shock associated with physical distancing and restriction of movements. However, in communities and countries where there were good social protection measures which moderated the economic shock, there was less deterioration in mental health. Social protection measures serve as a safety net against adverse life events and foster health and social equity [24].

**Social protection measures**

To reduce the socioeconomic and mental health impact of the COVID-19 containment measures, the government of Ghana put in place various social protection measures: GHS 1 billion to support small and medium-scale enterprises and a GHS 3 billion facility to support industry [35]. Additional social protection measures focused on

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direct relief to households were mentioned in Update No. 6 of the President's address to the nation on April 9, 2020: "As part of measures to mitigate the effects of the pandemic on the social and economic life of the country … government will absorb water bills for all Ghanaians for the next three months, i.e. April, May and June. The government will fully absorb electricity bills for the poorest of the poor: for all lifeline consumers, that is, providing free electricity to individuals who consume 0-50 kilowatt-hours per month during this period. Additionally, for all other consumers, including residential and commercial, the government will again absorb fifty percent (50%) of your electricity bill for this period, using your March 2020 bill as the benchmark. This was being done to support industry, enterprises and the service sector in these difficult times and to provide some relief to households for lost income" [36].

The Midyear Budget Review on July 23, 2020, extended the 100% water subsidies for another three months (July to September 2020), while the 100% electricity subsidy for lifeline users was extended until the end of 2020 [37]. Despite the good intentions of these social protection measures, those without access to piped water and electricity (typically those in urban slums and rural areas) did not benefit from most of these measures [38]. It is unfortunate that those who needed the benefits of the subsidies the most could not access them, even though the UN recommends that vulnerable populations receive the necessary attention for social protection and mitigation measures [39]. In addition to COVID-19, other factors such as physical distancing and restriction of movement policies led to deterioration in mental health, especially when these occurred together with economic difficulties [24]. Unfortunately, there is evidence that many governments responded inadequately to the huge burden of COVID-19-associated mental health distress [40]. Although many COVID-19 treatment centres in Ghana and the general public received professional support from members of the Ghana Psychological Association (GPA) and the Psychiatric Association of Ghana (PAG), this still fell short of meeting the mental health needs of the populace.

Despite the challenges, a study by Mendez-Lopez et al. showed that the adverse effects of closures, restrictions and physical distancing could be averted. Effective social protection measures can mitigate the possibility of mental health deterioration [24]. For instance, a United States study found that those living in states with supportive social policies experienced less negative mental health impacts when they experienced COVID-19-related economic shocks [41].

## DISCUSSION

### Mitigating the socioeconomic impact of the pandemic on mental health

Mental health is commonly neglected by governments and society in general. The WHO outlines the mental health effects action area for mitigation, which straddles all five UN response pillars of Health First, Protecting People, Social Cohesion and Community Resilience, Economic Response and Recovery, and Macroeconomic Response and Multilateral Collaboration [17]. One way to address the mental health impact in the post-COVID-19 era is to conceptualise it as a collective trauma, which is trauma that involves groups of people, communities, or societies [28]. This results in a widespread effect that goes beyond health; it affects economics, policies, relationships, and social order. The collective trauma of COVID-19 resulted in collective experiences of hopelessness, anguish, and distress [42]. This is illustrated by the case study involving Ghanaian students stranded in China at the beginning of the pandemic. Their collective experience of hopelessness, helplessness, haplessness, and anguish was palpable.

On the morning of February 7 2020, one of us (AKE) received a call from the Ministry of Foreign Affairs and Regional Integration. It concerned a request for psychological support for some of the Ghanaian students studying in China. These were students agitating to be airlifted back home because of the epidemic of SARS-CoV-2 in Wuhan and other cities in Hubei Province, China. Shortly afterwards, AKE was briefed on the plight of the students who had initiated the request for psychological support while waiting to be airlifted back home by Ghana's Ambassador to China. Two Zoom meetings took place that day regarding the psychological support to be provided. Three interactive online group sessions helped to establish community support networks, including self-help groups. Several online training and discussion sessions were held that provided education on mental health, psychological first aid, and signs and symptoms of mental health distress. These online sessions served as community outreach programs on effective, supportive, and coping skills, as well as accessing mental health resources and teletherapy. The leadership set up a WeChat counselling group to enable us to address some of the students' concerns. The discussion and training sessions helped with community capacity-building and community empowerment.

In all, a total of 70 teletherapy hour sessions with 34 students from 3 cities, Wuhan, Enshi, and Shiyan, were carried out. The medical students in Wuhan were at the epicentre of the outbreak, and to a lesser extent, Enshi and Shiyan were deeply affected. This was because they were housed on the hospital premises and thus witnessed the admission of patients while also observing the dead being taken out of the hospital, a situation that only aggravated their psychological and emotional trauma. According to the students, the therapy and counselling sessions were helpful, but they believed the fundamental solution to their problems was evacuation to Ghana.

The outcome of the interventions with the students and Ghanaians in China who were part of the online mental

health and psychosocial support (MHPSS) supports the evidence that healthcare strategies ( as illustrated in Figure 1) such as psychoeducational interventions, Psychological First Aid (PFA), and mental health promotion are effective in improving mental health and empowering people[43] and form important components of COVID-19 and pandemic mitigation efforts. In addition, it has been shown that training lay community members to provide psychoeducation and PFA intervention in their communities is effective in addressing common mental health disorders [44].

**Recommendations and key lessons for future pandemics**
**a. Strategic Interventions**

Tayyib recommends five strategies for developing an action plan that helps communities improve their mental health and recover from the collective trauma associated with infectious disease epidemics (Figure 2). They also improve the efficacy of building and increasing community resilience [28]. Tayyib's five strategic points can be effectively adapted to Ghana's unique cultural norms and leadership structures. Engaging community leaders and organisations is crucial, as chiefs, queen mothers, assemblymen, and faith leaders hold significant influence. Collaborating with traditional councils and faith-based groups can ensure culturally sensitive mental health interventions. Establishing community support networks can leverage Ghana's strong family and clan systems to create self-help groups and peer support initiatives. Community "warmlines," staffed by trained laypersons, can offer early intervention and emotional support, addressing stigma and building resilience.

For community mental health outreach and training, multilingual workshops and Psychological First Aid (PFA) training for community health nurses can be combined with radio and social media campaigns to extend mental health education, particularly in rural areas. Ghana's established CHPS program provides a platform to deploy community health workers (CHWs) for mental health education and referrals. CHWs, trusted figures in rural areas, can use culturally adapted materials to address beliefs about spiritual causes of mental illness. Finally, building community capacity and empowerment by training traditional healers and local leaders can integrate modern and traditional mental health approaches. Promoting accountability in mental health programs will build trust and ensure sustainability. Adapting these strategies within Ghana's cultural context can create a resilient and inclusive mental health system, addressing both societal needs and local norms. The account of the interventions to support the Ghanaian students in Hubei province during the pandemic provides a real-life illustration of Tayyib's five strategic points:


Figure 2. Tayibb's recommended strategies [8]. CBO – community-based organization; CL – community leader; CSN – community support network; SHG – self-help group.

Strategy 1: Engage and Partner with Community Leaders and Community-Based Organisations. Every community has its gatekeepers. To engage with the community, targeting community leaders is key. It is essential for planners of community mental health intervention programs to take time to build trust with identified leaders; their involvement in any community-based mental health intervention is crucial if the interventions are to be effective and sustainable [28]. Religious leaders are a group whose influence must be harnessed to improve community mental health. Their support for health interventions can be a catalyst for community acceptance. They can support and encourage their communities during difficult times. Among the Ghanaians in China, there were a few religious leaders who provided substantial encouragement to their colleagues during this difficult period.

Strategy 2: Establish (and Re-Establish) Community Support Networks Including Self-Help Groups. The most consistent sign of resilience after disaster or trauma is social support [45]. Considering that loneliness and isolation are linked to poorer physical and mental health, creative ways of social support must be implemented as soon as possible [46]. In addition, community warmlines can also provide social connection for those without social support and help for those who are not sure they need mental health support [47]. Warmlines are managed by those who have experienced mental health difficulties and can be effective in preventing those going through mental health distress from getting into a mental health crisis.

Strategy 3: Provide Community Mental Health Outreach, Education, and Training. It is important to be able to identify, evaluate, and connect community members experiencing emotional distress or mental health challenges to where they can get the needed mental health services. PFA is an effective program that can train community members in dealing with highly stressful situations, the basic features of mental illness, and how to cope better [28]. Based on three action principles — look, listen, and link —

PFA supports both calm and distressed persons, also offering coping mechanisms to address mental challenges. To provide PFA, one must care about the person in distress, show empathy, listen actively, pay attention to the response, and provide practical assistance [48]. PFA is effective in helping communities deal with trauma [45]. In Sierra Leone and Liberia, PFA was used to address the psychological impact of Ebola Virus Disease (EVD) [49].

Strategy 4: Deploy Community Health Workers to Engage and Educate the Community. Community Health Workers (CHWs) are often individuals from the community who share experiences and hold significant influence within their communities [28]. There is evidence to support the invaluable role they have played in previous infectious diseases. For instance, during the EVD outbreak in Nigeria in 2014, CHWs educated communities on culturally appropriate behaviours that could prevent the transmission of EVD, provided health education, collected data, and facilitated contact tracing. These measures helped reduce the spread of EVD [50]. The Friendship Bench programme that started in Zimbabwe provides evidence of the effectiveness of a brief psychological intervention for common mental disorders delivered by lay health workers, as shown in a cluster randomised controlled trial [44]. Involving CHWs in promoting community resilience through mental health-related efforts during the COVID-19 pandemic is recommended [28].

Strategy 5: Focus on Community Capacity Building and Community Empowerment. The final strategy for developing an action plan that helps communities improve their mental health and recover from collective trauma is building the capacity of the community and empowering them. Community engagement and empowerment are effective long-term strategies for recovery and building resilience [28]. Communities have inherent strength and can advocate for themselves when they are empowered. Communities can be empowered through community-led training and skill-building, as they are best positioned to identify their own needs. To have an empowered community, partners must ensure that there is transparency and accountability [51]. Empowered communities are more likely to exhibit collective efficacy, which has been associated with improved health outcomes and stronger community cohesion.

**b. Strategic Recommendations for Policymakers.**
We recommend that policymakers establish a comprehensive framework for integrating mental health considerations into socioeconomic policies, thereby effectively mitigating the impacts of the COVID-19 pandemic in the post-pandemic era and laying a resilient foundation for future public health challenges. Our recommendations include the following: Integrate economic support with mental health services. Implement economic support measures, such as direct financial assistance and subsidies for essential services, alongside accessible mental health services. Expand social protection measures. Broaden the scope and reach of social protection measures to include not only financial support but also access to mental health resources, ensuring that these measures are accessible to all, particularly targeting those in urban slums and rural areas who are less likely to benefit from programs such as water and electricity bill subsidies in Ghana.

Leverage community networks for support and outreach. Engage with community leaders and organisations to establish trust and deliver mental health education and services. Utilise community networks for disseminating information about mental health resources, creating self-help groups, and conducting outreach programs that provide PFA and coping strategies, as demonstrated by the Ghanaian students in China. Invest in training for community health workers. Train community health workers in PFA, mental health awareness, and referral processes to strengthen community-based mental health support. Their roles should include providing psychoeducation, offering early intervention, and connecting community members to professional mental health services.

Develop and support online mental health resources. Given the effectiveness of teletherapy and online support groups observed among Ghanaian students in China and those who seek mental health services in Ghana, invest in expanding online mental health resources and training. This includes developing platforms for teletherapy, online counselling, and mental health education, which would be provided by licensed mental health professionals and paraprofessionals to ensure widespread access, particularly in areas where in-person services are limited.

Beyond telepsychiatry, several digital mental health resources can be leveraged to enhance mental health care in Ghana. Locally developed applications such as MINDIT (https://minditgh.com) and mHealer (https://pure.ug.edu.gh/en/publications/a-digital-toolkit-m-healer-to-improve-care-and-reduce-human-right) are particularly promising. MINDIT provides psychoeducation, stress management tools, and referrals to local mental health services through a culturally tailored mobile interface. Similarly, mHealer focuses on reducing stigma by offering symptom checkers, self-guided cognitive behavioural therapy modules, and peer support networks designed for Ghanaian users. Global platforms, such as the World Health Organisation's iSupport programme (https://www.who.int/teams/mental-health-and-substance-use/treatment-care/isupport), also hold potential for adaptation in Ghana. iSupport delivers evidence-based training and emotional support for caregivers, equipping families to better manage mental health challenges. Inspired by Zimbabwe's Friendship Bench initiative, digital adaptations of its brief problem-solving therapy modules could also be deployed in Ghana to address depression and anxiety, particularly in rural areas.

For urban populations with reliable internet access, platforms such as BetterHelp (https://www.betterhelp.com/) offer online therapy via video, messaging, and calls, enabling access to licensed therapists across various specialties. Meanwhile, AI-powered tools such as Koko (https://koko-ai.com), which provide real-time peer support through structured conversations, can offer scalable and low-cost mental health interventions for diverse populations. In areas with limited internet connectivity, SMS-based mental health tools are a practical alternative. These text-message services provide tips for stress management, self-care reminders, and crisis support information, capitalising on the widespread availability of mobile phones in Ghana.

Promote Policies for Job Creation and Retention. Address economic insecurity and its mental health implications by promoting policies that support job creation, retention, and re-skilling. Encourage partnerships between the private and public sectors to create sustainable employment opportunities and support businesses in retaining employees during economic downturns.Ensure inclusivity and equity in the implementation of policies. Policies must be designed and implemented with a focus on inclusivity and equity, ensuring that the most vulnerable populations receive the support they need. This requires continuous monitoring and adaptation of policies to address emerging needs and disparities.

**Foster multi-sectoral collaboration**
Encourage collaboration across sectors, including health, finance, education, and social services, to ensure a coordinated approach to addressing the socioeconomic and mental health impacts of the pandemic. This includes sharing data and resources, aligning strategies, and jointly developing comprehensive support programs.

**Future research**
Future research should focus on the long-term impacts of integrating mental health and socioeconomic strategies, the scalability of digital tools in underserved areas, and the role of community leadership in mental health interventions. These areas hold significant potential to improve mental health outcomes in resource-constrained settings. Research into the long-term impacts of integrated strategies should evaluate the effectiveness and sustainability of combining mental health support with socioeconomic initiatives, such as cash transfers or employment programs. Studies should also explore how these strategies impact vulnerable groups, including women, youth, and those in extreme poverty, to ensure tailored and inclusive solutions.

The scalability of digital mental health tools in rural areas requires investigation into accessibility, user-friendliness, and cultural adaptability. Barriers such as low digital literacy and limited connectivity must be addressed. Cost-effectiveness studies are essential to determine how these tools can reduce mental health service disparities while being sustainable. The Mental Health Authority is uniquely placed to lead such interventions.

Understanding the role of community leadership is critical. Research should examine how traditional leaders, faith organisations, members of parliament, assemblymen, women and community influencers can promote mental health awareness and reduce stigma. Collaborative models that integrate formal health systems with community leadership structures should also be evaluated for their effectiveness in improving service delivery and outcomes. Finally, the integration of traditional and modern mental health practices warrants exploration. Studies should evaluate how traditional healers can complement formal systems and address culturally rooted beliefs about mental health. Research on community-led initiatives and the training needs of local leaders can further enhance grassroots mental health programs.

**Conclusion**
The mental health-related socioeconomic impacts of COVID-19 in the post-COVID-19 era is crucial for individual and public health and a strategic lever for effective pandemic mitigation. The pandemic highlighted the deep interconnection between socioeconomic factors, such as employment status, income level, and access to healthcare, and their impact on mental health outcomes. Economic uncertainty, job loss, and social isolation have significantly worsened mental health conditions for many, particularly among vulnerable populations. Addressing these socioeconomic determinants is crucial for enhancing mental health and resilience following the pandemic.

## DECLARATIONS

**Ethical consideration**
This review did not require ethics approval

**Consent to publish**
All authors agreed on the content of the final paper.

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**Competing Interest**
The authors declare no conflict of interest

**Author contribution**
AKE – conception, study design, literature review, manuscript writing. IK – revision of manuscript outline, analysis of evidence, and manuscript writing. EDzi, ED, and OA – analysis of evidence and manuscript revision. All authors read and approved the final version of the manuscript.

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**Availability of data**

Data is available upon request to the corresponding author

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# Crossed-fused renal ectopia: exploring the concerns of the asymptomatic

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**Keywords:** Crossed-fused renal ectopia, Fusion anomalies of kidney, incidental, CT angiography, patient concerns

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## INTRODUCTION

Crossed-fused renal ectopia is an anomaly where the kidneys are fused and located on the same side of the midline, with the opposite side empty. This was first described in 1654 by Dominicus Panarolus [1,2]. Another theory indicated that the anomaly may be due to arrest of kidney ascent, causing the kidneys to remain in the pelvis or meet on one side with subsequent fusion. Abnormal position of the umbilical artery influencing the cephalic migration of the kidneys to the contralateral side following a path of least resistance has also been proposed to lead to cross-fused renal-ectopia [3].

It becomes a single renal mass when there is fusion, which occurs in 90% of the cases. However, the urinary collecting systems remain separate. Wilmer is credited with first categorising the fusion anomalies of the kidney (1938). McDonald and McClellan 1957 modified the classification to include crossed ectopia with fusion, crossed ectopia without fusion, solitary crossed ectopia and bilateral crossed ectopia [4]. The current classification used comprises (i) Unilateral fused kidney (inferior ectopia), (ii) Sigmoid or S-shaped kidney, (iii) Lump kidney, (iv) L-shaped kidney, (v) Disc kidney and (vi) Unilateral fused kidney (superior ectopia) [4]. The current case is a unilateral fused kidney (inferior ectopia). The incidence is known to be 1 in 2000 births [2] and more common in males compared to females (3:2) [1,4]. A left-to-right positioning

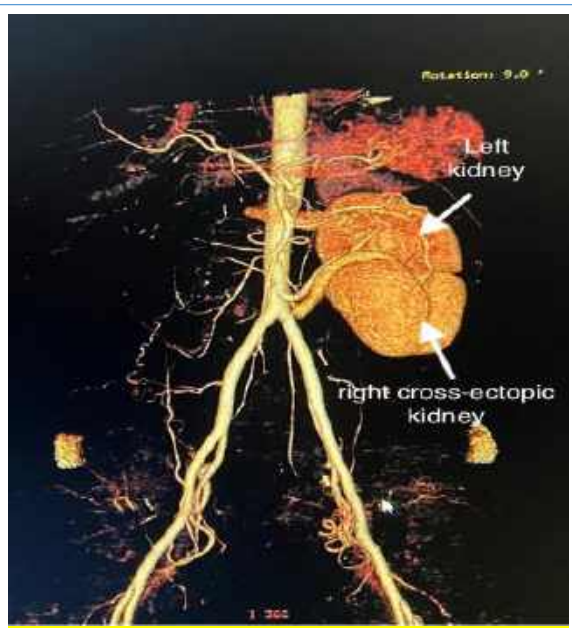


Figure 1. CT scan angiography showing a right to left crossed-fused renal ectopia (anterior-Posterior)

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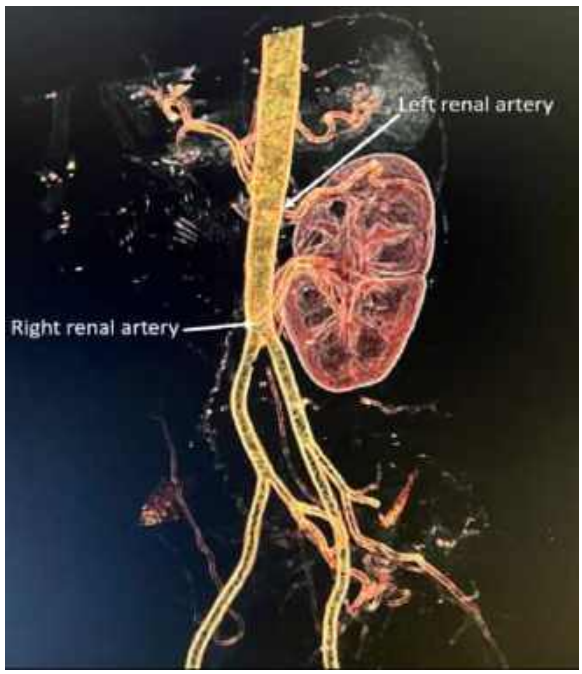


Figure 2. 3D Renal Angiography with Volume reconstruction (transparent) showing a right to left crossed-fused renal ectopia (Oblique)

is about three times more common compared to right-to-left [1,4]. This case of a right-to-left positioning is, therefore, rarer. About 50% of the patients present with symptoms such as urinary tract infection, hydronephrosis, and calculi formation [2,4]. It may also be associated with other urinary system abnormalities, such as vesico-ureteral reflux and pelvi-ureteric junction obstruction [3,5]. Clinically, most cases present in the paediatric age group.

The above patient was a 38-year-old female patient with an incidental finding on ultrasound of a crossed-fused left renal ectopia (fused kidneys, an anteriorly located notch, and differently oriented two collecting systems). She was not hypertensive and had normal renal function. A follow-up contrast-enhanced abdominal CT scan with CT angiography was performed to characterise it completely (Figures 1, 2 and 3). CT scan with CT angiography is considered the imaging modality of choice for the condition [4,6].

Magnetic resonance imaging could also serve as a useful alternative. These images are important when surgery is being contemplated due to variations in blood supply and the collecting systems. In this present case, the patient was adequately educated and reassured in accordance with standard practice, on possible complications that could arise and when to

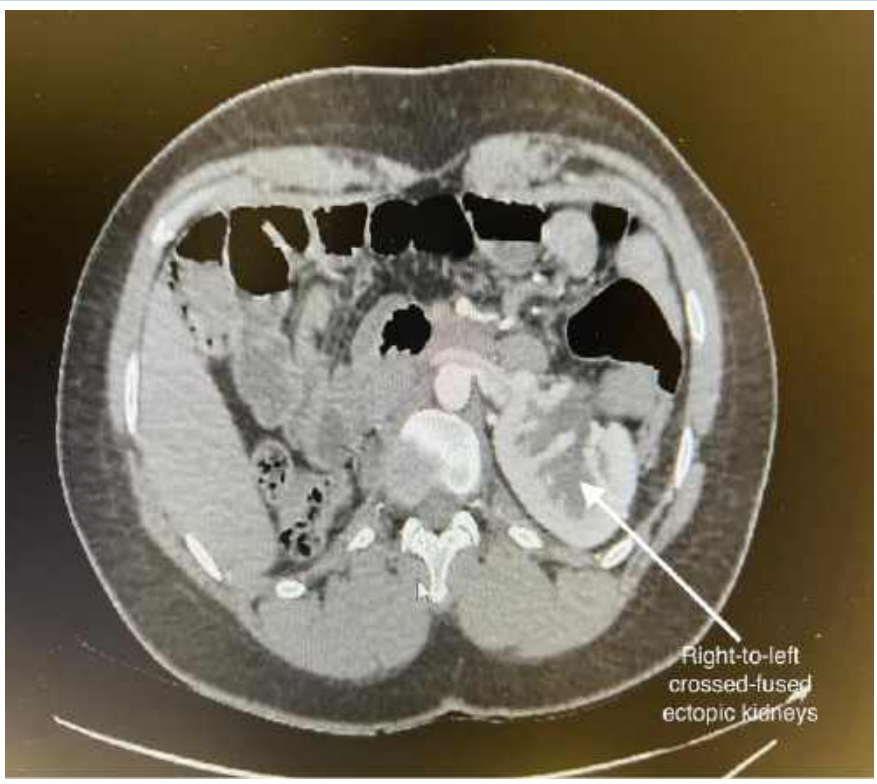


Figure 3. Contrast-enhanced abdominal CT scan showing a right-to-left positioning of the crossed ectopic kidneys with an empty right renal fossa.

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report back to the hospital for review. Indeed, it is important that patients with crossed-fused renal ectopia are educated on the possibility of developing urinary tract infections (especially if there is vesico-ureteric reflux), hydronephrosis from obstruction to urine flow and calculi formation. It may be necessary to exclude other abnormalities of the urinary system, such as vesico-ureteral reflux and pelvi-ureteric junction obstruction. Invariably, such medical conditions require long-term follow-up, as malignancies involving ectopic kidneys have been reported [7].

## DECLARATIONS

### Ethical consideration
Written informed consent was obtained from the study participant.

### Consent to publish
All authors agreed on the content of the final paper.

### Funding
None

### Competing Interest
The authors declare no conflict of interest.

### Author contribution
All authors contributed equally to the study's conceptualisation, design, data collection, analysis, drafting and finalisation of the manuscript.

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### Availability of data
Data is available upon request to the corresponding author.

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# Extraluminal granulomatous manifestation, a rare presentation of mixed intestinal schistosomiasis

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**Abstract**

Schistosomiasis is endemic in sub-Saharan Africa. The commonest intestinal pathology is an intestinal polyp. We report an atypical presentation of mixed *Schistosoma haematobium* and *Schistosoma mansoni* infestation. A 51-year-old male presented with a strangulated right inguinoscrotal hernia and had laparotomy. The findings at laparotomy were extensive granulomatous lesions on the serosa of the bowel and omentum. A biopsy for histopathology reported as a mixed *Schistosoma haematobium* and *Schistosoma mansoni* infestation.

**Keywords:** Intestinal schistosomiasis, granulomatous lesions, *Schistosoma haematobium*, *Schistosoma mansoni*

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## INTRODUCTION

Schistosomiasis is endemic in Sub-Saharan Africa, the Middle East and Asia. Over 90% of global schistosomiasis is reported in Africa. The prevalence of schistosomiasis in Ghana is 23.3%, with localised prevalence of > 50% in some areas [1]. There are two main clinical forms of schistosomiasis: the urogenital and intestinal schistosomiasis. The commonest pathological presentation of intestinal schistosomiasis is an intestinal polyp. We report a rare manifestation of mixed intestinal *Schistosoma haematobium* and *Schistosoma mansoni* infection with extra-luminal granulomatous lesions managed at the Korle Bu Teaching Hospital, Ghana.

## CASE

A 51-year-old man presented to the emergency department with 7 hours of painful irreducibility in a right groin swelling of 3 years. This was associated with generalised colicky abdominal pain, abdominal distension and absolute constipation but no vomiting. There was no history of previous laparotomy or abdominal trauma, no weight loss, no change in bowel movement and no history of bleeding per rectum. He was a fisherman who had been fishing in both freshwater bodies and the Atlantic Ocean since childhood. As a child, he experienced terminal haematuria that resolved, but he was not able to recall what treatment he received for this. He had a history of 12-pack years of cigarette smoking and drank alcohol regularly.

Clinical examination revealed a middle-aged man who looked acutely ill. He was not pale nor jaundiced, but was mildly dehydrated. There were no adverse findings during the chest examination. The pulse rate was 102 beats per minute, and his systolic blood pressure was 158/76 mmHg. His abdomen was distended, with a tender mass palpable centrally. Bowel sounds were increased in pitch and frequency. Further findings were a right irreducible inguinoscrotal swelling. His testes were palpable and normal. A clinical diagnosis of acute intestinal obstruction secondary to an obstructed right complete indirect inguinoscrotal hernia was made. He was admitted to the ward, resuscitated and consented to exploratory laparotomy and repair of the hernia.

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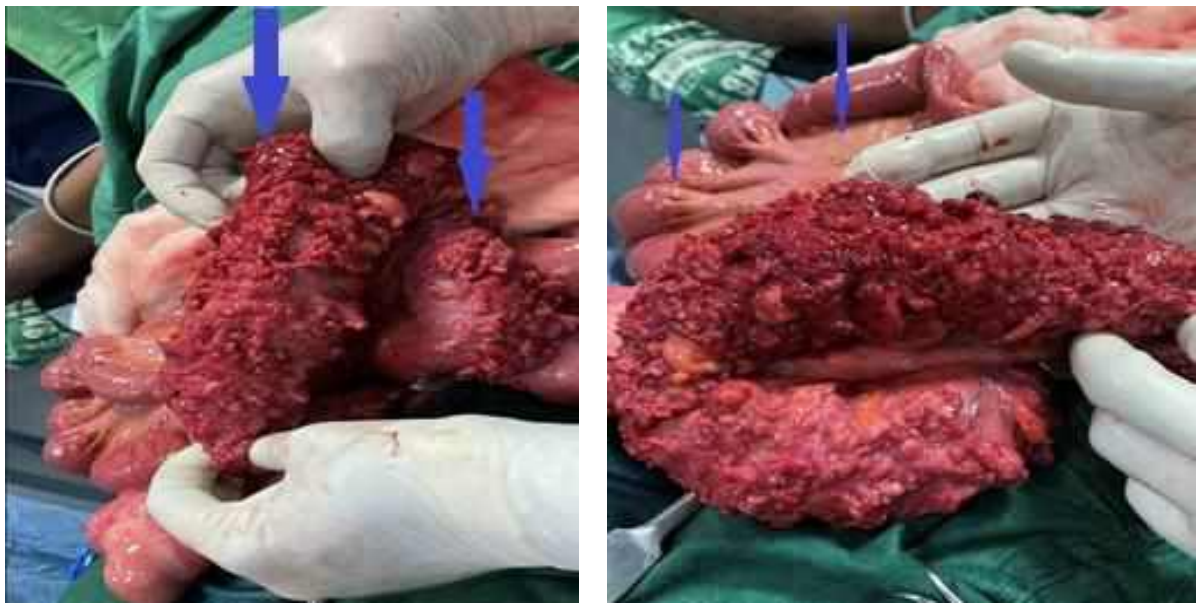

Figure 1. Laparatomy reveals extensive granulomatous lesions on the sigmoid colon and a few scattered granulomas on the small bowels and mesentery

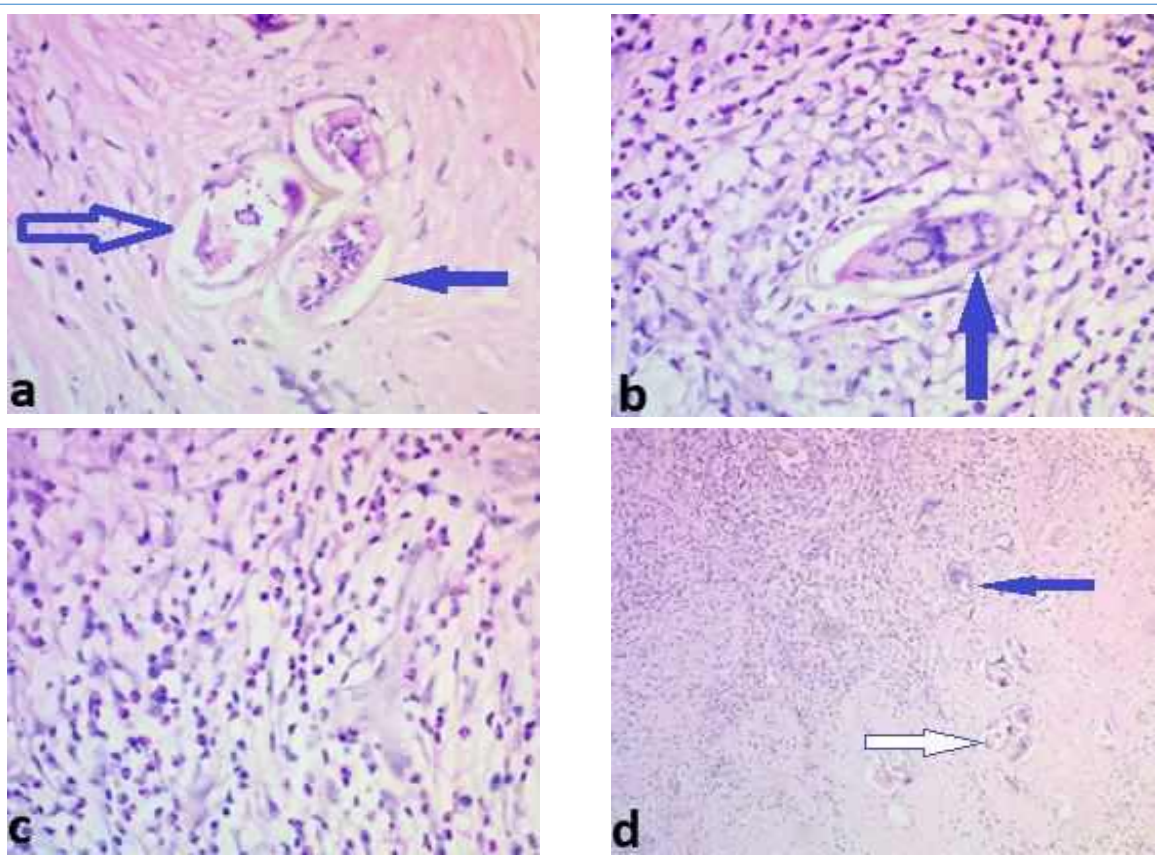


Figure 2. Histology showing mixed *schistosoma mansoni* ova (pictures a and d) with the lateral spine and *Schistosoma haematobium* ova with the terminal spine (pictures b and d) and marked eosinophilia (pictures c and d)

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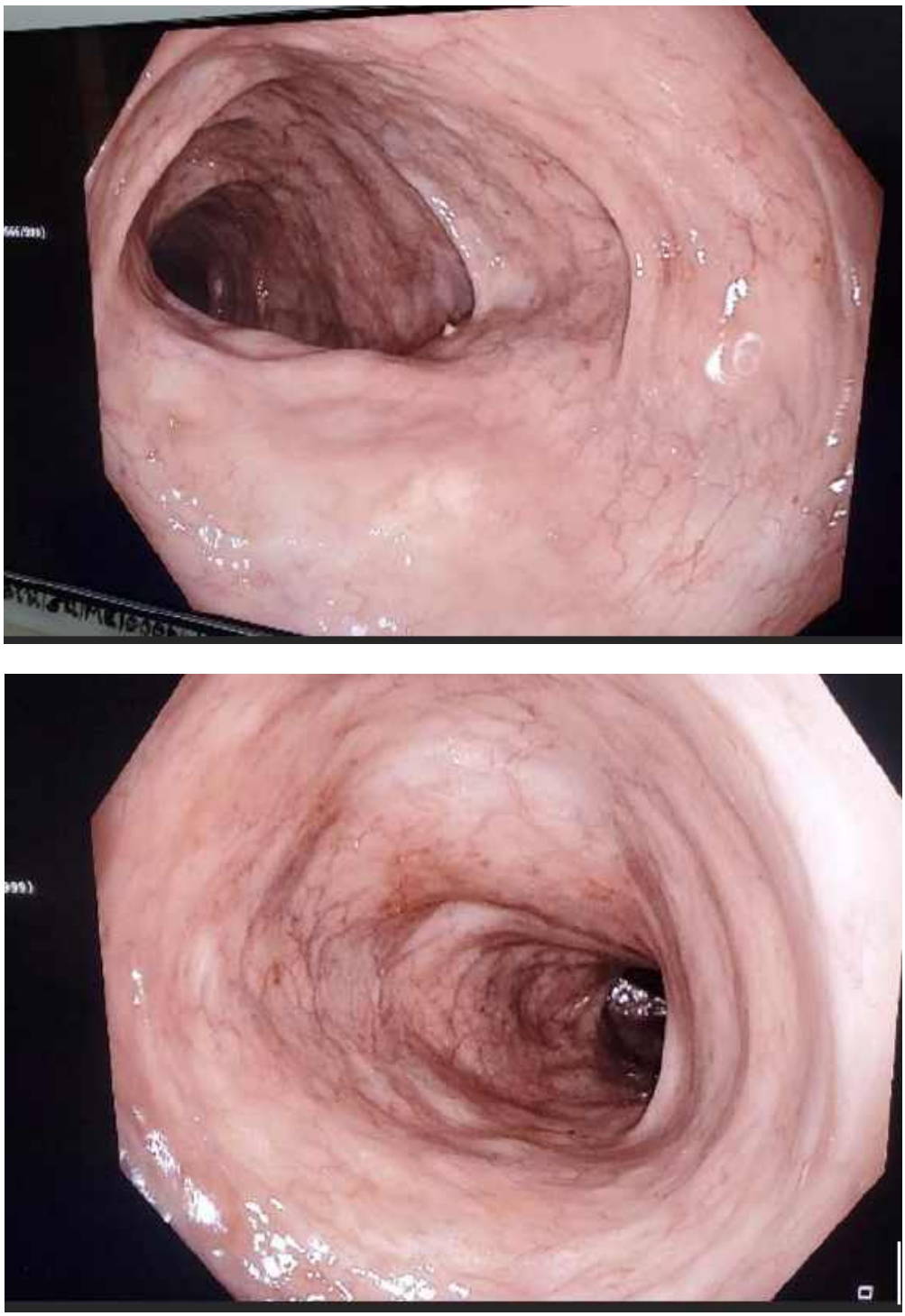

Figure 3. Colonoscopy images showing effacement of the large bowel luminal haustration and otherwise normal mucosa 8 months after treatment

Full blood count showed leucocytosis with differential eosinophilia. Blood urea and electrolytes were normal. At laparotomy the hernia sac contained ischaemic but viable redundant sigmoid colon and a portion of the greater omentum. There were generalised multiple fimbria-like granulomatous lesions on the serosa surface of the bowel and omentum, more clustered along the terminal ileum, cecum, proximal ascending colon, sigmoid colon and proximal rectum, with a thickened bowel wall but no tumour palpable in the wall or lumen (Figure 1). Three hundred millilitres of jelly-like peritoneal fluid were suctioned. The appendix, stomach, liver and pancreas were all normal. A biopsy of the granulomatous lesions was performed in addition to resection of a segment of the omentum. The peritoneum was lavaged, and the abdomen was closed after Nylon darn repair of the hernia had been completed. His recovery was uneventful.

Histopathology reported a florid mixed (S. haematobium and S. mansoni) schistosomiasis with granulomatous inflammation of the serosa of the bowel (Figure 2). He was treated with an initial oral dose of praziquantel 2400 mg as a single dose and discharged home on post-operative day 7. The praziquantel was repeated after 2 weeks. A follow-up colonoscopy was done after 8 months, which showed effacement of the large bowel luminal haustration, but it was otherwise normal (Figure 3). An ultrasound showed a normal portal system, and a cystoscopy also ruled out vesical schistosomiasis.

## DISCUSSION

Schistosomiasis is a parasitic infection caused by a trematode of the genus *Schistosoma* found in freshwater bodies in low- and middle-income countries. Of the over 20 different species of *Schistosoma* identified, only six (6) are known to cause human infection [2]. Three (3) major species are responsible for most of the infections in humans. These are *Schistosoma mansoni* and *Schistosoma haematobium* found mainly in Africa, South America, and the Middle East, and *Schistosoma japonicum* found mainly in Southeast Asia [2,3]. Schistosomiasis is endemic in the tropics and subtropics. About 290 million people are infected worldwide, with 97% of all infections in Africa [4,5]. The countrywide prevalence in Ghana is 23.3%, with localised prevalence of > 50% in some areas. 1 *Schistosoma haematobium* causes about 2/3 of all schistosomiasis infections in Ghana [1]. However, a recent publication has reported otherwise [6]. Coinfection has been reported with either two *Schistosoma* species or a *Schistosoma* species and another parasite or virus. Coinfection presents with more severe clinical features and worse morbidity [6-8].

The age group commonly infected are children aged 10 to 20 years, but clinical features and complications can present later, as observed in the index case [3]. The clinical manifestation of schistosomiasis is a result of the host's immune response to the eggs in the tissue. The pathogenesis of human schistosomiasis begins when eggs are destined to exit the body through faeces or urine and instead become embedded in the tissues of the human intestine or bladder. These trapped eggs induce inflammation, granulomas, and fibrosis, leading to several clinical sequelae including hepatic fibrosis and hepatosplenomegaly, haematuria, bladder fibrosis and obstruction, hydronephrosis and chronic renal disease. Infection with *Schistosoma* mansoni, S. japonicum, S. mekongi, or S. intercalatum is associated with chronic hepatic and intestinal fibrosis. Sandy patches develop when the submucosa becomes densely thickened by fibrous tissue containing immense numbers of calcified eggs; the overlying mucosa becomes atrophic and acquires a granular, dirty yellowish appearance.

The pathogenesis of intestinal polyp formation is characterised by deposition of *Schistosoma* eggs in the superficial layers of submucosa, where the connective tissue is loose and not bounded superficially by firmer tissue. This allows the accumulation of large amounts of reactive cellular debris and vascular granulation tissue. In the submucosa, the eggs produce a cell-mediated inflammatory response with granuloma formation and necrosis. As necrotic foci heal, fibrous connective tissue is formed, and the adjacent muscularis mucosa becomes hypertrophied. The fibrous tissue in the submucosa and the hypertrophied muscularis mucosa form a barrier to the usual route of ova transit from the mesenteric veins to the gut lumen. This entrapment of ova elicits an immune reaction with progressive inflammation and fibrosis. As this process continues, a nodule is formed that elevates the hypertrophied muscularis mucosa and mucosa to form the earliest detectable polyp. This mechanism can explain the main concentration of S. mansoni ova in the polyps rather than in the adjacent mucosa and submucosa.

Symptoms include tenesmus, the passage of blood and mucus per rectum, diarrhoea, abdominal pain, dyspepsia, and irreducible *Schistosoma papilloma* protruding from the anus which occurs in some patients. Malnutrition, weight loss, nail clubbing, pitting peripheral oedema, and pericolic masses may also be present. Iron deficiency anaemia, hypoalbuminemia, protein-losing enteropathy, and rectal prolapse are also documented manifestations. *Schistosoma appendicitis* is a rare complication [2,3,9,10]. Severe chronic intestinal disease may result in colonic or rectal stenosis and subsequently, intestinal obstruction. Colonic polyposis may manifest as protein-losing enteropathy. Inflammatory masses in the colon may even mimic cancer. There is enough evidence to implicate *Schistosoma japonicum* as an aetiological agent for colorectal cancer, but that of *Schistosoma mansoni* is inconclusive [11,12]. Chronic and advanced disease results from the host's immune response to schistosome eggs deposited in tissues and the granulomatous reaction evoked by the antigens they secrete. The disease may become chronic, lasting 3 – 8 years and even up to 20 – 30 years [10,13]. Several forms of intestinal schistosomiasis have been reported in the literature, including appendicitis, caecal perforation, diverticuli and intestinal obstruction [9,10,14].

We did not find serosal granulomatous presentation in this case study. This presentation is likely a disseminated schistosomiasis with ectopic deposition of *schistosoma* eggs in the peritoneum, omentum and serosa of the bowel. The granulomas on the bowel are a result of the chronic inflammatory response to these eggs. Salah et al. reported a case of disseminated schistosomiasis causing peritonitis [15]. The findings of *Schistosoma haematonium* and *Schistosoma mansoni* coinfection in this patient correlate with the burden of the disease. Studies have shown a high prevalence of Schistosoma haematobium and *Schistosoma mansoni* coinfection in Ghana and other African countries [6,8,16,17]. Coinfection is usually associated with increased intensity of infection and ectopic presentation of eggs (*Schistosoma haematobium* eggs in faeces and other sites other than the urogenital tract, and vice versa for *Schistosoma mansoni* eggs). Studies have shown that the two species can form a heterologous male-female pair, with the male determining the site of egg deposition and the female determining the type of eggs (species of eggs) deposited. In Ghana, a study by Anyan et al. [6] found a high prevalence of *Schistosoma haematobium* and *Schistosoma mansoni* coinfection as well as ectopic egg presentation.

### Conclusion

We report a case of atypical intestinal serosal granulomatous lesions of *Schistosoma haematobium* and *Schistosoma mansoni* coinfection presenting in a surgical unit as an obstructed hernia. The intraoperative findings posed a clinical dilemma and a difficult management decision. This presentation of extensive serosal and omental granulomatous lesions is uncommon.

## DECLARATIONS

### Ethical consideration

Written informed consent was obtained from the patient for publication.

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare no conflict of interest.

### Author contribution

NN and JA conceived the idea and drafted the manuscript. GDB, EKA, BFS, and ILA contributed to the literature review and discussion. KPA reviewed the histological slides and provided input to the discussion. LW and AT supervised the project and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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### Availability of data

Not applicable

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