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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) Mild anaemia: Hb 9.0 – 10.9 g/dL Moderate anaemia: Hb 5.0 – 8.9 g/dL 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) Mild thrombocytopaenia: platelet count 101-149 ×10^3/µL Moderate thrombocytopaenia: platelet count 51-100 ×10^3/µL 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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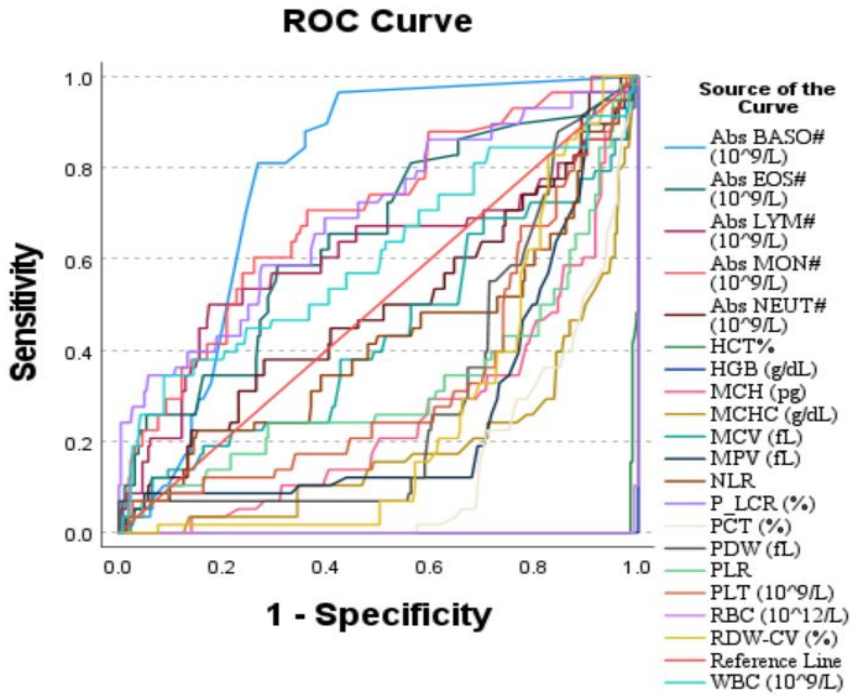

Variables	Cut-off point	AUC	95% CI	*P*-value	Sensitivity (%)	Specificity (%)
RBC (10^6/µL)	2.065	0.001	-0.001-0.002	<0.001	0	100
Hb (g/dL)	4.950	0.000	-	<0.001	0	100
HCT (%)	17.150	0.006	0.000-0.012	<0.001		
MCV (fL)	87.350	0.432	0.346-0.519	0.128	12.1	36
MCH (pg)	15.950	0.256	0.188-0.325	<0.001	100	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 ($\times 10^3$/µL)	12.960	0.605	0.516-0.695	0.021	34.5	91.3
NEUT ($\times 10^3$/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 ($\times 10^3$/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 ($\times10^3$/µL)	Normal	5.0-10.0	193	59.8
	Leucopaenia	<5.0	48	14.9
	Leucocytosis	>10.0	82	25.4
Neutrophils ($\times10^3$/µL)	Normal	2.0-7.5	276	85.4
	Neutropaenia	<2.0	19	5.9
	Neutrophilia	>7.5	28	8.7
Lymphocytes ($\times10^3$/µL)	Normal	1.0-4.0	223	69.0
	Lymphopaenia	<1.0	44	13.6
	Lymphocytosis	>4.0	56	17.3
Monocytes ($\times10^3$/µL)	Normal	0.2-0.9	132	40.9
	Monocytopaenia	<0.2	114	35.3
	Monocytosis	>0.9	77	23.8
Eosinophils ($\times10^3$/µL)	Normal	0-0-0.5	294	91.0
	Eosinophilia	>0.5	29	9.0
Basophils ($\times10^3$/µL)	Normal	0.0-0.20	323	100
	Basophilia	>0.20	0	0
Platelet ($\times10^3$/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

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.

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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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