Hematological Indices and Abnormalities Among Patients With Uncomplicated Falciparum Malaria in Kosti City of the White Nile State, Sudan: a Comparative Study

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Abstract

**Background:** Hematological abnormalities are common features in falciparum malaria but vary among different populations across countries. Therefore, we compared hematological indices and abnormalities between *Plasmodium falciparum*-infected patients and malaria-negative subjects in Kosti city of the White Nile State, Sudan.

**Methods:** A comparative, cross-sectional study was conducted at the Medical Technology Laboratory Unit of Kosti Teaching Hospital from June to December 2018. A total of 392 participants (192 *P. falciparum*-infected patients and 200 malaria-negative subjects) were recruited in the study. Hematological indices of hemoglobin (Hb), red blood cells (RBCs), white blood cells (WBCs) and platelets were measured and their median values were statistically compared.

**Results:** The majority of *P. falciparum*-infected patients (64.6%) showed a low-level parasitemia. The median values of Hb concentration, RBC count, mean corpuscular Hb and mean corpuscular Hb concentration were significantly lower in *P. falciparum*-infected patients, with anemia being significantly higher among infected patients than malaria-negative subjects (60.4% vs. 29.5%, respectively). The median total WBC count was non-significantly higher in *P. falciparum*-infected patients, with leucopenia being non-significantly different between both groups. The median platelet count was significantly lower in *P. falciparum*-infected patients, with thrombocytopenia being significantly higher among infected patients than malaria-negative subjects (72.4% vs. 5.0%, respectively).

**Conclusions:** Most falciparum malaria infections among patients in Kosti city of the White Nile State – Sudan are of low-level parasitemia. Nevertheless, falciparum malaria is significantly associated with anemia and thrombocytopenia with lower median values of Hb, RBC count, MCH, MCHC and platelet count in *P. falciparum*-infected patients than malaria-negative subjects. In contrast, leucopenia is not useful to predict falciparum malaria. Further large-scale studies in community and healthcare settings and inclusion of patients with complicated or severe malaria and those with high parasite densities are recommended.

**Background**

Despite intensive control efforts, malaria remains a major public health concern on a global scale, where 229 million cases and 405,000 deaths from severe malaria were estimated in 2019 with the African region accounted for 94.0% of cases [1]. In Sudan, over 85.0% of the population are at high risk of malaria, with over 1.7 million malaria cases and 1,663 malaria-related deaths being reported in 2019 [1]. The majority of confirmed malaria cases are caused by *Plasmodium falciparum*, either as mono-infection or mixed infection with *P. vivax* [1]. Clinically, falciparum malaria ranges from asymptomatic and uncomplicated to severe and complicated disease [2]. In addition, it can lead to abnormalities in the hematological indices, including those related to red blood cells (RBCs), white blood cells (WBCs) and platelets [3-5].
Hematological abnormalities can contribute to the pathogenesis and complications of the disease [3] and differ according to disease endemicity, nutritional and immune status, co-existence of hemoglobinopathies and demographic factors [6-15]. Therefore, the profile of hematological indices can help physicians to predict malaria consequences and to improve malaria case management in different epidemiological situations [12-15]. Malaria is a leading cause of anemia worldwide and contributes to approximately 25.0% of anemia prevalence in sub-Saharan Africa [16]. Anemia and thrombocytopenia are the two most recognized hematological findings associated with malaria [17, 18]. A few studies have been published on the hematological alterations among Sudanese patients with uncomplicated and complicated malaria [13, 19-22]. A recent study among patients with falciparum malaria in West Kordufan state concluded that antimalarial treatment was effective in reverting abnormal blood counts to normal values two weeks after the completion of treatment, suggesting the need for treating such patients irrespective of malaria parasite positivity [22]. Therefore, the present study compared hematological indices of RBCs, WBCs and platelets between Sudanese malaria-infected patients attending Kosti Teaching Hospital and apparently healthy, malaria-negative individuals.

**Methods**

**Study design, setting and population**

A comparative, cross-sectional study was conducted at the Medical Technology Laboratory Unit of Kosti Teaching Hospital, Sudan, from June to December 2018 to compare hematological indices of RBCs, WBCs and platelets among malaria-infected patients and malaria-negative subjects. Kosti is a major city of the White Nile State at the geographic coordinates 13°10′N 32°40′E. It lies on the western bank of the White Nile to the south of Khartoum, the Capital of Sudan (Fig. 1). A total of 392 participants were recruited in the study (192 patients with *P. falciparum* mono-infection and 200 malaria-negative subjects). Those who did not give written informed consent to participate, suffered from hematological diseases, or were using medicines altering blood picture were excluded from the study. In addition, patients co-infected with other *Plasmodium* species or showing signs and symptoms of complicated or severe malaria were excluded.

**Data and sample collection**

Data were collected using a pre-designed data collection sheet. Blood drops were collected by finger-prick for preparing thick and thin blood films. About 5 ml of venous blood were withdrawn from all participants into pre-labeled EDTA tubes for the measurement of hematological indices.

**Malaria microscopy**

Thick and thin blood films were stained with Giemsa and microscopically examined for malaria parasites according to well-established guidelines [23, 24] at the Parasitology Laboratory of the Medical Laboratory Technology Unit of Kosti Teaching Hospital. Parasite density per µl of blood was estimated by counting...
the asexual stages against 200 WBCs on thick films according to standard procedures and calculations [23, 24].

Measurement of hematological indices

The hematological indices of hemoglobin (Hb) concentration, mean corpuscular volume (MCV), mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC), RBC count, total and differential WBC counts and platelet count were measured using Sysmex XK-21 Hematology Analyzer (Sysmex Corporation, Kobe, Japan) at the Hematology Laboratory of the Medical Laboratory Technology Unit at Kosti Teaching Hospital.

According to the criteria of WHO, anemia was defined as an Hb concentration <11.5 g/dL in children, <12.0 g/dL in non-pregnant women and <13.0 g/dL in men [25]. Thrombocytopenia was defined as a platelet count <150.0 × 10^9/L, while leucopenia was defined as a total WBC count <4.0 × 10^9/L [26].

Data analysis

Data were analyzed using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies and proportions. Non-normally distributed continuous data were expressed as median ± interquartile range (IQR). The median values of hematological indices were compared using the Mann-Whitney U test, and the association between falciparum malaria and hematological cytopenias was tested using the chi-square test. Statistical significance was considered at P-values <0.05.

Results

Characteristics of the study subjects

Table (1) shows that 50.0% and 55.7% of malaria-infected patients were females and older than 30 years, with a median age of 33.0 ± 22.0 years (range: 1–47). On the other hand, 52.0% and 53.0% of malaria-negative subjects were females and aged older than 30 years, with a median age of 31.0 ± 26.0 years (range: 1–67). The median density of P. falciparum was 677.5 600.1 parasites/µl of blood (range: 26–10040). The majority of P. falciparum-infected patients (64.6%) showed a low-level parasitemia, while only 1.0% of patients showed a high-level parasitemia.
Table 1
Characteristics of malaria patients and malaria-negative subjects in Kosti city of the White Nile State, Sudan (2018)

| Characteristics          | \( P. falciparum \)-infected patients (\( N = 192 \)) | Malaria-negative subjects (\( N = 200 \)) |
|--------------------------|-----------------------------------------------------|------------------------------------------|
|                          | \( n (\% ) \)                                      | \( n (\% ) \)                             |
| **Gender**               |                                                    |                                          |
| Male                     | 96 (50.0)                                          | 96 (48.0)                                |
| Female                   | 96 (50.0)                                          | 104 (52.0)                               |
| **Age (years)**          |                                                    |                                          |
| \( \leq 30 \)            | 85 (44.3)                                          | 94 (47.0)                                |
| \( >30 \)                | 107 (55.7)                                         | 106 (53.0)                               |
| Median ± IQR             | 33.0 ± 22.0                                        | 31.0 ± 26.0                              |
| Range                    | 1–47                                               | 1–67                                     |
| **\( P. falciparum \) density (parasites/\( \mu l \))** |                                                    |                                          |
| Median ± IQR             | 677.5 ± 600.1                                      |                                          |
| Range                    | 26–10040                                           |                                          |
| **Parasitaemia level**   |                                                    |                                          |
| Low                      | 124 (64.6)                                         |                                          |
| Moderate                 | 66 (34.4)                                          |                                          |
| High                     | 2 (1)                                              |                                          |

IQR, interquartile range; N/A, not applicable.

Comparison of RBC indices between \( P. falciparum \)-infected patients and malaria-negative individuals

The median indices of Hb concentration, RBC count, MCH and MCHC were significantly lower in \( P. falciparum \)-infected patients compared to malaria-negative individuals. In contrast, MCV was not significantly different between both groups (Table 2).
Table 2

RBC indices in *P. falciparum*-infected patients and malaria-negative subjects in Kosti city of the White Nile State, Sudan (2018)

| Indices         | *P. falciparum*-infected patients (*n* = 192) | Malaria-negative subjects (*n* = 200) | *P* value |
|-----------------|----------------------------------------------|----------------------------------------|-----------|
| **Median ± IQR**|                                              |                                        |           |
| Hb concentration (g/dL) | 11.6 ± 3.8                                | 14.0 ± 2.2                              | <0.001    |
| RBC count (×10^{12}/L) | 4.5 ± 1.0                                | 4.7 ± 0.7                              | 0.001     |
| MCV (fL)         | 86.0 ± 12.0                               | 87.0 ± 9.8                              | 0.452     |
| MCH (pg)         | 28.5 ± 3.0                                | 29.0 ± 2.8                              | <0.001    |
| MCHC (g/dL)      | 31.5 ± 3.0                                | 32.5 ± 2.5                              | 0.037     |

IQR, interquartile range; Hb, hemoglobin; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

**Comparison of WBC and platelet indices between *P. falciparum*-infected patients and malaria-negative individuals**

The median total WBC count was higher in *P. falciparum*-infected patients compared to malaria-negative individuals, but the difference was not statistically significant. The median percentages of neutrophils and lymphocytes were significantly lower in *P. falciparum*-infected patients. Meanwhile, the median platelet count was significantly lower in *P. falciparum*-infected patients compared to malaria-negative individuals (Table 3).
Table 3

WBC and platelet indices in *P. falciparum*-infected patients and malaria-negative subjects in Kosti city of the White Nile State, Sudan (2018)

| Indices                | *P. falciparum*-infected patients (n = 192) | Malaria-negative subjects (n = 200) | p-value |
|------------------------|---------------------------------------------|-------------------------------------|---------|
| **Median ± IQR**       |                                             |                                     |         |
| Total WBC count (×10^9/L) | 7.0 ± 4.0                                  | 6.5 ± 3.0                           | 0.275   |
| Neutrophil count (%)   | 37.0 ± 11.0                                 | 38.0 ± 8.0                          | 0.001   |
| Lymphocyte count (%)   | 24.0 ± 12.0                                 | 26.0 ± 18.0                         | 0.004   |
| Monocyte count (%)     | 5.0 ± 2.0                                   | 5.0 ± 2.0                           | 0.021   |
| Platelet count (×10^9/L)| 140.0 ± 38.0                               | 230.0 ± 115.0                       | <0.001  |

WBC, white blood cell; IQR, interquartile range.

**Comparison of hematological cytopenias between *P. falciparum*-infected patients and malaria-negative subjects**

The prevalence of anemia was significantly higher among patients infected with *P. falciparum* compared to malaria-negative subjects (60.4% vs. 29.5%, respectively), where *P. falciparum*-infected patients were 3.6-fold more likely to have anemia. Meanwhile, the prevalence of thrombocytopenia was significantly higher among patients infected with *P. falciparum* compared to malaria-negative subjects (72.4% vs. 5.0%, respectively), where *P. falciparum*-infected patients were approximately 50-fold more likely to be thrombocytopenic. In contrast, there was no statistically significant difference between both groups regarding leucopenia (Table 4).

Table 4

Hematological cytopenias among patients with falciparum malaria and malaria-negative subjects in Kosti city of the White Nile State, Sudan (2018)

| Hematological abnormality | *P. falciparum*-infected patients (N = 192) | Malaria-negative subjects (N = 200) | OR (95% CI) | p-value |
|---------------------------|---------------------------------------------|-------------------------------------|-------------|---------|
|                           | n (%)                                       | n (%)                               |             |         |
| Anemia                    | 116 (60.4)                                  | 59 (29.5)                           | 3.6 (2.4–5.5) | <0.001  |
| Thrombocytopenia          | 139 (72.4)                                  | 10 (5.0)                            | 49.8 (24.5–101.4) | <0.001  |
| Leucopenia                | 24 (12.5)                                   | 22 (11.6)                           | 0.9 (0.5–1.6) | 0.754   |
Discussion

Sudan is the most afflicted country with malaria in the Eastern Mediterranean, accounting for approximately 46% of cases in the region with a predominance of *P. falciparum* [1]. This study revealed that the majority of patients infected with *P. falciparum* in Kosti city had low-level parasitemia. Although hematological indices in *P. falciparum*-infected patients can provide clues to the associated hematological abnormalities, no published study was found among patients from Kosti. In the present study, *P. falciparum*-infected patients showed significantly lower median values of Hb, RBC count, MCH, MCHC, neutrophils, lymphocytes and platelets compared to malaria-negative counterparts. In line with the present study, a significantly lower median platelet count was found among Sudanese children with falciparum malaria compared to malaria-negative ones [13]. In contrast, a significantly higher median WBC count and non-significant differences between the median values of Hb and RBC count were observed in infected children [13]. The significantly lower values of hematological indices among *P. falciparum*-infected patients in Kosti city are consistent with those reported in malaria-endemic areas elsewhere [9, 27-31].

Substantial proportions of patients with falciparum malaria and malaria-negative subjects in Kosti city were anemic. However, the majority of *P. falciparum*-infected patients (60.4%) were anemic compared to less than a third of malaria-negative subjects, with a significant association between falciparum malaria and anemia. In contrast, anemia was reported among approximately 21.0% of patients and was not significantly associated with falciparum malaria in West Kordufan state [22]. In agreement with the present findings, a slightly higher anemia prevalence of 67.0% with a significant association with malaria was reported among Ethiopian patients [9]. Malaria-associated anemia is multi-factorial and could be attributed, among other factors, to mechanical or autoimmune hemolysis, splenic sequestration of infected and non-infected RBCs and suppressed erythropoiesis following cytokine release [18, 32-34].

Thrombocytopenia has been assumed to occur in *P. falciparum*-infected patients irrespective of exposure frequency or disease severity [35]. In line with this assumption, more than two-thirds of *P. falciparum*-infected patients in Kosti were thrombocytopenic. Thrombocytopenia was a significant predictor of falciparum malaria, which is consistent with that recently reported for patients with falciparum malaria in West Kordufan, even though a lower thrombocytopenia prevalence of 21.3% (75/353) was found [22]. In another context, malaria-positive blood donors were found to have significantly higher platelet counts than malaria-negative ones in Khartoum [36]. The significantly lower platelet count among patients in the present study is consistent with the findings reported among patients in other malaria-endemic countries [8, 9, 28-31]. The inclusion of thrombocytopenia as a criterion for the re-definition of severe malaria has been proposed [37]. Likewise, a recent study among Sudanese children in Gezira state recommended thrombocytopenia as a prognostic tool for assessing falciparum malaria severity [38]. In Khartoum state, the prevalence of thrombocytopenia was significantly higher among children with severe malaria compared to those with uncomplicated malaria [39]. Several factors contribute to malaria-related
thrombocytopenia, including platelet agglutination at early stages of the disease, splenic sequestration and pooling of platelets and immune-mediated destruction [17, 40, 41].

The present study revealed normal total WBC counts among *P. falciparum*-infected and malaria-negative subjects, with comparable and non-significantly different proportions of leucopenia. Nevertheless, the prevalence of leucopenia among patients in the present study is higher than that (6.3%) reported from West Kordufan [22]. The lack of association between falciparum malaria and thrombocytopenia among patients from Kosti city disagrees with the significant association reported for patients from West Kordufan [22]. Despite the significant differences in the median percentages of differential WBC counts between the infected and non-infected populations, these were within normal ranges. This makes the total and differential WBC counts not useful in predicting falciparum malaria in the study area and could be partially attributed to the low parasitemia and uncomplicated nature of falciparum malaria among the study participants. Low-to-normal WBC counts in malaria patients is a frequent observation that could also be explained by their localization outside the peripheral blood [42]. Therefore, the mobilization of WBCs could not be ruled out in case of severe falciparum malaria.

This study is limited by the fact that it was hospital-based, and the hematological findings might not reflect the situation at the population level. However, it provides information that can guide clinical predictions about malaria of low-level parasitemia among patients with abnormal hematological indices in the study area. With the lack of previous studies, this could be a pilot one that warrants further community-based assessment of the profile of hematological indices and abnormalities in falciparum-infected patients in relation to malaria exposure frequency and severity.

**Conclusions**

Most falciparum malaria infections among patients in Kosti city of the White Nile State – Sudan are of low-level parasitemia. Nevertheless, falciparum malaria is significantly associated with anemia and thrombocytopenia with lower median values of Hb, RBC count, MCH, MCHC and platelet count in *P. falciparum*-infected patients than malaria-negative subjects. In contrast, leucopenia is not useful to predict falciparum malaria. Further large-scale studies in community and healthcare settings and inclusion of patients with complicated or severe malaria and those with high parasite densities are recommended.

**Declarations**

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**Authors’ contributions**
AMEE, AGTN, NEE, MMA and EAB conceived, designed and supervised the study as well as wrote the initial draft. AMEE and RA wrote the final draft of the manuscript and provided logistic support. AK, FAD and OAMA contributed to data collection and laboratory investigations. All authors critically read, revised and approved the final draft of manuscript submitted to the journal.

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**Availability of data and materials**

Data are available when requested by email.

**Ethics and consent to participate**

The study protocol was approved by the Research Ethics Committee of the Faculty of Medical Laboratory Sciences, El Imam El Mahdi University, Sudan. Written informed consent was obtained from all participants or their guardians/ legal representatives before data and sample collection.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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