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RESEARCH ARTICLE

Platelet distribution width, mean platelet volume and haematological parameters in patients with uncomplicated *plasmodium falciparum* and *P. vivax* malaria [version 1; referees: 1 approved, 2 approved with reservations]

Elrazi A. Ali[1], Tajeldin M. Abdalla[2], Ishag Adam [iD] [1]

[1]Faculty of Medicine, University of Khartoum, Khartoum, Sudan
[2]Faculty of Medicine, Kassala University, Kassala, Sudan

Abstract

Background: The association between the haematological profile (including abnormal platelets) and malaria is not completely understood. There are few published data on haematological profiles of malaria patients in areas with unstable malaria transmission. The current study was conducted to investigate if the haematological parameters, including platelet indices, were reliable predictors for microscopically-diagnosed malaria infection.

Methods: A case-control study with a total of 324 participants (162 in each arm) was conducted at the out-patient clinic of New Halfa hospital during the rainy and post rainy season (August 2014 through to January 2015). The cases were patients with uncomplicated *Plasmodium falciparum* (107; 66.9%) and *P. vivax* malaria (55, 34.0%) infections. The controls were aparasitemic individuals. The haematological parameters were investigated using an automated hemo-analyser.

Results: There was no significant difference in the mean (±SD) age between the study groups; however, compared to the controls, patients with uncomplicated malaria had significantly lower haemoglobin, leucocyte and platelet counts, and significantly higher red cell distribution width (RDW), platelet distribution width (PDW) and mean platelet volume (MPV).

Conclusions: The study revealed that among the haematological indices, PDW and MPV were the main predictors for uncomplicated *P. falciparum* and P. *vivax* malaria infection.

Abbreviations: OR: odds ratio.

Open Peer Review

Referee Status: ✓ ? ?

	Invited Referees		
	1	**2**	**3**
version 1 published 12 Jun 2017	✓ report	? report	? report

1 **Con J.F. Fontes** [iD] , Hospital Universitário Júlio Müller, Rua Prof Luiz Phelippe Pereira Leite s/n Alvorada, Brazil

2 **Alberto Tobón-Castaño** [iD] , University of Antioquia, Colombia

3 **Walter R.J. Taylor**, Mahidol Oxford Tropical Medicine Research Unit, Thailand

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Corresponding author: Ishag Adam (ishagadam@hotmail.com)

Author roles: A. Ali E: Conceptualization, Investigation, Writing – Original Draft Preparation; **M. Abdalla T**: Conceptualization, Data Curation, Investigation, Writing – Original Draft Preparation; **Adam I**: Conceptualization, Data Curation, Writing – Original Draft Preparation

Introduction

In spite of the preventative measures, malaria remains a major public health concern. Malaria is responsible for 781,000 deaths in a year, the majority of which are in Sub -Saharan Africa[1]. A correct diagnosis is one of the most important tools in the management of malaria. It has been recommended that all persons with suspected malaria should have a parasitological confirmation of diagnosis[1]. Microscopic examination of malaria consists of the identification of parasite species in thin and/or thick blood films, which is the "gold standard" for malaria diagnosis[1,2]. Microscopy requires trained technicians, and well-maintained microscopes with a perfect quality management system. However, acceptable microscopy services are not widely available for the diagnosis of malaria in some areas where malaria is endemic e.g. in communities in Sub-Saharan Africa[1].

Previously, measurement of haematological blood parameters was unreliable due to intra and inter-method variation. Nowadays, automated analysers have replaced the traditional methods. Automated analysers are available in most settings and can give reliable results within a short period of time. There is a universal trend toward using these to aid the presumptive diagnosis of malaria infection[2,3].

Previous studies have reported different results levels of sensitivity and specificity of haematological parameters as predictors of malaria infection[4–8]. There is no published data on haematological changes in patients infected with malaria parasites in Sudan, where malaria in the major health problem[9]. The current study was conducted in New Halfa, eastern Sudan to investigate the haematological changes observed during malaria infection and to assess the reliability of the haematological parameters used for diagnosis.

Methods

A case-control study was conducted at the out-patient clinic of New Halfa hospital during the rainy and post rainy season (August 2014 through to January 2015). The cases were patients with symptoms and signs of uncomplicated malaria and who were confirmed to be infected with *P. falciparum or P. vivax* by microscopic examination of Giemsa stained blood smears during the study[10]. The controls were the patients that presented to the same clinic with symptoms of malaria but were found to have negative blood films for malaria. After the participants (or their parents/legal guardians if they were minors) provided written informed consent, a clinical history was gathered using questionnaires. Weight and height were measured and body mass index was expressed as kg/m².

2ml of blood was taken from each participant and placed in a container with EDTA, and a complete hemogram was performed using an automated hematology analyser (Sysmex XN-9000; Hyogo, Japan), following the manufacturers' instructions as previously described[11–13]. The hemogram included measuring the haemoglobin level, leucocyte count and platelet indices, namely platelet count, mean platelet volume (MPV), and platelet distribution width (PDW).

Thick and thin blood films were prepared and stained with 10% Giemsa to microscopically confirm which participants were infected. If the slide was positive, the parasite density was measured by counting the number of asexual parasites per 200 leukocytes, and multiplied against the participants own leucocytes number/μL. The blood films were considered negative if no parasites were detected in 100 oil immersion fields of a thick blood film.

Statistical analysis

A minimum sample size of 162 participants for each arm of the study was calculated assuming that 10% of participants would have incomplete data. In this way, it would be possible to calculate a significant difference (at α = 0.05) in the means of the proposed variables - mainly haemoglobin, red cell distribution width (RDW), leucocytes, platelets counts and PDW - between the cases and the controls, at 80% power.

Statistical analysis was performed using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). Proportions of the studied groups were expressed as percentages and compared using the chi-squared test. Continuous data were checked for normality using the Shapiro-Wilk test. The means (±SD) or median (IQR) were used to describe the studied variables, depending if they were normally or non-normally distributed. The t-test (or Mann-Whitney U test if the data were not normally distributed) evaluated the differences between the studied groups. Binary regression was calculated, where malaria was the dependent variable and medical and haematological indices were the independent variables. Diagnostic screening tests were used to determine the diagnostic cut-offs of various parameters (based on test sensitivity and specificity) using the receiver operating characteristic (ROC) curve. $P < 0.05$ was considered statistically significant.

Results

107 (66.9%) and 55 (34.0%) of the uncomplicated malaria cases were infected with *P. falciparum* and *P vivax*, respectively. There was no significant difference in the age or BMI between the cases and the controls. Patients had significantly higher body temperature than the controls (Table 1). Their ages ranged between 1.1−55 years

Table 1. Comparing the mean (±SD) age, BMI and body temperature between patients with malaria and negative controls.

Variables	Patients with malaria (n=162)	Controls (n=162)	P-value
Age, years	20.7(19.6)	20.0 (19.0)	0.738
Body mass index, kg/m²	19.8(6.2)	19.9(14.3)	0.947
Temperature	38.0 (0.9)	37.6(1.0)	0.002

in the cases and 1.1–42 years in the controls. Around one third of the cases (53, 32.7%) and one third of the controls (49, 30.2%) were children that were under five years old (p=0.665). There were 81 (50.0%) vs. 79 (48.8%) males in the cases and controls, respectively (p=0.912).

Compared with the controls, patients with uncomplicated malaria had significantly lower haemoglobin levels and lower leucocyte, lymphocyte, neutrophil, and platelet counts, but significantly higher RDW, PDW and MPV (Table 2).

A receiver operating characteristic (ROC) curve was used to determine the cut-offs for haemoglobin levels, RDW, leucocytes and platelet counts, PDW and MPV for prediction of malaria infection. The area under the ROC curve is shown in Table 3 and Figure 1, which failed to confirm predictability of hemoglobin, RDW, leucocytes and platelet count. Poor and fair predictability of PDW and MPV for malaria infection was demonstrated; the areas under the curves were 0.637 and 0.726, respectively.

When the cut-off levels were evaluated using binary regression analysis, PDW ≥14.550 % (OR =2.9, 95% CI =1.64–5.43, P < 0.001) and MPV≥ 9.05fL (OR =2.25, 95% CI =1.12–4.51, P < 0.001) were the most important predictors for malaria infection, (Table 4).

There was no significant difference in the hemoglobin, leucocytes, lymphocytes, neutrophils, platelets counts, RDW, PDW, MPV and the parasite count (P=0.201) when the cases of *P. falciparum* and *P. vivax* were compared (Table 5).

> **Dataset 1. Raw data collected as the basis for this study**
>
> http://dx.doi.org/10.5256/f1000research.11767.d164010
>
> Plasmf = Blood film for *P. falciparum*.

Discussion

According to our present findings, PDW and MPV are the two most important haematological predictors of *P. falciparum* and *P. vivax* malaria infection. This is in line with a recent finding

Table 2. Comparing the median (IQR) of the blood parameters measured in patients with and without malaria. Data is displayed as mean (±SD), and the t-test was used because the data was normally distributed.

Variables	Patients with malaria (n=162)	Controls (n=162)	P-value
Hemoglobin, g/dl*	9.3(2.3)	10.2 (2.0)	0.003
Red cell distribution width,%	16.0(14.2–19.1)	15.1 (13.6–18.3)	0.034
Leucocytes, X10³/mm³	6.5(5.2–8.4)	8.2 (5.65–10.37)	0.009
Lymphocytes, X10³/mm³	2.448 (1.668–3.501)	2.53 (1.70–4.03)	0.041
Neutrophils, X10³/mm³	3.209(2.185–4.686)	4.64 (2.77–6.31)	0.003
Platelet count, X10³/mm³	121.(78.0–186.5)	280.0 (227.0–350.0)	< 0.001
Platelets distribution width, %	14.7(14.4–15.0)	14.5 (14.3–14.8)	0.003
Mean platelet volume, fL	9.6(9.2–10.0)	8.8 (8.5–9.4)	< 0.001

Table 3. The reliability of haematological indices in predicting malaria.

Variable	Area under the curve	P-value	Sensitivity	Specificity	Cut-off
Hemoglobin, g/dl*	0.365	0.001			
Red cell distribution width, %	0.587	0.039			
Leucocytes, X10³/mm³	0.396	0.014			
Platelet count, X10³/mm³	0.143	< 0.001			
Platelets distribution width, %*	0.637	0.001	72.8	56.8	14.550
Mean platelet volume, fL*	0.726	0.000	77.2	60.1	9.05

Key:

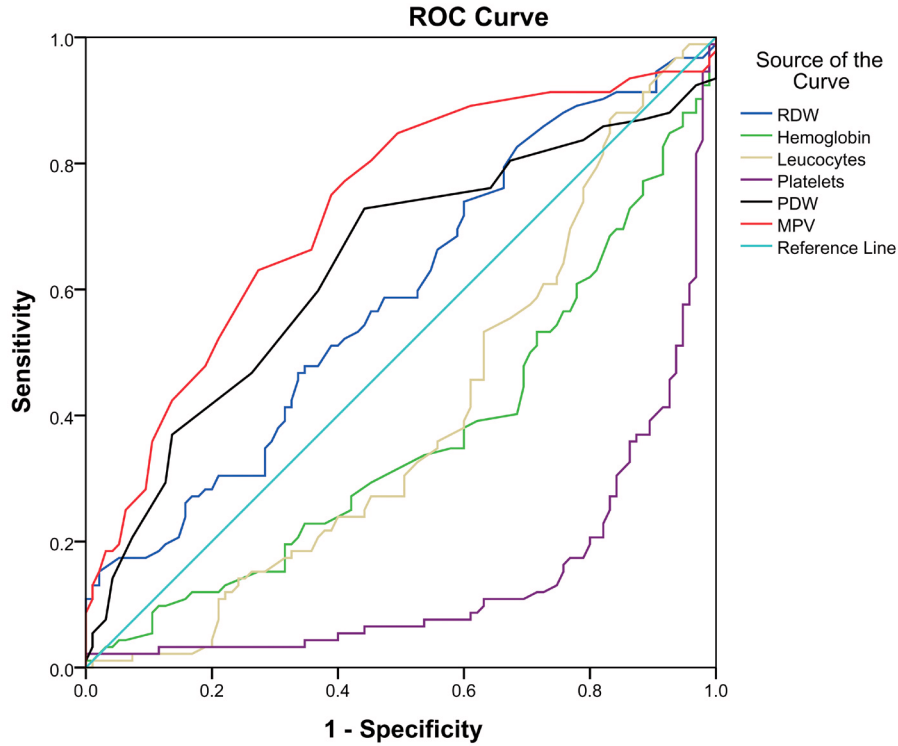*: These were considered because of fair predictability of the area under the curve

Figure 1. Receiver operating characteristic (ROC) curve and the associated reliability of blood parameters in predicting malaria in eastern Sudan.

Table 4. Binary logistic regression analysis of the factors associated with *P. falciparum* and *P. vivax* malaria in eastern Sudan. OR: odds ratio.

Variable	OR	95% CI	P-value
Age	0.99	0.93–1.06	0.986
Male gender	0.93	0.39–2.19	0.870
Body mass index	1.09	0.94–1.26	0.222
Temperature	1.33	0.87–2.03	0.185
Hemoglobin	0.90	0.72–1.13	0.382
Red cell distribution width	1.16	0.99–1.36	0.054
Leucocytes	0.96	0.84–1.10	0.605
Platelets count	0.98	0.98–0.99	0.000
Platelets distribution width ≥14.550 %	2.9	1.64–5.43	< 0.001
Mean platelets volume ≥ 9.05fL	2.25	1.12–4.51	< 0.001

Table 5. Comparing the median (IQR) blood parameters in patients with *P. falciparum* and *P. vivax* malaria. Data is displayed as mean (±SD), and the t-test was used because the data was normally distributed.

Variables	Patients with *P. falciparum* malaria (n=107)	Patients with *P. vivax* malaria (n=55)	P
Hemoglobin, g/dl*	9.3(2.3)	10.2 (2.0)	0.003
Red cell distribution width,%	15.5 (14.1–19.0)	17.1(14.1–19.8)	0.225
Leucocytes , X10³/mm³	6.5 (5.1–8.1)	6. 4 (5.1–9.5)	0.504
Lymphocytes, X10³/mm³	2.454 (1.654–3.373)	2.43 (1.82–3.95)	0.677
Neutrophils, X10³/mm³	3.090 (1.958–4.389)	3.27 (2.38–5.31)	0.641
Platelet count, X10³/mm³	115.0 (70.5–183.5)	133.5 (98.7–205.7)	0.168
Platelets distribution width, %	14.8 (14.5–15.0)	14.6 (14.2–14.9)	0.186
Mean platelets volume, fL	9.7 (9.1–10.1)	9.4(9.1–9.9)	0.366

where Al-Salahy *et al.* reported that patients in Hajjah, Northwest Yemen with malaria parasitemia had significantly lower hemoglobin, hematocrit, leucocytes, lymphocytes, and platelet counts compared to healthy subjects[14]. Previous studies have shown that patients with complicated malaria had reduced haematological parameters such as platelet, leucocyte, and RBC counts, which provided relatively good predictors for the diagnosis of malaria

infection[8,15]. On the other hand, the significant differences observed in the haematological parameters between parasitemic Ugandan patients and non-parasitemic Ugandans were only observed in the monocyte and the platelet count[16]. No significant difference was found between the haemoglobin levels, MCV, MCH, neutrophils, lymphocyte counts or MPV[16].

In the current study, a PDW ≥14.550% and MPV ≥ 9.05fL were the main predictors for malaria (OR =2.9 and 2.3). Previous studies have reported an increased MPV level in malaria[15,17]. Interestingly, Chandra *et al* reported that an MPV > 8 fL had a sensitivity and specificity of 70.8% and 50.4% for the diagnosis of malaria, respectively[8].

The higher PDW and MPV values in malaria could be explained by bone marrow formation of megakaryocytes to compensate for the low absolute platelet count during acute malaria infection[8,15]. A significantly higher level of the key platelet growth factor (thrombopoietin) has been reported in patients with malaria[18]. Furthermore, the parasitized RBCs could increase in platelet sensitivity to adenosine diphosphate (ADP), prompting secretion of dense granules[19,20].

Nutritional deficiency and haemoglobinopathies were not investigated in the current study and have to be mentioned as study limitations. Haematological parameters formalaria-infested blood may vary depending on the level of malaria endemicity, presence of haemoglobinopathies and nutritional status[21,22]. Another limitation of the is that we relied on microscopy only for the malaria diagnosis. Some of negative controls may have had undetected parasitemia (submicroscopic parasitemia). We have previously observed that the majority of febrile patients who were parasite negative by microscopy had *P. falciparum* infection according to PCR results[23]. Lastly, other infections that might have an effect on blood parameters were not ruled out in both the cases and controls. In conclusion, the study revealed that a PDW ≥14.550% and MPV ≥ 9.05fL were the main predictors for uncomplicated *P. falciparum* and *P. vivax* malaria infection.

Data availability

Dataset 1: Raw data collected as the basis for this study. Plasmf = Blood film for *P. falciparum*. DOI, 10.5256/f1000research.11767. d164010[24]

Consent

The study was approved by the Institutional Review Board of the Medical College, University of Khartoum (3# 2015 1114).

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Data Source

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Current Referee Status: ✔ ? ?

Version 1

Referee Report 31 July 2017

? **Walter R.J. Taylor**

Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand

This is a nice academic paper that deals with haematological parameters in malaria. Using a case control approach, the authors have identified a mean platelet distribution width and mean platelet volume as possible markers of acute symptomatic malaria in their setting.

This is interesting but of limited practical application. Therefore, this paper should emphasise the academic aspects of their findings.

I think this paper can be accepted but with major revisions in two areas, in particular.

Sample size calculation – this has been determined using continuous variables yet we do not see any examples. This must be addressed.

Discussion – this should be more thorough comparing and contrasting the current data with previously published data. Moreover, readers will want to know important causes of increased RDW, PDW and MPV and where in haematological practice these parameters play an important role.

The authors should let us know if their research has led to any new research questions and future avenues of research.

Minor comments
- The number of malaria related deaths are higher than those reported by the WHO. The authors should obtain the latest data.

- No mention of the role of malaria rapid diagnostic tests

- The second line of the Discussion does not follow. Did the Yemeni study report PDW and MPV ?

- Page 6 left hand column penultimate paragraph:

  Remove 'in' in this sentence:
  Furthermore, the parasitized RBCs could increase in platelet sensitivity to adenosine diphosphate (ADP), prompting secretion of dense granules.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Malaria and tropical medicine

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Referee Report 11 July 2017

? **Alberto Tobón-Castaño** (iD)

Malaria Group, Faculty of Medicine, University of Antioquia, Medellín, Colombia

1. The objective of the study should be re-examined in the introduction. The terms "reliability" and "validity" should be differentiated. Reliability refers to the degree to which the measurement procedure can be reproduced.

2. Thus, if the objective is to study the validity of the hematological parameters to make a diagnosis, the methodology must be revised since these studies require a sample size that considers the prevalence and the expected sensitivity. Since this is a case-control study the objective should be consistent with this methodology.

3. It must be specified what a case is; What are the signs and symptoms of uncomplicated malaria?

4. It should be explained why 100 oil inmmersion fields were used as criteria to consider a thick blood film as negative. This does not correspond to international recommendations.

5. The calculation of the sample should be presented with the elements of a case-control study i.e. case-control relation, expected O.R., frequency of outcomes in exposed and unexposed.

6. RESULTS. If the clinical history is available, the time of evolution of the disease could be compared, which may lead to differences in hematological profiles.

7. The results presented in the Tables 2 and 5 are confusing. It is not clear whether the averages or medians are compared and what was the statistical test of comparison. It is not explicitly stated which variables presented normal distribution.

8. The presumptive diagnosis of malaria with haematological analyzers does not seem to be the appropriate way of solving malaria diagnosis problems in endemic areas. In this sense, it is not clear whether the study intends to contribute to the malaria diagnosis using a method that would be non-specific.

The study contributes to show hematological differences between cases and controls and this should serve to identify early lesions, but clearly is no a useful method for malaria diagnosis.

There is no relevant discussion about the findings. The reference values of the hematological parameters according to age and sex are not presented; the comparisons must take into account this variation.

Some aspects related to platelet changes are analyzed but superficially. Leukocyte count and cell line analysis are neglected; no mention is made of the significance of alterations, monocytes and eosinophils are neglected. There are no correlations with parasitemias which is also a variable that can contribute significantly to the hematological alterations as a function of the greater or lesser inflammatory response.

REFERENCES.
Reference 1. Who are the authors?
Ref 6 and 8 are the same.
Ref. 16. The titlle is incomplete? The journal name?

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Referee Expertise: Malaria, clinical and epidemiological studies

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Referee Report 07 July 2017

Con J.F. Fontes (iD)

Laboratório de Malária, Hospital Universitário Júlio Müller, Rua Prof Luiz Phelippe Pereira Leite s/n
Alvorada, Cuiabá, Brazil

Mr Ali and colleagues present a study that revealed the mean platelet volume and
platelet distribution width as good parameters to predict uncomplicated malaria parasite infection.The manuscript is well written and presented. The analysis of the results is adequate and correct. Some minor points should be reviewed:

1. As the authors used several statistical tests to compare the results between cases and controls, it is important to make these tests explicit for each p-value presented in the tables, as a footnote.

2. The title of Table 5 is not clear. In fact, Table 5 compares means (SD), and non-median (IQR).

3. In the last paragraph of the Discussion section the sentence "...parameters formalaria-infested blood..." should be changed by "... for malaria-infected blood...".

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.