**Correlation between Thrombocytopenia and Anaemia in *Plasmodium falciparum* malaria among patients in Kisumu County-Western Kenya**

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**Summary**

**Background: Malaria is associated with haematological complications which may be avoided by early diagnosis and treatment. Microscopic diagnosis showing presence of malarial parasites is needed for confirmation which requires technical expertise. The study was therefore carried out determine the correlation between thrombocytopenia and anaemia in *P.falciparum* malaria.**

**Methods: The study was conducted in Kisumu County-Kenya which is a highly endemic malaria region. Both thick and thin blood smears were used to determine *P. falciparum* infection status in a total of 228 patients presenting with acute febrile illness. All participants' demographics and Haematological parameters i.e. Haemoglobin level, platelet count, Mean platelet volume and platelet distribution width were analysed.**

**Results: Haemoglobin and platelet count were significantly lower in the malaria infected group ($p<0.001$ in both cases). Conversely, mean platelet volume and platelet distribution width were higher in comparison to non-infected group ($p<0.001$). Severe to moderate anaemia was present in 78 %( n=122) of malaria infected patients against 47 %( n=33) of the non-infected group. Thrombocytopenia was present in 87 %( n=137) of the infected patients against 10 % (n=7) of the non-infected group. There was a positive correlation between anaemia and thrombocytopenia in malaria($r= 0.26$, $p<0.001$).**

**Conclusion: Low platelet count and Haemoglobin levels positively correlate and are important predictors of *P .falciparum* malaria. This could to avoid performing unnecessary expensive tests to rule out other febrile conditions. The above findings also have therapeutic implications of avoiding unnecessary platelet infusion in malaria.**

**Key words:** thrombocytopenia, pseudo-thrombocytopenia, anaemia and haemoglobin.

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## Introduction

In 2013, 97 countries had ongoing malaria transmission. An estimated 3.4 billion people are at risk of malaria, of which 1.2 billion are at high risk. In high-risk areas, more than one malaria case occurs per 1000 population [1]. In 2012, malaria killed an estimated 482 000 children under five years of age in sub-Saharan Africa. This translates to one child almost every minute [1]. There were an estimated 207 million cases of malaria in 2012 (uncertainty range: 135 – 287 million) and an estimated 627 000 deaths (uncertainty range: 473 000 – 789 000) of which 90% of all malaria deaths occur in sub-Saharan [1].

Malaria infection is associated with various haematological abnormalities including anaemia and thrombocytopenia ([1]. The possible pathogenesis of the hematological abnormalities may be parasite, products-cell-derived cytokines, macrophage activation, macrophage-derived factors such as tumour necrosis factor-α, and macrophage functional abnormalities dysfunction [2]. Platelets play a critical role in the pathogenesis of malaria by causing sequestration of infected red blood cells [2]. Platelets attach malarial-infected red cells and kill the parasite within; indicating a protective function of platelets in the early stages of erythrocyte infection distinct from their role in cerebral malaria [3].

Thrombocytopenia is a haematological disorder referring to the reduction in the number of platelets in the peripheral blood to below the reference range. The normal platelet count in adult is between 150 x $10^9$/ L and 400x$10^9$/L. Severe thrombocytopenia results in excessive bleeding when a minor injury occurs to a blood vessel.

The mechanism behind thrombocytopenia during malaria infection, however, remains unclear. Both immunological as well as non-immunological destruction of platelets have been implicated [4]. The aim of this study was to determine the frequency and severity of abnormal Hb and platelet parameters and to identify their significance in malaria patients in Kisumu County. The study was also to determine the relevance of these haematological parameters as an early diagnostic tool in malaria and how the two variables correlate.

## Materials and Methods

The study was approved by Jaramogi Oginga Odinga Teaching and Referral Hospital Scientific and Ethics Review Committee (ACCREDITATION NO.01713). An informed, written and voluntary consent was sought from the adult patients and parents/guardians of children before obtaining blood samples for malaria test and complete blood count. The consent included strict confidentiality of the information generated during the study and their use for research.

**Study Site**. This research work was carried out at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) which is located within the headquarters of Kisumu County in Kenya. The laboratory analyses of clinical specimens were done at the three major laboratories of this hospital namely: Obama (Paediatric laboratory), main laboratory and casualty laboratory.

**Study Population**. Both in-patients and out patients with history of acute febrile illness (temperature above 37°C) attending the health facility from the month of August 2013 to April 2014. Those who turned positive upon the demonstration of the asexual forms of *P.*

*falciparum* through microscopic examination of their thick and thin blood films formed the study population.

Patients with history of acute febrile illness and confirmed negative upon microscopic examination of thick and thin smears attending this health facility from the month of August 2013 to April 2014 were included in the study as control population.

**Inclusion criteria:** Naive patients of both sexes, 3 months and above of who presented with acute febrile illness and found to have a positive or negative slide for malaria upon microscopic examination of either thick or thin smear of peripheral blood smears. Patients were relatively clinically stable, willing and able to sign the consent form.

**Exclusion Criteria.** Patients with acute febrile illness and positive or negative for malaria parasite on peripheral blood examination but with cases of cerebral malaria (rare in holoendemic area) or prior hospitalization were not included in the study. Patients with known history of haematological disorders, immunosuppression, co-infection with bacterial, viral infections or HIV positive individuals as well as those unwilling to participate in the study and unable to sign the consent form were excluded.

The investigations were performed on both capillary and venous blood sample drawn into EDTA tubes for preparation of the thick and thin smears for malaria parasites and automated determination of Complete Blood Counts (CBCs). Blood counts were performed using ACT5 Diff Haematology Analyzer (Beckman Coulter Inc, Miami, Florida, USA) as per local SOPs within 1 hour.

Daily Quality Assurance checks were performed and recorded. Commercial controls were used in accordance with manufacturer's recommendations for the blood counts. The Analyzer provided data on WBCs, RBCs, haemoglobin level, platelet counts, Mean platelet volume, platelet distribution width, (PDW) red cell distribution width (RDW) and five part differentials. The Analyzer also detected and flagged platelet aggregation and cold agglutinins based on the particle size using a 256-channel pulse-height analyzer of platelet histogram region. Since sickle cell disease affects the Hb levels, Sickling test was done to demonstrate haemoglobin S and those found positive were excluded in the study.

Two blood slides both thick and thin were prepared and stained with Giemsa, alongside control slides i.e. both negative and positive controls. One thick and one thin slide from each study participant were examined independently by the Medical Laboratory Scientist and another set of a thick and thin slide was counter checked by one of the Laboratory Scientist. A semi-quantitative assessment of parasitaemia was performed according to the WHO standard of reporting (see laboratory procedures).

**Evaluation of thrombocytopenia**

Patients with thrombocytopenia were graded into three categories i.e.

(i) Mild thrombocytopenia $<150X10^9/L$ but $>50X10^9/L$

(ii) Moderate thrombocytopenia$<50x10^9/L$ but $> 20X10^9/L$

(iii) Severe thrombocytopenia $< 20x10^9/L$.

**Evaluation of anaemia**

The degree of anaemia was evaluated through blood haemoglobin (Hb) quantification and analysis. The following parameters were used:

(i) Male adult individuals were considered anaemic when the Hb level was less than or equal to 13 g/dl of blood.

(ii) Adult women, adolescents, and children (more than 2 years of age) of both sexes were considered anaemic when the Hb level was less than or equal to 12 g/dl of blood.

**Classification of various Degrees of Anaemia**

Anaemia was classified as:

(i) Mild Anaemia when the Hb level was between 10 and 12 or 13 g/dl of blood depending on the sex and on the age.

(ii) Moderate Anaemia when the Hb level was equal to or above 7 and below 10 g/dl. And

(iii) Severe Anaemia when the Hb level was lower than 7 g/dl.

To exclude eventual cases of anaemia associated with sickle cell disease, sickling test was performed for all studied individuals below 15 years of age.

**Laboratory procedures**

Complete blood count was done for all the patients using ACT5 Diff Haematology Analyzer (Beckman Coulter Inc, Miami, Florida, USA) as per manufacturer's instructions. Thick and thin smears were made for identification and speciation of malaria parasite species respectively. The slides were stained with 10% Giemsa (Sigma-Aldrich, Germany), alongside quality control slides and examined using oil immersion objective. Thin smears were examined in the ideal area of thickness for trophozoites, gametocytes and schizonts and graded according to the WHO.

**Blood collection for automated count:**

**Capillary blood in children:** Pre-cleaned slides were labelled (preferably at the frosted-end) with the patient's name (or other identifier), date and time of collection. The site was cleaned well with 70% alcohol and allowed to air dry. A deep prick was made at the side of the pulp of the 3rd or 4th finger and the first drop of blood wiped away with clean gauze and squeezed to obtain a free flow of capillary blood into 1.5 ml EDTA vacutainer tube (BD and Company, WJ 07417 USA). A clean dry swab was applied to prevent excessive bleeding as the content of vacutainer tube was properly mixed to prevent clotting.

**Venous blood in adults:** Venous blood was obtained from the median cubital vein as per established SOPs. The blood was transferred to a 5mls EDTA vacutainer tube and mixed thoroughly to prevent clotting.

**Automated Complete Blood count:** Automated blood count was preceded by mixing of anticoagulated whole blood in a mixer. The patients' details e.g. name, lab number, age and sex were fed manually through the touch screen monitor of coulter counter followed by putting the vacutainer tube into the tube holder. This was followed by pressing the run button as the automated counter does the self-priming, sizing, enumeration blood cell and calculation of blood cell indices. The results were automatically displayed on the coulter counter screen and printed on the machines printer.

**Procedure for thick and thin smear:** Both thick and thin smears were made on the same slide. The frosted end of the slide was labelled with the patient number and a drop of blood put next to the frosted end and another smaller drop at the middle of the slide. The first drop was spread using a corner of the spreader in one circular direction to make even thick film, of a 1 cm diameter in size. For the thin film the spreader slide was placed in contact with second drop at an angle and gently pushed backwards to obtain even spread of

blood and pushed gently towards the other end of the slide. The slide was allowed to air dry.

**WHO Grading of Malaria Parasitaemia:** The WHO grades malaria parasitaemia upon examination of slide through battlement method as follows: 1–10 parasites per 100 high power fields (+), 11–100 parasites per 100 high power fields (++), 1–10 parasites per high power field (+++) and >10 parasites per high power field (++++). The three important haematological parameters analysed included Hb level, platelet count and platelet indices i.e. mean platelet volume (MPV) and platelet distribution width (PDW).

**Data analysis:** Statistical analyses were performed using SPSS (Version 17.0) and Graph Pad prism software (Graph Pad software, Inc., San Diego Calif.). Student's t-test with two tailed p values was used to compare normally distributed data. Quantitative comparisons involving unpaired data not conforming to normal distribution were made using Mann–Whitney U test and Kruskal–Wallis test. Correlations between two continuous variables were computed by Spearman's rank correlation.

## Results

**Laboratory, demographic, and clinical, characteristics of the study participants.**

Cross sectional analysis was conducted on both out patients and inpatients (n=228, age 3 months to 54 years) presenting with acute febrile conditions (temperature above 37°c). Clinically the study participants were classified into two categories based on infection status as the infected and non-infected group.

The distribution of gender was significantly different between the clinical categories (p=0.007). Moreover, the proportions of Hb level, platelet count, MPV and PDW were also significantly different between clinical groups (p<0.001) (Table1). Haematological parameters of the malaria parasitaemic group were compared with that of control using t-test (Mann-Whitney U test). The median values for Haemoglobin, platelet count were significantly lower for the parasitaemic group relative to the controls (p<0.001 in both cases). Conversely, the mean platelet volume (MPV) and platelet distribution width (PDW) were significantly higher in the parasitaemic group with p <0.001 in both cases (Figure 5; (A) and (B) respectively).

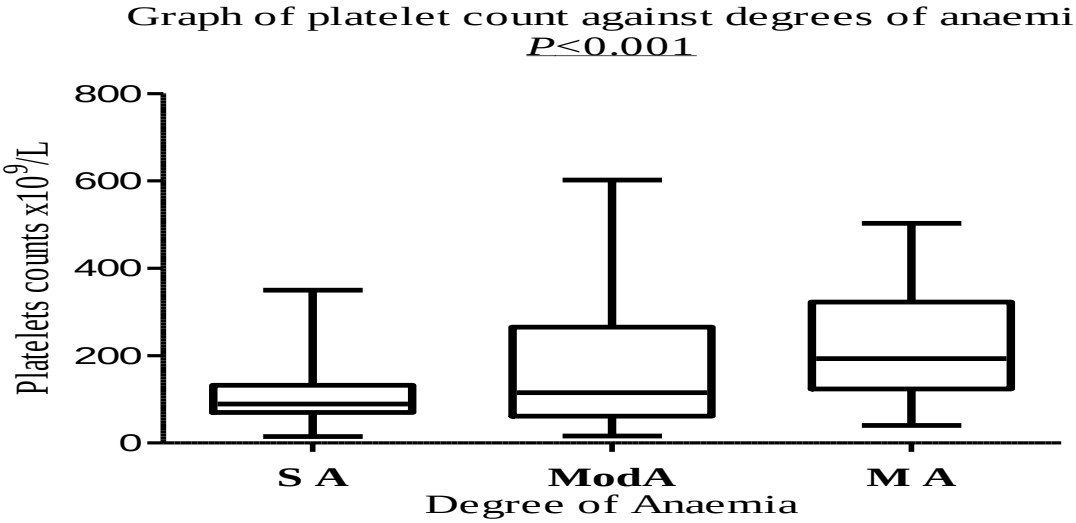
**Table 1. Laboratory, demographic, clinical, characteristics of the study participants.**

| Characteristics | Non-infected group | InfectedGroup | *p*-value |
|---|---|---|---|
| No. of participants (n=228) | 71 | 157 | |
| Gender, n (%) | | | |
| Male | 33 (46.9) | 109 (69.4) | **0.007**[a] |
| Female | 38 (53.1) | 46(30.6) | |
| Age, years | 3.5 (4.8) | 3.5 (6.0) | 0.76[b] |
| Haemoglobin level, g/dL | 10.2 (2.7) | 7.75 (3.9) | **<0.001**[b] |
| Platelet count×$10^9$/L | 297 (137) | 88.0 (67.8) | **<0.001**[b] |
| MPV,fL | 7.7 (1.3) | 8.8 (0.7) | **<0.001**[b] |
| PDW,% | 1.3(1.5) | 17.9(1.1) | **<0.001**[b] |

Data are the median (interquartile range; IQR) unless otherwise stated. Patients with acute febrile illness (n=228) were categorized on the basis *P. falciparum* infection status. Non-infected group (n=71) and Infected group (n=157). [a] Statistical significance was determined by the $\chi^2$ test. [b] Statistical significance was determined by the Mann-Whitney U test. Values in bold are statistically significant at $p \leq 0.05$.

**Association between Anaemia and thrombocytopenia:** Since anaemia and thrombocytopenia have profound haematological complications in malaria, the association between these two variables was assessed (Figure 1). Spearman's rank correlation revealed a positive correlation between platelet count and haemoglobin level in malaria ($r=0.26$, $p<0.001$).

**Figure 1: Association between thrombocytopenia and anaemia.**




Data are represented in box-plots. The boxes represent interquartile range; the line through boxes is the median while the whiskers show the $10^{th}$ and the $90^{th}$ percentiles. Across group comparisons were determined using Kruskal-Wallis test. **SA:** Severe anaemia, **ModA:** Moderate anaemia, **MA:** Mild anaemia

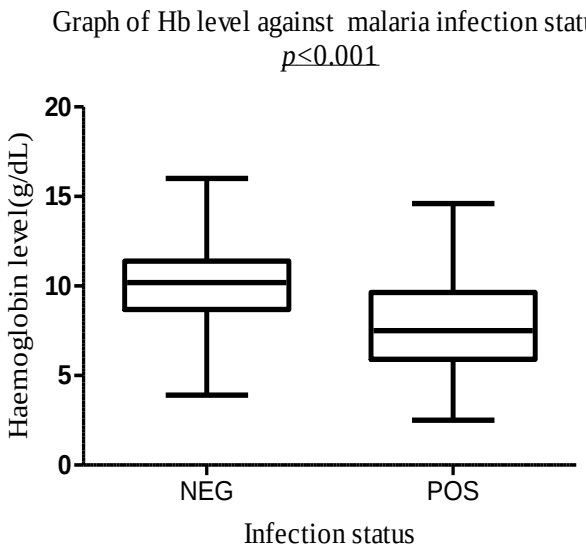
**Association between anaemia and malaria:** Anaemia was defined as haemoglobin level <13 g/dl for adult males, <12g/dl for women and adolescents and children (more than 2 years of age).It was further classified as mild, moderate and severe (Table 2).Severe malarial anaemia was eventually defined as Hb<7g/dl in the presence of parasitaemia. The median Hb value of the malaria infected group was significantly lower than the negative group (7.7g/dl vs. 10.2g/dl, $p<0.001$, Figure 2). One hundred and twenty two (78%) of the malaria infected patients had severe to moderate anaemia compared to thirty three (46%) of the non-infected group (Table 2).

**Table2: Distribution of Haemoglobin level in the study group**

| Category of anaemia | Hb level in g/dl | Malaria positive (n=157) | Malaria negative (n=71) |
|---|---|---|---|
| Severe | >7g/dl | 64(41%) | 10(14%) |
| Moderate | 7-10 g/dl | 58(38%) | 23(33%) |
| Mild | 10-13g/dl | 29(18%) | 37(51%) |
| Non anaemic | >13g/dl | 6(3%) | 1(1%) |

The percentages of the Hb levels in malaria negative and malaria positive were determined using cross-tabulations.

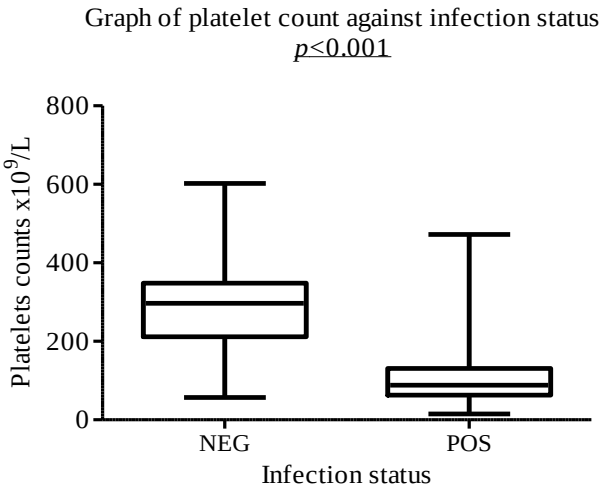
**Figure 2: Association between Haemoglobin level and malaria infection status.**




Data are represented as box-plots. The boxes represent interquartile range; the line through boxes is the median while the whiskers show the $10^{th}$ and the $90^{th}$ percentiles. Difference in Haemoglobin levels were considered significant at $p<0.05$ using Mann-Whitney U test. NEG- negative, POS- positive.

**Association between thrombocytopenia and malaria:** Thrombocytopenia was defined as platelet count $<150\times10^9$/l and further defined as severe if the platelet count is $<20\times10^9$/l. The median platelet count for the malaria infected group was significantly lower than non-malaria infected ($88\times10^9$/l vs. $297\times10^9$/l); ($p<0.001$) (Figure3). Thrombocytopenia was reported in 87%(n=136) of the malaria infected patients with 17 % being severe to moderate as compared to 10% (n=7) of non-infected group which had no cases of severe or moderate thrombocytopenia (Table 3).

**Figure 3: Association between platelet count and malaria infection status.**



Data are represented in box-plots. The boxes represent interquartile range; the line through boxes is the median while the whiskers show the $10^{th}$ and the $90^{th}$ percentiles. Between groups comparisons were determined using Mann-Whitney U test. **NEG**-Negative, **POS**-positive

**Table 3: Distribution of platelet among the study group**

| Degree of thrombocytopenia | Platelet count | Malaria positive N=157 | Malaria Negative N=71 |
|---|---|---|---|
| Severe | $<20\times10^9$/l | 5 (3%) | 0% |
| Mild | $20-50\times10^9$/l | 22 (14%) | 0% |
| Moderate | $50-150\times10^9$/l | 110 (70%) | 7 (10%) |
| Non -thrombocytopaenic | $>150\times10^9$/l | 20 (13%) | 64 (90%) |

The percentages of the platelet counts in malaria negative and malaria positive were determined using cross-tabulations.

**Correlation between platelet counts and MPV:** Since malaria infection is likely to alter platelet counts and MPV, analysis was also done to determine the relationship between platelet counts and MPV in both malaria infected and non-infected individuals. The spearman's rank correlation analysis revealed a strong inverse correlation between platelet count and MPV ($r=-0.36$, $p<0.001$). There was a marked increase in MPV as platelet count decreased in both malaria infected and the non-infected group (Figure 4).

The line through the plots measures and shows a negative correlation between MPV and platelet count.

**Association between MPV, PDW and malaria:** Since mean platelet volume (MPV) and platelet distribution width (PDW) could play an important role in the differential diagnosis of malaria, these two variables were also analyzed. Both mean platelet volume (MPV) and platelet distribution width (PDW) were increased as opposed to platelet count among the *P.faciparum* infected patients (Figure 5). The Mann Whitney U test confirmed a significant association of both variables with a $p<0.001$.

**Figure 4: Graph of relationship between MPV and platelet count.**

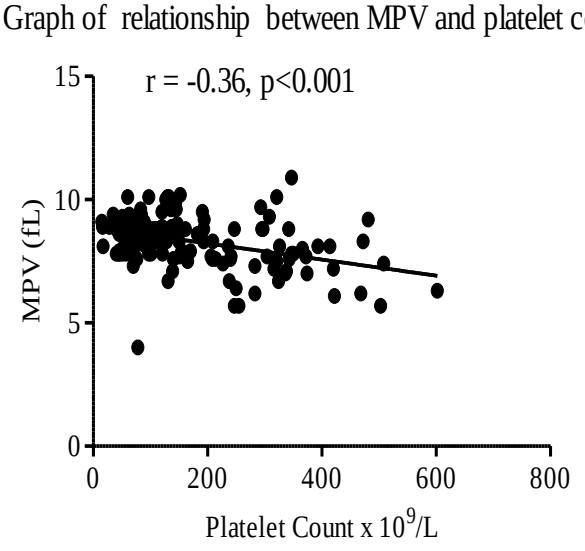
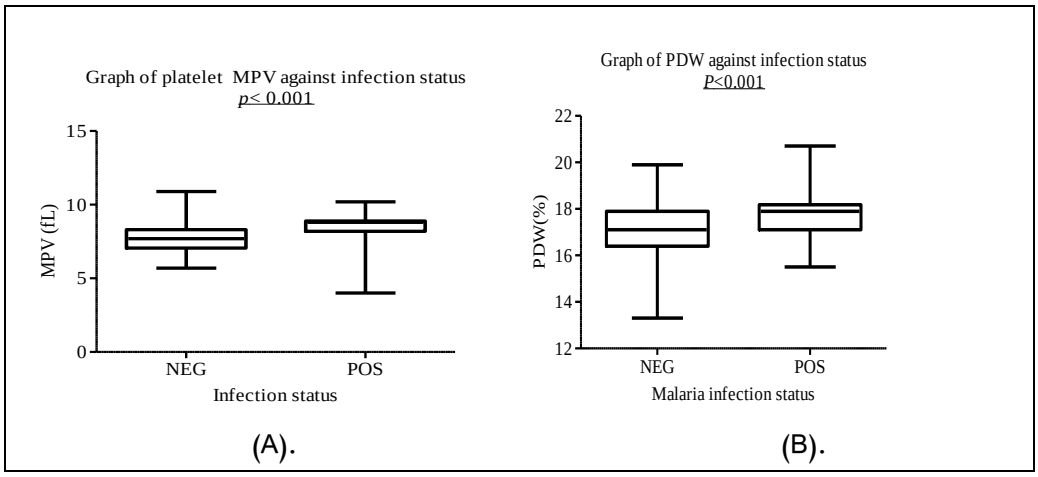


**Figure 5**: (A) and (B): **Association between MPV and infection status and PDW and infection status respectively**




Data are represented as box-plots. In both cases, the boxes represent interquartile ranges; the line through each box is the median while the whiskers show the $10^{th}$ and the $90^{th}$ percentiles. Differences in mean platelet volume (MPV) and platelet distribution width (PDW) were considered significant at $p<0.05$ using Mann-Whitney U test. NEG- negative, POS- positive.

**Sensitivity, Specificity and Predictive values of the haemoglobin level and platelet count among other analysed haematological parameters.**

The diagnostic values of Hb level and platelet count were determined by computing sensitivity, specificity and predictive values of the two variables using sensitivity and specificity calculator (www.wikihow.com/sample/sensitivity-and-specificity-calculator) (Table 4). Hb level and platelet count had good sensitivity and specificity (77.71% and 53.52% vs.87.26% and 90.14%) respectively to diagnose *P. falciparum* malaria.

**Table 5: Sensitivity, specificity and predictive values of Haemoglobin level and platelet count among other analysed haematological parameters.**

| | **Hb level** | **Platelet count** |
|---|---|---|
| Sensitivity | 77.71% | 87.26% |
| Specificity | 53.52% | 90.14% |
| PPV | 78.71% | 95.14% |
| NPV | 52.05% | 76.19% |

**Discussion**

This study vividly confirms that haematological abnormalities are more pronounced in *P. falciparum* infection. Based on the current study results, the major haematological changes include, lower Hb levels and platelet count and other platelet abnormalities among other parameters generated from complete blood count resulting in defective thromboplastic and disseminated intravascular haemolysis [2, 5]. One of the most common complications in malaria especially in high transmission areas in children under five years and pregnant women is malaria anaemia [6]. This could be due to haemolytic mechanisms and accelerated removal of parasitized red blood cells by erythro-phagocytosis and ineffective erythropoiesis [2, 7]. Abnormally high tumor necrosis factor(TNF), in malaria has been associated with impairment of bone marrow

activity [2] and imbalance in erythrocyte surface markers such as C reactive protein 1(CR1) [8]. Severe anaemia (Hb <7g/dl) was only seen in 47% of the infected group and in 14% of the non-infected group. The severe anaemia in the infected group and the non-infected group could in part be contributed to by other anaemia promoting conditions in *P. falciparum* infected individuals such as HIV-1 and bacteraemia which were not screened for in the current study [9, 10]. Mild anaemia reported in 51% in the non-malaria infected group and 18% of the malaria infected patients may partially reflect poor nutritional status, background haemoglobinopathy and previous and/or repeated malaria infections in this area. Sickle cell trait incidence of 28% [11] is common in Western Kenya. This compounded by high malaria transmission poses significant health problems in this region due to hereditary and acquired haemolytic anaemia although these patients are protected from severe disease.

Both qualitative and quantitative platelet abnormalities occur in malaria. In this study, platelet counts were markedly reduced in malaria infected patients compared to non-malaria infected patients. Thrombocytopenia occurred in 87% of the infected patients. Thrombocytopenia occur through peripheral destruction [12], platelet consumption by disseminated intravascular coagulation process [13] as well as excessive platelet removal by splenic pooling [14, 15]. This study equally confirms lack of bleeding in thrombocytopenic malaria patients as previously reported [16]. Reports of adequate or increased number of megakaryocytes in the bone marrow, makes decreased thrombopoiesis an unlikely cause of thrombocytopaenia in malaria [14].

Immune-mediated destruction of circulating platelets has been postulated as a cause of thrombocytopaenia seen in malaria. Platelets have also been shown to mediate clumping of *P. falciparum* infected erythrocytes [17]. This could lead to pseudo-thrombocytopenia. Malaria infected patients have elevated levels of specific IgG in their blood which binds to platelet-bound malaria antigens [18] possibly leading to accelerated destruction.

Clumping of platelets was the most important platelet functional abnormality seen in this study. A large number of small platelets are seen mixed or clumped with a few giant platelets possibly due to the cytokine interference of megakaryopoiesis [19] since cytokine milieu is a common feature of severe malaria anaemia. Virtually all the peripheral blood smears from samples with platelet aggregate flag revealed small platelet aggregates mixed with giant platelets (platelets that nearly approach or exceed the size of a red cell), which could have triggered the platelet aggregation. The platelets clumps comprising three to 10 platelets are falsely counted as single platelet by the analyzer thus causing pseudo-thrombocytopenia. These observations suggest that, in as much as patients with malaria are likely to develop thrombocytopenia, a reduced platelet count in some patients may be attributed in part to pseudo-thrombocytopenia further explaining the lack of bleeding tendency. Although, presence of giant platelets as well as increased MPV argues against pseudo-thrombocytopenia being the most likely cause of thrombocytopenia in malaria-infected individuals. Besides, a number of samples did not have microscopically detectable platelet aggregates despite having significant thrombocytopenia.Hb level positively correlated with platelet count. This was consistent with results of a similar study in Nigeria [20]. The MPV was significantly higher and inversely correlated to the platelet counts in the parasitaemic

group consistent with the finding of a similar study involving the investigation of haematological parameters in children living in Western Kenya [21]. MPV increased as the platelet count decreased in both the infected and non-infected patients. This may reflect an early release of platelets from the bone marrow in a compensatory response to reduced platelet levels in the peripheral blood. The raised MPV may be explained by the presence of the giant platelets observed in some of the peripheral blood films examined. A combination of thrombocytopenia and anaemia with high sensitivity and specificity makes it a better predictor towards malaria.

**Conclusion**

This study vividly confirms a strong positive correlation between thrombocytopenia and anaemia in *P.falciparum* malaria and may be a marker of disease severity. Clinicians in Kisumu County should pay adequate attention to low platelet count and low Hb level in malaria. This could add a significant diagnostic value in malaria between molecular and other conventional diagnostic techniques. Pseudo-thrombocytopenia may be partially related to low platelet count in some patients but immune mediated thrombocytopenia may not be ruled out. Combination of all these haematological findings together with clinical presentations from malaria endemic areas may be useful diagnostic tool in situations where conventional microscopy and rapid diagnostic tests may be sub-optimal as may be the case with low parasite density. This can prompt timely initiation of anti-malarial therapy.

**Recommendations**

Further studies are required to characterize the platelet aggregates and explain their association with falciparum malaria. A more robust research should be undertaken to elucidate both cellular and molecular mechanisms of thrombocytopenia in *P. falciparum* malaria.

**Competing interests**

All authors declare no conflict of interest in the results of the study.

**Authors' contributions**

**KPM**- coordinated participants' recruitment, specimen collection and analysis of clinical specimens, statistical analysis, and manuscript writing and participated in study design. **POS** participated in study design, data analysis and manuscript writing. **NJO** and **AFK** participated in data analysis and manuscript writing. **AOM** conceived the study, participated in the study design, data analysis, manuscript writing, and was the lead study investigator. All authors read and approved the final manuscript.

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