

Assessment of Platelet Numbers and Prevalence of Thrombocytopenia among Children with Severe Malaria at a Tertiary Teaching Hospital

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Abstract

Background: Thrombocytopenia plays an important role in the diagnosis of malaria in most countries because of the rapid decrease of platelets during malaria onset and also in severe forms of the disease. The study sought to assess platelet numbers and determine the prevalence of malarial thrombocytopenia among children with febrile malaria at the Korle-Bu Teaching Hospital (KBTH). **Methodology:** It was a cross-sectional study carried out in the Department of Child Health and the Polyclinic of KBTH from April to July 2018. A total of 100 children aged from 1 to 12 years who tested malaria positive for both thick and thin blood film and Rapid Diagnostic Tests (RDTs) were recruited into the study. Venous blood sample was obtained from the children and analyzed for platelet count using a haematology auto analyzer. Parasite speciation and quantification was used to classify the disease into mild, moderate and severe, and platelet numbers were also categorized into low, normal and high. Data obtained was then analyzed for prevalence of malarial thrombocytopenia in severe malaria. **Results:** The total studied participants were 100, 61 (61%) were males whiles 39 (39%) were females. Both severe malaria and thrombocytopenia were mostly seen in children less than 5 years of age and the males recorded more thrombocytopenia (66%) and normal platelet numbers 34 (64.2%) than the females. There was a significant higher percentage of malaria children with thrombocytosis being females

(64%) as compared to those being males (36%). 53 (53%) children had normal platelet numbers, 33 (33%) had thrombocytopenia, and 14 (14%) had thrombocytosis. The prevalence of uncomplicated malaria and complicated malaria were 80% and 20% respectively. The overall prevalence of thrombocytopenia was 33%, and the prevalence of thrombocytopenia in uncomplicated and severe malaria was 18.8% and 90% respectively. The prevalence of malaria types among children with thrombocytopenia was assessed. Out of the 33 (33%) patients who had thrombocytopenia, 15 (45.5%) of them had uncomplicated malaria and 18 (54.5%) of them had complicated or severe malaria. No child was found to have thrombocytosis during complicated malaria. **Conclusion:** The study indicates a significant higher prevalence of thrombocytopenia in severe malaria among children at the Korle-Bu Teaching Hospital, and this could be used as a useful indicator to investigate malaria or as a diagnostic clue for malaria in children.

Keywords

Thrombocytopenia, Malaria, *Plasmodium falciparum*, Platelet, Korle Bu Teaching Hospital-KBTH

1. Introduction

Malaria is estimated to be directly responsible for about one million deaths annually worldwide, with the morbidity and mortality burden caused by malaria being nearly 3% [1] [2] [3]. Africa also accounts for 90% of the mortality burden despite progress in intensive care and antimalarial treatment and by contrast, *Plasmodium falciparum* is the deadliest species and the subject of most malaria related research [4] [5]. Malaria complications involve the nervous, respiratory, renal, and hematopoietic systems. The hematological changes that may occur include thrombocytopenia which is a common clinical finding in *Plasmodium falciparum* malaria infection and occasionally, profound thrombocytopenia may occur in severe *falciparum* malaria [3] [6]. However, in general, an insignificant reduction in platelet numbers is unrelated to the severity of the infection [3] [7]. Malaria causes haemostatic abnormalities that range from asymptomatic thrombocytopenia to fulminant disseminated intravascular coagulation (DIC). Early investigations suggested that the major coagulation abnormality of malaria was DIC, [8] but in recent years clinicians are recognizing that thrombocytopenia is a common and early sign of malaria infections whereas DIC is rare. Thrombocytopenia might be a useful indicator of malaria in children [6] [9] and the mechanism of thrombocytopenia in malaria is probably the consequence of several factors. Some experimental data and clinical studies have successively emphasized the role of immune factors and the destruction or sequestration of platelets, and in severe forms, platelet and erythrocyte sequestrations are frequent and thrombocytopenia is present [10]. Thrombocytopenia is a common finding

in malaria but its correlation with the type of malaria and prognosis in context with severity of the low platelet count has not been evaluated in many studies [11] [12]. Platelets have been implicated in animal, clinical and experimental studies of malaria pathogenesis. Histopathological studies of children who have died of severe malaria showed that platelet clumps with and without infected erythrocytes are frequently found in the vasculature [13]. Infected erythrocytes may adhere to platelets and the clumps of these erythrocytes and platelets have been associated with severe malaria [14]. Therefore, there remains a paradox that, while thrombocytopenia is associated with infection and platelets have been implicated in the pathogenesis of severe malaria, most studies suggest that low counts of platelets are not associated with an adverse outcome. Without understanding this paradox, it is not possible to evaluate the true contribution of platelet to the pathogenesis of severe malaria [15]. The causes of thrombocytopenia in acute and severe malaria are also poorly understood even in Ghana. Increased platelet destruction is significant during malaria infection and the platelet lifespan is reduced during malaria, which seems to be associated with a diffuse pattern of platelet sequestration [16] [17]. The contribution of abnormalities in platelet production to thrombocytopenia during malaria infection is less clear. The study therefore sought to assess platelet numbers and prevalence of thrombocytopenia among children with severe malaria at a tertiary teaching hospital in Ghana. It again sought to provide baseline data for future reviews and molecular research to see if thrombopoietic growth factors could be used as therapy for malarial thrombocytopenia.

2. Materials and Method

2.1. Study Area

The study was carried out in the laboratories of the Department of Child Health and the Polyclinic of the Korle-Bu Teaching Hospital in the Greater Accra region Ghana from April to July 2018.

2.2. Study Design

This was a cross-sectional study which involved children with malaria parasite infection who were between the ages of 1 to 12 years. They were randomly selected based on clinical examination, signs and symptoms of malaria and again with prior knowledge of family history. According to the Ghana 2016 Malaria Indicator Survey [18], the malaria prevalence in children ranges from a low of 5% in Greater Accra to a high of 31% in Eastern region of Ghana. The regional prevalence of 5% in Greater Accra was used. Using 0.05 margin of error at a 95% confidence interval, the sample size was calculated as shown below:

$$n = \frac{Z^2 p(1-p)}{m^2}$$
 Where n = sample size, Z is reliability coefficient = 1.96, p is

prevalence = 5%, m is margin of error = 0.05, $n = 73$. The sample size was therefore run to 100 to make amends for any possible sampling error of refusal to

participate.

2.3. Study Population

The study involved 100 children both males and females with both complicated and uncomplicated malaria using World Health Organization (2000) criteria at the two health care facilities between the months of April and July 2018. Children between the ages of 1 to 12 years who tested positive for malaria and whose parents and guardians gave consent to participate were included in the study. Children who were receiving intensive chemotherapy or radiotherapy, diagnosed with HIV/AIDS or had any of the haematological malignancies, those with sickle cell disease and those whose guardians refused consent were totally exempted from the study.

2.4. Sample Collection and Processing

Three (3) milliliters of venous blood were taken from each child and were dispensed into dipotassium ethylene diamine tetra acetic acid (K_2EDTA) tube. Thick and thin blood films smears were made from each sample on clean slides and labelled accordingly. The smeared slides were air-dried and were stained with Giemsa using 1 in 10 dilution followed by subsequent observation under the light microscopy using $\times 100$ oil immersion for parasite determination and count. The parasite determination and count were categorized into mild (<1000 parasites/ul of blood), moderate (1000 - 4999 parasites/ul of blood), high (5000 - 99,999 parasites/ul of blood) and hyperparasitaemia ($\geq 100,000$) [19]. The high and the hyperparasitaemia categories were together considered as severe malaria. Platelets count was also determined by doing full blood count on all the samples using Sysmex Xt-2000i haematology analyzer. Platelet numbers that were given out were classified into one of three categories as normal ($150 - 400 \times 10^9/L$), low-thrombocytopenia ($<150 \times 10^9/L$) or high-thrombocytosis ($>400 \times 10^9/L$) depending on whether they fell within, below or above the platelet reference range.

2.5. Statistical Analysis

The data collected were computed and analyzed using statistical package for social sciences (SPSS20.0). Descriptive statistics such as frequency tables and pictorial statistics such as bar chart were used to summarize the data obtained. Categorical variables were presented and reported as simple frequencies with their corresponding percentages. Means with their standard deviation and median (ranges) were used to summarize continuous variables.

3. Results

3.1. Gender Distribution of Platelet Numbers among Children with Malaria

Figure 1 shows gender distribution of platelet numbers among children with

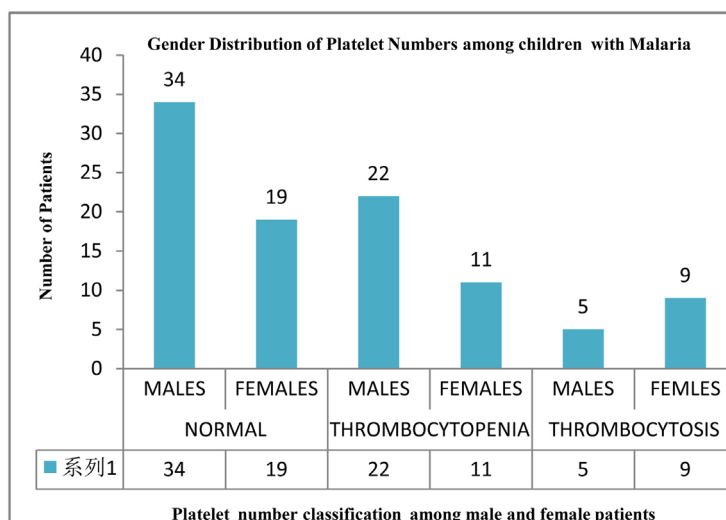


Figure 1. Gender distribution of platelet numbers among children with malaria.

malaria. The total studied participants were 100 and out of that 61 (61%) were males while 39 (39%) were females. 53 children with normal platelet numbers were recorded, 34 (64.2%) were males while 19 (35.8%) were females. 14 children with thrombocytosis (high platelet numbers) were also recorded and the males were 5 (36%) while the females were 9 (64%). Malaria children with thrombocytopenia (low platelet numbers) were 33, males accounted for 22 (66%) and the females were 11 (33%). There was a significant higher percentage of malaria children with thrombocytopenia being males as compared to those being females. The female children who had malaria and with thrombocytosis also recorded significant higher percentage compared to the males.

3.2. Distribution of Platelet Numbers and Malaria Types According to Age Groups

Table 1 shows the distribution of platelet numbers and malaria types according to the age groups of the children. Platelet numbers were classified as normal, thrombocytopenia and thrombocytosis among these age categories 1 to 4, 5 to 8 and 9 to 12 years. Children with Normal platelets numbers between 1 to 4 years was 37, with thrombocytopenia and thrombocytosis between same age group was 17 and 5 respectively. Children with Normal platelets numbers between 5 to 8 years was 15, with thrombocytopenia and thrombocytosis between same age group was 12 and 7 respectively. Children with Normal platelets numbers between 9 to 12 years was 1, with thrombocytopenia and thrombocytosis between same age group was 4 and 2 respectively. The age category that recorded frequent thrombocytopenia was seen among the 1 to 4 years followed by 5 to 8 years. Malaria types were also classified as Uncomplicated and Complicated among same age categories 1 to 4, 5 to 8 and 9 to 12 years. Children with Uncomplicated malaria between 1 to 4 years was 52, 5 to 8 years was 24 and 9 to 12 years was 4. Children with Complicated malaria between 1 to 4 years was 7, 5 to

Table 1. Distribution of platelet numbers and Malaria types according to age groups.

Category	1 to 4 years	5 to 8 years	9 to 12 years	Total
Platelet classification				
Normal	37	15	1	53
Thrombocytopenia	17	12	4	33
Thrombocytosis	5	7	2	14
Malaria Type				
Uncomplicated	52	24	4	80
Complicated	7	10	3	20

8 years was 10 and 9 to 12 years was 3. Complicated malaria was seen to be more frequent among lesser age group below 9 years and this age groups 1 to 8 accounted for 85% of all the complicated cases.

3.3. Prevalence of Malaria Infection and Platelet numbers According to Types and Based on Classification Respectively

Table 2 shows the prevalence of malaria infection and platelet numbers according to types and based on classification respectively. Mild and moderate malaria infection was categorized as Uncomplicated and it accounted for 80% (80) of the studied participants while Complicated accounted for 20% (20). Platelet numbers were also categorized into normal, thrombocytosis and thrombocytopenia based on the reference range. 53 children (53%) had normal platelet numbers, 33 (33%) had thrombocytopenia, and 14 children (14%) had thrombocytosis.

3.4. Prevalence of Malaria Types in Children with Thrombocytopenia

Table 3 shows the prevalence of malaria types among children with thrombocytopenia. Out of the 33 (33%) patients who had thrombocytopenia, 15 (45.5%) of them had uncomplicated malaria and 18 (54.5%) of them had complicated or severe malaria.

3.5. Distribution and Prevalence of Platelet Numbers in Uncomplicated Malaria

Table 4 shows classification of platelet numbers and their prevalence among children with uncomplicated (mild to moderate) malaria. Out of the 80 (80%) patients who had uncomplicated malaria, 15 (18.8%) children had thrombocytopenia, 51 (63.8%) had normal platelet numbers and 14 (17.5%) children had thrombocytosis.

3.6. Distribution and Prevalence of Platelet Numbers in Complicated/Severe Malaria

Table 5 also shows the distribution and prevalence of platelet numbers among children with complicated or severe malaria. In all the 20 children diagnosed

Table 2. Prevalence of malaria infection and platelet numbers according to types and based on classification respectively.

Category	Frequency	Percent (%)	Valid Percent (%)	Cumulative Percent (%)
Malaria Types				
Uncomplicated	8080		80	80
Complicated	20	20	20	20
Total	100	100	100	100
Plateles Classification				
Normal	53	53	53	53
Thrombocytopenia	33	33	33	33
Thrombocytosis	14	14	14	14
Total	100	100	100	100

Table 3. Prevalence of malaria types in children with thrombocytopenia.

Category	Frequency	Percent (%)	Valid Percent (%)	Cumulative Percent (%)
Malaria Types				
Uncomplicated	15	45.5	45.5	45.5
Complicated	13	54.5	54.5	54.5
Total	33	100	100	100

Table 4. Distribution and prevalence of platelet numbers in uncomplicated malaria.

Category	Frequency	Percent (%)	Valid Percent (%)	Cumulative Percent (%)
Plateles Classification				
Normal	51	63.8	63.8	63.8
Thrombocytopenia	15	18.8	18.8	18.8
Thrombocytosis	14	17.5	17.5	17.5
Total	80	100	100	100

Table 5. Distribution and prevalence of platelet numbers in complicated/severe malaria.

Category	Frequency	Percent (%)	Valid Percent (%)	Cumulative Percent (%)
Plateles Classification				
Normal	2	10.0	10.0	10.0
Thrombocytopenia	18	90.0	90.0	90.0
Thrombocytosis	0	0.0	0.0	0.0
Total	20	100	100	100

with complicated malaria, 18 (90%) of them were found to have thrombocytopenia while 2 (10%) of them were found to have normal platelet numbers. No child was found to have thrombocytosis during complicated malaria.

4. Discussion

Malaria is a Protozoal disease caused by infection with parasites of the genus

Plasmodium and transmitted to man by certain species of infected female Anopheles mosquito, Haematological abnormalities have been observed in patients with malaria [20] but much attention has been placed on haemoglobin as the key indicator of relevance in relation to malaria infection in children with little or no regards to other haematological parameters including platelets. Malaria infection, especially an infection with *Plasmodium falciparum* is hazardous and deadly in children whose immune system is generally compromised, suppressed or incompetent. Thrombocytopenia is a common finding in malaria in children, and though it is a useful indicator of the disease, its prognostic value is not being addressed. In severe cases of the malaria, children presenting with a platelet count of less than $100 \times 10^9/L$ are more likely to die because multivariate analysis identifies thrombocytopenia as an independent predictor of death [21]. Studies of malaria and thrombocytopenia began as early as 1967 where Dennis and Inman [22] studied depletion of coagulation factors in *P. falciparum* malaria and found out that platelet numbers tend to decrease somehow during the disease. In the 100 malaria patients studied, 61% were males and 39% were females. However, in assessing their platelet numbers, it was observed that the males had more normal platelet numbers than the females and at the same time were also the ones with more thrombocytopenia than the females. However, with thrombocytosis, the females had higher numbers than the male. This is in contrast to the literature reviewed which indicates that the parameters are unaffected by gender, the findings in this paper could be the results of the uneven nature of the male to female ratio in the sampling as there is no known correlation between gender and platelet count in malaria infections. Among the 33 malaria children with thrombocytopenia, 17 were between 1 to 4 years of age, 12 were between 5 to 8 years and only 4 were between 9 to 12 years. This also gives the impression that children under 5 years are more likely to develop thrombocytopenia during malaria as the effect of malaria is more severe in this group, [23] possibly owing to the fact that these children have not yet acquired the partial immunity to the disease that is usually acquired during childhood in high transmission areas [24]. Hence the positive association between lower ages and decreased platelet counts during malaria could be supported. Also, it could be deduced that children under 8 years have their malaria progressing to more severe forms than children above 9 years, again, as a result of undeveloped immunity in the absence of pathological suppression. 15 children with thrombocytopenia representing 45.5% had uncomplicated malaria while 18 children with thrombocytopenia, representing 54.5%, had severe or complicated malaria. This can also be explained to indicate that there is a positive association between thrombocytopenia and severity of the malaria or the level of the parasitaemia of the infection. This finding is consistent with the data obtained by [21] which showed an association between thrombocytopenia and either severity or prognosis in childhood *falciparum* malaria infection. The prevalence of severe or complicated malaria was 20%, while that of uncomplicated (mild to moderate) malaria was 80%. This implies that most the

children's condition had not yet progressed to its severity stage and is likely to have complicated malaria during the infection. It was also found that age groups 1 to 8 accounted for 85% of all the complicated cases, which further strengthens the deduction that children under 8 years are more likely to have their malaria progress to more severe forms. The overall prevalence of thrombocytopenia in children with malaria (not categorized) is 33% as compared to 53% for normal platelet numbers and 14% for thrombocytosis. This prevalence of thrombocytopenia closely agrees with the works done by [25] (22%) and [6] (43%). In mild to moderate forms of *P. falciparum* malaria, thrombocytopenia is not common because the disease has not yet progressed to its severe stage to cause depletion of the coagulation factors. This was observed in the study where thrombocytopenia in uncomplicated malaria gave a prevalence of 18.8% in 15 children. This is closely followed by thrombocytosis with 17.5% in 14 children. Half of the total number of children had normal platelet numbers, which represents 63.8%. This implies that in non-severe forms of malaria, normal platelet numbers are more prevalent. In 1999, Kakar and his workers [8] carried out a research on malaria and thrombocytopenia and reported that 80% of the patients infected with either *P. falciparum* or *P. vivax* malaria develop thrombocytopenia during their infection, and it is more evident in those with the severe forms of the disease. Patel and his friends [26] also followed up on this in 2004 and concluded that thrombocytopenia complicates up to 60% to 80% cases of malaria, and its occurrence is a diagnostic clue for malaria in endemic areas. The main aim of this project was to determine the prevalence of thrombocytopenia among children with severe forms of malaria. 18 children with complicated or severe malaria had thrombocytopenia while only 2 of such children had normal platelet numbers. None of the children with severe malaria had thrombocytosis. These 18 children gave a prevalence of thrombocytopenia in severe malaria to be 90%, and 10% for the normal platelet numbers. This thrombocytopenia prevalent result closely agrees with the works of [8] and [26] as stated previously. Moreover, [27] and [28] separately followed up on the reports of [8] and [26] in 2005 and 2010 respectively and came out respectively with a prevalence of thrombocytopenia in severe malaria children to be 85% and 90.9%. These results strongly agree with that obtained in this project and it could therefore be deduced that thrombocytopenia is a useful indicator of malaria in children.

5. Conclusion

Platelet numbers decrease in malaria infection but very profound in severe malaria. The decrease is more evident in children below 5 years and slightly seen in children between 5 to 8 years. Platelet numbers are mostly normal in uncomplicated malaria and the detection of thrombocytosis in mild, moderate or severe malaria is insignificant. The prevalence of thrombocytopenia among children with severe malaria at the Korle Bu Teaching Hospital (KBTH) was found to be 90%. It can therefore be concluded that mild to severe thrombocytopenia should

alert the possibility of malaria infection and it is usually more common in *Plasmodium falciparum* malaria, the main species of malaria parasite in Ghana. The results also show that thrombocytopenia is more frequent and more profound in severe forms than mild to moderate forms. Whatever the clinical presentation, it is predictive of fatal death, and also an undetected and contributing factor to the deaths caused by malaria in children. In conclusion, the findings indicate a significant prognostic value of *falciparum* malaria-related thrombocytopenia among children in Ghana living in a high and seasonal transmission setting. The role of platelets in the pathogenesis of severe malaria should be further investigated in future studies.

6. Limitations

One of the limitations was our inability to get some guardians and parents' consent to the study. Another challenge was our limitation to rely solely on the subject's clinical and family history to rule out some disease conditions in order to recruit children suffering from malaria only. Notwithstanding that, the findings depict true reflection of the target population of children suffering from malaria alone.

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Conflicts of Interest

We say on authority that there was no competing interest, as the study did not get any funding from any organization.

Author's Contribution

DMA and MHA designed and conducted the study and contributed in the preparation and drafting of the manuscript. AFS, JBA and SA participated in data interpretation, contributed to the performing the statistical analysis and the manuscript drafting. All authors read and approved the final manuscript.

Availability of Data and Materials

The supporting data for this study is available on request but restrictions apply to the availability of the data. Data are however available from the authors upon reasonable request and with permission from the institutions and facilities that were involved.

Ethical Approval and Consent to Participate

Approval for this study was obtained from the Ethical and Protocol Review Committee of the School of Allied Health Sciences of the University of Ghana,

and the heads of the Department of Child Health and the Polyclinic of the Korle-Bu Teaching Hospital.

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