Hematological Profile of Children With Malaria in Sorong, West Papua, Indonesia

Sylvia Jiero¹, Ayodhia Pitaloka Pasaribu²

¹Department of Child Health, Sorong Regional General Hospital, Sorong, West Papua, Indonesia
²Department of Child Health, Medical Faculty, Universitas Sumatera Utara

*Corresponding author: Dr. Ayodhia Pitaloka Pasaribu
Department of Child Health, Medical Faculty, Universitas Sumatera Utara
Dr. Mansur Street No. 5, Medan 20156, Indonesia
E-mail: ayodhia_pitaloka@yahoo.com

Keywords: Hematological profile, Plasmodium falciparum, Plasmodium vivax, Malaria, West Papua

Word count for abstract: 355
Word count for text: 2983
Number of figures: 0
Number of tables: 6
Hematological Profile of Children With Malaria in Sorong, West Papua, Indonesia

Syilvia Jiero¹, Ayodhia Pitaloka Pasaribu²*

Abstract

Background:
Malaria remains a major public health problem in Indonesian Papua, with children under five years of age being the most affected group. Hematological changes such as cytopenia that occur during malaria infection have been suggested as potential predictors and can aid in the diagnosis of malaria. This study aimed to assess the hematological alterations associated with malaria infection in children presenting with signs and symptoms of malaria.

Methods:
A retrospective study was performed by collecting data from the medical records of malaria patients at Sorong Regional General Hospital, Sorong, West Papua, Indonesia, both from outpatient and inpatient clinics, from January 2014 until December 2017. The laboratory profile of children suffering from malaria was evaluated.

Results:
One hundred and eighty-two children aged 1 month to 18 years old were enrolled. The subjects were mostly male (112, 61.5%) with a mean age of 6.45 years (SD = 4.3 years). Children <5 years suffering from malaria had the highest number at 77 (42.3%). One hundred two subjects (56%) were infected with Plasmodium falciparum. Half of the enrolled subjects (50%) had hemoglobin level (Hb) between 5.1 and 10 gr/dL. A total of 41 children (53.2%) less than 5 years old suffered from P. falciparum infection. In the age group of 5-10 years, there were 34 children (57.6%) who suffered from P. falciparum, and in the age group >10 years, 27 children (58.7%) suffered from P. falciparum infection. Only 4 subjects (5.2%) in the less than 5 years old age group had mixed malaria infection. Of the eight parameters of the hematological profile, there were five parameters that were significantly associated with the diagnostic criteria, namely hemoglobin, hematocrit, leukocytes, platelets and monocytes (p <0.05). Generally, clinical symptoms are not significantly associated with a malaria diagnosis, and only one variable showed a significant relationship, pale, with a p value of 0.001.

Conclusions:
Children with malaria had changes in some hematological parameters, with anemia, low platelet count, white blood count, and lymphocyte count being the most important predictors of malaria infection in our study area. These parameters could improve malaria diagnosis when used in combination with other clinical diagnoses and microscopy.
Keywords: Hematological profile, Plasmodium falciparum, Plasmodium vivax, Malaria, West Papua

*Corresponding author: ayodhia_pitaloka@yahoo.com

2 Department of Child Health, Medical Faculty, Universitas Sumatera Utara
Dr. Mansur Street No. 5, Medan 20156, Indonesia
A full list of author information is available at the end of the article.

Author details
1 Department of Child Health, Sorong Regional General Hospital, Sorong, West Papua, Indonesia, Kampung Baru, Sorong Subdistrict, Sorong City, West Papua 98411, Indonesia
2 Department of Child Health, Medical Faculty, Universitas Sumatera Utara, Dr. Mansur Street No. 5, Medan 20156, Indonesia
INTRODUCTION

Malaria is a life-threatening protozoan disease caused by parasites that are transmitted to humans through the bite of infected female *Anopheles* mosquitoes [1]. The World Health Organization (WHO) estimates that there were an estimated 219 million cases of malaria worldwide in 2017, with 435,000 deaths, most of which occurred in Africa, followed by Southeast Asia. Sixty-one percent of all malaria deaths were in children under 5 years of age. Thus malaria continues to be viewed as a highly significant disease of global public health importance [2]. There are six major *Plasmodium* species infecting humans: *Plasmodium falciparum* (*P. falciparum*), *Plasmodium vivax* (*P. vivax*), *Plasmodium malariae* (*P. malariae*), *Plasmodium ovale curtisi* (*P. ovale curtisi*), *Plasmodium ovale wallikeri* (*P. ovale wallikeri*) and *Plasmodium knowlesi* (*P. knowlesi*) [3]. *P. falciparum* and *P. vivax* are the two main causes of human malaria infections. *P. falciparum* malaria poses a risk of severe complications and contributes to the majority of deaths [4].

In Southeast Asia, Indonesia contributes 9% of all malaria cases and has the second highest burden of disease after India [5]. The WHO estimated that 27% of the 257,563,815 people in the Indonesian population lives in malaria endemic areas. One of the endemic areas of malaria in Indonesia is Papua [6].

Hematological alterations that are thought to characterize malaria are related to the overt biochemical changes that occur during the asexual stage of the life cycle of the malaria parasite [7]. Patients infected with malaria tend to have significantly lower platelet, leukocyte, lymphocyte, eosinophil, red blood cell, and hemoglobin (Hb) counts, while the number of monocytes and neutrophils was significantly higher than that in nonmalaria-infected patients [8-11]. Anemia [12], leukopenia [13,14] and thrombocytopenia [15,16] are commonly seen in *P. falciparum* infection, probably as a result of the higher levels of parasitemia found in these patients [17,18]. Thrombocytopenia is most commonly seen in malaria infection [10,19,20]. People with platelet counts <150,000/μL are 12-15 times more likely to develop malaria infection than people with a platelet count >150,000/μL [10]. Pancytopenia and bicytopenia
are common hematological problems encountered in clinical practice [8,9] that have multiple causes, and the underlying pathology determines the potential predictors and can aid in the diagnosis, management and prognosis of malaria [21,22]. It plays a major role in fatality [23,24].

The gold standard for malaria examination is microscopic slide examination [25]. Knowledge of changes in various hematological parameters in children suffering from malaria can increase the diagnosis of malaria by increasing suspicion of malaria and encouraging a careful search for parasitemia using a microscope [21]. There has been no research to investigate the effects of malaria on the hematological profile of Indonesian Papuan children.

METHODS

A retrospective study of data from medical records of malaria patients at Sorong Regional General Hospital, Sorong, West Papua, Indonesia Outpatient and Inpatient Clinic from January 2014 until December 2017 was performed. It included 182 children from 1 month to 18 years old with signs and symptoms of malaria at Sorong Regional General Hospital, Sorong, West Papua, Indonesia. Blood samples were collected from children into ethylenediaminetetraacetic acid (EDTA) tubes and used to prepare thin and thick blood films, which were then used for Giemsa microscopy to detect malaria parasites and malaria species. Patients' hematological parameters were determined using an automated hematology analyzer.

Study population.

The study involved male and female children aged one month to 18 years presenting with signs and symptoms with suspected malaria who were referred to the laboratory for investigation after consultation with a physician.
The study included children from inpatient and outpatient clinics at Sorong Regional General Hospital, Sorong, West Papua, Indonesia from January 2014 until December 2017. The target populations were children aged one month to 18 years who suffered from malaria infection. The study was approved by the Research Ethics Committee of the Medical School of the Universitas of Sumatera Utara.

**Study design.**

*Inclusion criteria*

- Children in age group 1 month-18 years
- Any acute febrile illness lasting for 2-7 days
- Peripheral blood smear or rapid malaria antigen test positive for *P.vivax* and/or *P. falciparum* malaria
- Complete medical record data

*Exclusion criteria*

- Symptomatic malaria without confirmation with either rapid diagnostic test or microscopy

**Diagnosis**

**Sample Collection**

Two to three milliliters of venous blood was collected from each participant using a 5 ml sterile disposable syringe and dispensed into an EDTA anticoagulated test tube, followed by preparation of the thick and thin smears and automated for determination of the complete blood count (CBC). The EDTA test tubes containing the blood samples were gently inverted approximately 8 times to ensure the complete mixture of blood cells. The blood samples were collected by a trained medical laboratory scientist.
Peripheral blood smear examination

Peripheral blood smears were prepared using venous blood samples. We used separate slides for thick and thin smears. For thin film, we brought a clean spreader slide, held at a 45° angle, toward the drop of blood on the specimen slide. We waited until the blood spread along the entire width of the spreader slide. While holding the spreader slide at the same angle, we pushed it forward rapidly and smoothly. For thick film, we used the corner of a clean slide and spread the drop of blood in a circle to the size of a dime (diameter 1-2 cm). We did not make the smear too thick or it would fall off the slide. (We were able to read newsprint through it.) We waited until the thin and thick films were completely dry before staining. We fixed the thin film with methanol (100% or absolute) and allowed it to dry completely before staining. The thick film was not fixed. Thick and thin films of peripheral smear (PS) examination blood slides were prepared and stained with Giemsa. Peripheral blood smear examination for the type of malaria parasite was performed systematically under low power, high power and oil immersion using an Olympus CX21 Microscope.

Definitions and endpoints

- Although a wide and confusing variety of anemia grades have been proposed, the most commonly used definitions in malaria studies, based on hemoglobin concentrations, are as follows: mild anemia if the Hb value is ≤11 g/dL, moderate anemia if the Hb value is ≤ 8 g/dL, and severe anemia if the Hb value is ≤ 5 g/dL [26].
- Lymphocytopenia in children is defined as a total lymphocyte count less than 3.0 × 10⁹/L [27].
- Leucopenia was defined as white blood cells (WBCs) < 4 x 10³/μl [28].
- Monocytosis was defined as an absolute monocyte count > 3 x 10³/μl [27].
- Thrombocytopenia was defined as platelet count <1.5 x 10³/μl [28].
**Statistical analysis.** The data are presented as the means, percentages, standard deviations, medians, and ranges. Statistical analysis was performed using ANOVA, the Kruskal-Wallis test, contingency coefficient correlation, the Mann-Whitney U test, and the independent t-test. The data were analyzed using SPSS version 21 statistical software with appropriate statistical methods. Differences with P-values of less than 0.05 were considered significant.

**RESULTS**

**Demographic Characteristics and Hematological Profile of Research Subjects**

This study included 182 subjects who met the inclusion and exclusion criteria. The subjects were mostly male (112, 61.5%) with a mean age of 6.45 years (SD = 4.3 years). Children <5 years suffering from malaria had the highest number, 77 (42.3%). The mean body weight of the subjects was 18.95 kg (SD = 11.27 kg). A total of 102 subjects (56%) were infected with *P. falciparum*. Some subjects (50%) had a Hb level between 5.1 and 10 gr/dL. The results of the hematological profile examination of the subjects are presented in Table 1 below.

Forty-one subjects who were less than five years old suffered from *P. falciparum* infection (53.2%). Only four subjects (5.2%) less than five years old had mixed infections (Table 2).

Table 3 shows the hematological profiles based on the age group of the study subjects. Of the eight parameters in the hematological profile, there are five parameters that were significantly associated with the diagnostic criteria, namely hemoglobin, hematocrit, leukocytes, platelets and monocytes (p <0.05) (Table 4).

Generally, clinical symptoms are not significantly associated with a malaria diagnosis, and only one variable shows a significant relationship, pale, with a p value of 0.001.
DISCUSSION

In our study, there were more male patients infected with malaria than female patients, which is similar to the results of a study in South Sorong [29]. One hundred two subjects (56%) were infected with *P. falciparum*. Our study also shows that the most common type of *Plasmodium* infection in Sorong, West Papua, is *P. falciparum*. Unlike in other provinces in Indonesia, *P. falciparum* is the predominant malaria species in Papua.

Malaria is a preventable and treatable condition and remains the most important parasitic disease globally. In 2016, it was still endemic in 91 countries, placing 3.8 billion people at risk. Considerable progress has been made due to aggressive malaria control and elimination efforts since 2000, resulting in a global reduction of 41% in morbidity and 62% in mortality [6]. Many efforts have been made to minimize malaria transmission worldwide; however, this infection remains high among humans [30]. All species of *Plasmodium* have been documented in Indonesia, including small numbers of human *P. knowlesi* cases in Kalimantan and Sumatra islands [31,32]. All four species of human malaria parasites are found in Indonesia. *P. vivax* is the predominant species except in Papua where *P. falciparum* slightly predominates. *P. malariae* and *P. ovale* were mostly found in the eastern part of Indonesia, Nusa Tenggara Timur and Papua. In the past few years, *P. knowlesi* was documented in humans in Kalimantan [5].

*P. falciparum* is the most prevalent malaria parasite in the WHO African region, accounting for 99.7% of estimated malaria cases in 2017, as well as in the WHO regions of Southeast Asia (62.8%), the Eastern Mediterranean (69%) and the Western Pacific (71.9%). *P. vivax* is the predominant parasite in the WHO region of the Americas, representing 74.1% of malaria cases [2]. *P. vivax* contributed 4% of the total global cases in 2015, but outside Africa the proportion was 41% among all malaria infections. Its high burden of disease is maintained in part due to dormant liver stage parasite forms known as hypnozoites which can induce clinical relapse episodes [33].
Our study showed that children suffering from malaria in the < 5 years age group had the highest number, at 77 (42.3%). According to WHO data in 2017, children aged under 5 years are the most vulnerable group affected by malaria. They accounted for 61% (266,000) of all malaria deaths worldwide [2].

This study shows that hematological abnormalities in children with malaria infection are common. Some subjects (50%) had a Hb level between 5.1 and 10 gr/dL. The prevalence of anemia in our study was 77.4%; 14.8% of subjects had mild anemia, 35.7% had moderate anemia, and 26.9% had severe anemia. The rate of anemia in children < 5 years old was higher than that in children 5-10 years old and > 10 years old, with a mean Hb of 8.71 gr/dL. Data from household surveys conducted in 16 high-burden African countries between 2015 and 2017 show that, among children who tested positive for malaria, the prevalence of any anemia was 79%, mild anemia 21%, moderate anemia 50% and severe anemia 8% [2]. A laboratory trial study of 30 patients in Iran observed significantly lower values of Hb/dl, hematocrit (Ht)%, mean corpuscular volume (MCV)/ fl and mean corpuscular hemoglobin (MCH)/ μl, WBC/ μl, and platelet/ μl among malaria-infected children compared to healthy children [9,11,34,35]. Our finding is consistent with this previous reports.

Cytopenia is a disorder in which the production of one or more blood cell types ceases or is greatly reduced. The types of cytopenia are anemia, which is a reduction in red blood cells (RBCs); leukopenia, which is a reduction in white blood cells (WBCs); neutropenia (neutrophils make up over half of all WBCs), which is a deficiency in neutrophils; and thrombocytopenia, which is deficiency in platelets. Bicytopenia is defined as a condition in which two out of three cell lines (RBCs, WBCs, and platelets) are reduced. The simultaneous reduction in all three formed cell lines is termed pancytopenia [36]. These kinds of cytopenias are not uncommon in malaria; bone marrow diagnosis of adults with bicytopenia and pancytopenia has shown that 3% of bicytopenia and 6% of pancytopenia were caused by malaria [37,38].
The rate of change varies with malaria level, endemicity, hemoglobinopathy background, nutritional status, demographic factors, and malaria immunity [10,39,40]. The occurrence of cytopenias may be attributed to bone marrow suppression and hemophagocytosis [41]. Bicytopenia and pancytopenia usually result from direct or indirect decreasing effects on hematopoietic cell production in the bone marrow [42,43].

Anemia is also a common manifestation, particularly in infants with *P. vivax* and in children with *P. knowlesi* infection [44-46]. Anemia is one of the most common complications in malaria infection, especially in younger children and pregnant women in high transmission areas [41,47]. The pathogenesis of anemia during malaria infection is not clearly understood. However, it is estimated that the main targets of parasites are RBCs, which results in damage to RBCs, acceleration of parasite growth and nonparasitic removal [40], bone marrow dysfunction [48], and the level of parasitemia [49].

Anemia in malaria, however, is associated with a combination of hemolysis of parasitized RBCs, accelerated removal of both parasitized and unparasitized RBCs, depressed and ineffective erythropoiesis due to tumor necrosis factor alpha, anemia of chronic disease, and splenic phagocytosis or pooling [50-52].

Thrombocytopenia was seen in 97 children (53.3%) and was highly significant in the age group > 10 years, with a median 105 x10³/µL. Thrombocytopenia was observed in malaria-infected children in this study, which is consistent with earlier reports [9,34]. There were both qualitative and quantitative changes in platelet abnormalities in malaria. In this study, platelet counts were significantly reduced in children infected with malaria. Thrombocytopenia occurs in 84.9% of patients with malaria infection. This observation may imply that thrombocytopenia can be a marker of *Plasmodium* infection [9,53,54].

There are various hypotheses about thrombocytopenia that occurs in malaria infections. Thrombocytopenia seems to occur through peripheral damage [55], excessive removal of platelets by spleen pooling [56,57] and platelet consumption by the process of disseminated intravascular coagulopathy (DIC) [58]. Sufficient or increased numbers of
megakaryocytes in the bone marrow affect the decrease in thrombopoiesis, which is a possible cause of thrombocytopenia in malaria [56]. The destruction of circulating platelets mediated by immunity has been postulated as the cause of thrombocytopenia seen in malaria infections. Platelets have also been shown to mediate clumping of erythrocytes infected with *P. falciparum* [59]. This can cause apparent thrombocytopenia. Patients infected with malaria experience increased levels of specific immunoglobulin G (IgG) in the blood that binds to malaria antigens bound to platelets, which may lead to acceleration of platelet destruction [19]. Previous studies revealed that platelet aggregation, which is the clumping of platelets, was incorrectly calculated as a single platelet by the analyzer, causing pseudothrombocytopenia [9]. In addition, during malaria infection, endothelial activation is activated and can contribute to the loss of endothelium barrier function and organ dysfunction. This process can use released platelets and proteins as important regulators of endothelial permeability, resulting in thrombocytopenia [60]. However, thrombocytopenia in malaria infection has also been associated with sequestration and pooling of platelets in the spleen, immune-mediated destruction of circulating platelets, and platelets mediating the clumping of *P. falciparum*-infected erythrocytes, leading to pseudothrombocytopenia [9,34,59]. Maximum thrombocytopenia occurred on the fifth or sixth day of infection and gradually returned to normal within 5-7 days after parasitemia ceased [61].

This study has shown, however, that there was no significant difference in total white blood cell count in malaria-infected children. A study by Maina et al also showed that there was no significant difference in the total white blood cell count in malaria-infected children compared to control subjects [9]. The difference in values can be related to environmental factors, socioeconomic status, or malaria immunity, among other factors [10,39,40]. Different views have been expressed on the total WBCs in subjects infected with malaria because leukopenia has been reported by several authors [10,34], and leukocytosis has also been documented by other authors [11,55]. Leucopenia is often seen in malaria-infected patients
confirmed by other studies showing leucopenia [10,62], in contrast to other studies that show leukocytosis [9].

Our study showed lymphocytopenia in 97 children (53.3%). The study has further revealed that there were no statistically significant differences in granulocyte and lymphocyte counts between malaria-infected and noninfected children, and these findings are in agreement with many earlier reports [9,10,11,39,40,54,63,64] but disagree with the findings of George and Ewelike- Ezeani [34]. In some cases of acute malaria, however, lymphocytopenia has been reported, but this has been associated with redistribution of lymphocytes with sequestration in the spleen [65,66].

Generally, clinical symptoms are not significantly associated with a malaria diagnosis, and only one variable shows a significant relationship, pale, with a p value of 0.001. The first symptoms of malaria are nonspecific and characterized by headache, fatigue, abdominal discomfort, and muscle and joint aches, followed by fever, chills, perspiration, anorexia, vomiting and worsening malaise. These features often lead to overdiagnosis of malaria in developing countries, where diagnosis is frequently based only on clinical judgment with limited resources for parasitological testing [67].

Conversely, in children, these manifestations of uncomplicated malaria can be misinterpreted and attributed to other prevalent infections, such as pneumonia, gastroenteritis, and sepsis [68]. In high transmission areas, high and repeated exposure to parasites has an impact on the acquisition of immunity, resulting in a high proportion of asymptomatic infections, particularly in older children and adults [69].

CONCLUSION

Children infected with malaria revealed changes in some hematological parameters, with anemia, low platelet counts, white blood counts, and lymphocyte counts being the most important predictors of malaria infection in our study area. These parameters could improve malaria diagnosis when used in combination with other clinical diagnoses and microscopy.
Abbreviations

P. falciparum: Plasmodium falciparum; P. vivax: Plasmodium vivax; P. malariae: Plasmodium malariae; P. ovale curtisi: Plasmodium ovale curtisi; P. ovale wallikeri: Plasmodium ovale wallikeri; P. knowlesi: Plasmodium knowlesi; Hb: hemoglobin; WHO: World Health Organization; EDTA: ethylenediaminetetraacetic acid; CBC: complete blood count; PS: peripheral smear; WBCs: white blood cells; Ht: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; RBCs: red blood cells; DIC: disseminated intravascular coagulopathy.

Availability of data and materials

The datasets analyzed in this study are available from the corresponding author on request.

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Research Ethics Committee of the Medical School of the Universitas of Sumatera Utara.

Consent for publication

Not applicable.

Competing Interests

The authors have no conflict of interest to declare regarding the publication of this manuscript.

Funding

The authors did not receive any financial support for the research.
Author’s contributions

SJ conceived the study, undertook a literature review, fieldwork, analysed and drafted the manuscript. APP was involved in the critical revision of the manuscript. All authors read and approved the final manuscript.

Acknowledgments

The authors thank the medical records staff at Sorong Regional General Hospital for their help in providing data.

Author’s information

1Department of Child Health, Sorong Regional General Hospital, Sorong, West Papua, Indonesia

2Department of Child Health, Medical Faculty, Universitas Sumatera Utara

*Corresponding author: Dr. Ayodhia Pitaloka Pasaribu

Department of Child Health, Medical Faculty, Universitas of Sumatera Utara

Dr. Mansur Street No. 5, Medan 20156, Indonesia

E-mail: ayodhia_pitaloka@yahoo.com
Hematological Profile of Children With Malaria in Sorong, West Papua, Indonesia

References

1. WHO. World malaria report 2015. Geneva: World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/200018/9789241565158_eng.pdf?jsessionid=A63034A5EF79C858F9DE80D3349C82AD?sequence=1. Accessed July 2020.
2. WHO. World malaria report 2018. Geneva: World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/275867/9789241565653-eng.pdf?ua=1. Accessed July 2020.
3. Sutherland CJ, Tanomsing N, Nolder D, Oguike M, Jennison C, Pukrittayakamee S, et al. Two nonrecombining sympatric forms of the human malaria parasite *Plasmodium ovale* occur globally. J Infect Dis. 2010;201:1544-50.
4. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Makuolu OA, Dondorp AM. Malaria. Lancet. 2013;383:723-35.
5. WHO. National malaria control programme review: Republic of Indonesia. Indonesia: WHO Country Office for Indonesia; 2011. https://apps.who.int/iris/bitstream/handle/10665/253960/9789791947749-eng.pdf;jsessionid=DABF97E279DB585057E086467F1EAB5A?sequence=1. Accessed July 2020.
6. WHO. World malaria report 2016. Geneva: World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/252038/9789241511711-eng.pdf?sequence=1. Accessed July 2020.
7. Muwonge H, Kikomeko S, Sembajjwe LF, Seguya A, Namugwanya C. How reliable are hematological parameters in predicting uncomplicated *Plasmodium falciparum* malaria in an endemic region? ISRN Trop Med. 2013;2013:1–9.
8. Bakhubaira S. Hematological parameters in severe complicated *Plasmodium falciparum* malaria among adults in Aden. Turk J Haematol. 2013;30:394–9.
9. Maina RN, Walsh D, Gaddy C, Hongo G, Waitumbi J, Otieno L, et al. Impact of *Plasmodium falciparum* infection on haematological parameters in children living in Western Kenya. Malar J. 2010;9:S4.
10. Erhart LM, Yingyuen K, Chuanak N, Buathong N, La boonchachai A, Miller RS, et al. Hematologic and clinical indices of malaria in a semi-immune population of western Thailand. Am J Trop Med Hyg. 2004;70:8-14.
11. Adedapo AD, Falade CO, Kotila RT, Ademowo GO. Age as a risk factor for thrombocytopenia and anaemia in children treated for acute uncomplicated falciparum malaria. J Vector Borne Dis. 2007;44:266-71.
12. Helegbe GK, Goka BQ, Kurthals JA, Addae MM, Ollaga E, Tetthe JK, et al. Complement activation in Ghananian children with severe *Plasmodium falciparum* malaria. Malar J. 2007;6:165.
13. McKenzie FE, Prudhomme WA, Magill AJ, Forney JR, Permpanich B, Lucas C, et al. White blood cell counts and malaria. J Infect Dis. 2005;192:323–30.
14. Alves-Junior ER, Gomes LT, Ribatski-Silva D, Mendes CRJ, Leal-Santos FA, Simões LR, et al. Assumed white blood cell count of 8,000 cells/μL overestimates malaria parasite density in the Brazilian Amazon. PLoS ONE. 2014;9:e94193.
15. Lacerda MV, Mourão MP, Coelho HC, Santos JB. Thrombocytopenia in malaria: who cares? Mem Inst Oswaldo Cruz. 2011;106:52-63.
16. Horstmann RD, Dietrich M, Bienzle U, Rasche H. Malaria-induced thrombocytopenia. Ann Hematol. 1981;42:157–64.
17. Latif I, Jamal A. Hematological changes in complete blood picture in paedriatric patients of malaria caused by *Plasmodium vivax* and *falciparum*. J Ayub Med Coll Abbottabad. 2015;27(2):351-5.

18. Chianura L, Errante IC, Travi G, Rossotti R, Puoti M. Hyperglycemia in severe falciparum malaria: a case report. Case Rep Crit Care. 2012;2012:312458.

19. Moulin F, Lesage F, Legros AH, Maroga C, Moussavou A, Guyon P, et al. Thrombocytopenia and *Plasmodium falciparum* malaria in children with different exposures. Arch Dis Child. 2003;88:540-1.

20. Mahmoud A, Yasir M. Thrombocytopenia: a predictor of malaria among febrile patient in Liberia. Infectious Diseases Journal. 2008;14:41-4.

21. Njunda AL, Ngoadjeu DTE, Nsagha DS, Nyanjoh EM, Kwen TD, Assob NJC. Haematological profile of children with malaria in Kumba Health District, South West Region Cameroon. African Journal of Integrated Health. 2016;6:23-9.

22. Kumar R, Kalra SP, Kumar H, Anand AC, Madan H. Pancytopenia--a six year study. J Assoc Physicians India. 2001;49:1078-81.

23. Zaki SA, Shanbag P. Atypical manifestations of malaria. Research and Reports in Tropical Medicine. 2011;2:9-22.

24. WHO. WHO World malaria report 2010. Geneva: World Health Organization. 2010. Accessed July 2020.

25. White NJ. Anaemia and malaria. White Malar J. 2018;17:371.

26. Ullah I, Ali MU, Ali S, Rafiq A, Sattar Z, Hussain S. Hematological profile of patients having malaria-positive peripheral blood smears: a cross-sectional study at a diagnostic research center in Khyber Pakhtunkhwa, Pakistan. Cureus. 2018;10(9):e3376.
36. Anabire NG, Aryee, PA, Helegbe, GK. Hematological abnormalities in patients with malaria and typhoid in Tamale Metropolis of Ghana. BMC Res Notes. 2018;11:353.

37. Durrani SH, Sayyar M, Lal A, Aslam R. Incidentally diagnosed bicytopenia showing a wide spectrum of pathologies on bone marrow morphology. KJMS. 2015;8:247-50.

38. Sweta, Barik S, Chandoke RK, Verma AK. A prospective clinico-hematological study in 100 cases of pancytopenia in capital city of India. J Appl Hematol. 2014;5:45-50.

39. Wickramasinghe SN, Abdalla SH. Blood and bone marrow changes in malaria. Best Pract Res Clin Haematol. 2000;13:277-99.

40. Price RN, Simpson JA, Nosten F, Luxemburger C, Hkirjaroen L, ter Kuile F, et al. Factors contributing to anaemia after uncomplicated falciparum malaria. Am J Trop Med Hyg. 2001;65(5):614-22.

41. Menendez C, Fleming AF, Alonso PL. Malaria-related anaemia. Parasitol Today. 2000;16:469-76.

42. Kar M, Ghosh A. Pancytopenia. J Indian Acad Clin Med. 2002;3:29-34.

43. Savage DG, Allen RH, Gangaizdo IT, Levy LM, Gwanzura C, Moyo A, et al. Pancytopenia in Zimbabwe. Am J Med Sci. 1999;317:22-32.

44. Kenangalem E, Karyana M, Burdarm L, Yeung S, Simpson JA, Tjitra E, et al. Plasmodium vivax infection: a major determinant of severe anaemia in infancy. Malar J. 2016;15:321.

45. Barber BE, William T, Jikal M, Dhararaj P, Menon J, et al. Plasmodium knowlesi malaria in children. Emerg Infect Dis. 2011;17:814-20.

46. Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM. Vivax malaria: neglected and not benign. Am J Trop Med Hyg. 2007;77:79-87.

47. Ugwu EO, Dim CC, Uzochukwu BS, Iloghalu EI, Ugwu AO. Malaria and anaemia in pregnancy: a cross-sectional study of pregnant women in rural communities of Southeastern Nigeria. Int Health. 2014;6:130–7.

48. Quintero JP, Siqueira AM, Tobón A, Blair S, Moreno A, Arévalo-Herrera M, et al. Malaria-related anaemia: a Latin American perspective. Mem Inst Oswaldo Cruz. 2011;106 Suppl 1:91-104.

49. Kitua AY, Smith TA, Alonso PL, Urassa H, Masanja H, Kimario J, et al. The role of low level Plasmodium falciparum parasitaemia in anaemia among infants living in an area of intense and perennial transmission. Trop Med Int Health. 1997;2:325-33.

50. Perrin LH, Mackey LJ, Miescher PA. The hematology of malaria in man. Semin Hematol. 1982;19:70-82.

51. Clark IA, Chaudhri G. Tumour necrosis factor may contribute to the anaemia of malaria by causing dyserythropoiesis and erythrophagocytosis. Br J Haematol. 1988;70:99-103.

52. Dondorp AM, Angus BJ, Chotivanich K, Silamut K, Ruangveerayuth R, Hardeman MR et al. Red blood cell deformability as a predictor of anaemia in severe falciparum malaria. Am J Trop Med Hyg. 1999;60:733–7.

53. Gérardin P, Rogier C, Ka AS, Jouvencel P, Brousse V, Imbert P. Prognostic value of thrombocytopenia in African children with falciparum malaria. Am J Trop Med Hyg. 2002;66:686-91.

54. Lathia TB, Joshi R. Can hematological parameters discriminate malaria from nonmalarious acute febrile illness in the tropics? Indian J Med Sci. 2004;58:239-44.
55. Ladhani S, Lowe B, Cole AO, Kowuondo K, Newton CR. Changes in white blood cells and platelets in children with falciparum malaria: relationship to disease outcome. Br J Haematol. 2002;119:839-47.
56. Beale PJ, Cormack JD, Oldrey TB. Thrombocytopenia in malaria with immunoglobulin (IgM) changes. Br Med J. 1972;1:345-9.
57. Skudowitz RB, Katz J, Lurie A, Levin J, Metz J. Mechanisms of thrombocytopenia in malignant tertian malaria. BMJ. 1973;2:515-8.
58. Essien EM. The circulating platelet in acute malaria infection. Br J Haematol. 1989;72:589-90.
59. Pain A, Ferguson DJ, Kai O, Urban BC, Lowe B, Marsh K, et al. Platelet-mediated clumping of Plasmodium falciparum-infected erythrocytes is a common adhesive phenotype and is associated with severe malaria. Proc Natl Acad Sci U S A. 2001;98(4):1805-10.
60. Brouwers J, Noviyanti R, Fijnheer R, de Groot PG, Trianty L, Mudaliana S, et al. Platelet activation determines angiopoietin-1 and VEGF levels in malaria: implications for their use as biomarkers. PLoS ONE. 2013;8(6):e64850.
61. JadHAV UM, Patkar VS, Kadam NN. Thrombocytopenia in malaria--correlation with type and severity of malaria. J Assoc Physicians India. 2004;52:615-8.
62. Kotepui M, Phunphuech B, Phiwklam N, Chupeerach C, Duangmano S. Effect of malarial infection on haematological parameters in population near Thailand-Myanmar border. Malar J. 2014;13:218.
63. Greenwood BM, Armstrong JR. Comparison of two simple methods for determining malaria parasite density. Trans R Soc Trop Med Hyg. 1991;85:186-8.
64. Nwanjo HU, Opara AU. Effects of falciparum malaria infection on some haematological indices and renal functions. J Med Lab Sci. 2005;14:6–10.
65. Kueh YK, Yeo KL. Haematological alterations in acute malaria. Scand J Haematol. 1982;29:147-52.
66. Lisse IM, Aaby P, Whittle H, Knudsen K. A community study of T lymphocyte subsets and malaria parasitaemia. Trans R Soc Trop Med Hyg. 1994;88:709-10.
67. Reyburn H, Mbatia R, Drakeley C, Carneiro I, Mwakasungula E, Mwerinde O, et al. Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. BMJ. 2004;329:1212.
68. Crawley J, Chu C, Mtov G, Nosten F. Malaria in children. Lancet. 2010;375(9724):1468-81.
69. Baird JK, Krisin, Barcus MJ, Elyazar IRF, Bangs MJ, Maguire JD, et al. Onset of clinical immunity to Plasmodium falciparum among Javanese migrants to Indonesian Papua. Ann Trop Med Parasitol. 2003;97(6):557-64.