HAEMATOLOGICAL PROFILE IN MALARIA WITH SPECIAL REFERENCE TO THROMBOCYTOPENIA

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ABSTRACT

BACKGROUND

Malaria is a well-known disease caused by protozoan parasite of the genus *Plasmodium* that is transmitted to humans by the bite of infected female *Anopheles* mosquito. It is one of the deadliest parasitic diseases of humans causing 1.5-2.7 million deaths annually with around 2.5 billion people are at risk for malaria. Malaria is known to cause various haematological abnormalities like anaemia, thrombocytopenia, leucopenia, monocytosis and even fulminant disseminated intravascular coagulation (DIC). This study analyses and statistically evaluates the various haematological alterations in patients infected with malaria and compare the presence and severity of thrombocytopenia in different species of malaria.

METHODS

This cross-sectional observational study was conducted in Clinical Pathology Laboratory, GMC Thrissur, a tertiary care hospital in Kerala over a period of 18 months from January 2015 to June 2016. A total of 1293 patients aged more than 12 years with a clinical suspicion of malaria were evaluated. The diagnosis of malaria was confirmed by blood smear examination (thick and thin smear stained with Leishman stain). Complete blood picture with platelet count was obtained for all confirmed cases using an automated SYSMEX machine (five-part cell counter).

RESULTS

The findings showed that 67 out of 1293 patients (5.2%) were diagnosed to have malaria by a positive smear report. Males outnumbered females with male to female ratio 12.4:1. Maximum number cases were seen in 21-30 years age group. *P. vivax* was the most common species (57%). Overall 96% of patients had thrombocytopenia, 65.67% of patients had Anaemia and 35.82% of patients had leucopenia.

CONCLUSIONS

P. falciparum as well as *P. vivax* can cause significant haematological changes of which thrombocytopenia was a common finding. There was no significant difference in incidence of thrombocytopenia between *P. vivax* and *P. falciparum* infection.

KEY WORDS

Haematological Abnormalities, Malaria, *P. vivax*, *P. falciparum*, Anaemia, Thrombocytopenia, Leucopenia

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BACKGROUND

Malaria is a well-known disease caused by protozoan parasite of the genus *Plasmodium* that is transmitted to humans by the bite of infected female *Anopheles* mosquito.[1] It is one of the most deadly parasitic diseases of humans causing 1.5-2.7 million deaths annually[2] with around 2.5 billion people are at risk for malaria.[2,3,4] There are four species of the genus *Plasmodium*. These are *P. vivax*, *P. falciparum*, *P .malariae*, and *P. ovale*.[1,5] Infections with *P. falciparum* are the major form of malaria in Southeast Asia and Africa and *P. vivax* is most common in India and Central America.[1,6]

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Studies have indicated that various haematological abnormalities like anaemia, thrombocytopenia, atypical lymphocytosis, rarely disseminated intravascular coagulation (DIC) are associated with malaria. There have also been reports of neutropenia, monocytosis, eosinophilia and leucocytosis.[7-13] Thrombocytopenia in particular is considered to be an important finding, could be encountered even in mild/uncomplicated disease and low platelet count is an important marker for diagnosis of malaria in febrile patients living in endemic area.[14] The objective of this study is to evaluate the effects of malaria on various haematological parameters. Also, to assess the presence and severity of thrombocytopenia in different species of malaria.

METHODS

This is a cross sectional descriptive study conducted in the clinical pathology laboratory Govt. medical college Thrissur during the period January 2015 to June 2016. All clinically suspected cases of malaria were included in this study. The diagnosis of malaria was confirmed by thick and thin blood films stained with Leishman stain. Minimum of 200 fields (Oil immersion) were assessed before labelling a smear as negative. All malaria positive smears were further studied for identification of species and review of smear was done for

platelets count and other haematological changes. Haematological profile including Hb, total WBC count, haematocrit, MCV, MCH, MCHC, RDW and platelet count were assessed using an automated SYSMEX machine (Five-part cell counter). In all samples, differential WBC count was done from peripheral blood film by counting 100 WBCs. Corrected WBC count were applied wherever required. Patients aged < 12 years and with history suggestive of leukemia, MDS or liver diseases were excluded from this study. Patients on drugs causing thrombocytopenia and who were on or had been on antimalarial medication for past one week prior to study were also excluded. Anaemia was graded into Mild (11-12.9 g/dl) Moderate (8-10.9 g/dl) and Severe (< 8 g/dl) according to WHO criteria. Thrombocytopenia was graded into Grade 1 (75,000 to 150,000 cells/cumm), Grade 2 (50,000 to <75,000 cells/cumm), Grade 3 (25,000 to <50,000 cells/cumm) and Grade 4 (<25,000 cells/ cumm) thrombocytopenia (According to NCI criteria).Data collected were entered in Microsoft Excel and analysed using Epi info software version 7. Frequency of different variables were estimated.

RESULTS

Out of 1293 clinically suspected cases of malaria evaluated 67 patients were diagnosed to have malaria by positive smear report of which 38(57%) had *P. vivax* infection, 17(25%) had mixed infection (both *P. vivax* and *P. falciparum*) and 12(18%) had *P. falciparum* infection. Patient's age ranged from 17-63 years. Most of the cases were between_21-30 years accounting for 34.33 %. Mean age was 30.6 years and median age was 26 years. In the present study the number of males (92.54%) outnumbered the number of females (7.46%).

Anaemia was seen in 65.67% of total patients, of which 38.81% had mild anaemia 20.90% had moderate anaemia and 5.97% had severe anaemia. The peripheral smear showed the majority of cases, the anaemia was normocytic normochromic type (49.25%). coming to total WBC count, 58.21% had normal total leucocyte count ranging from 4000-10,000. Leucopenia was observed in 24 (35.82%) cases. Differential leucocyte count showed normal neutrophil count in majority of the patients (68.66%). Neutropenia and neutrophilia were observed in some. Normal lymphocytes were observed in 46 (68.66%). In all the cases, the monocyte count, basophil count and eosinophil count were normal. Reactive lymphocytes was observed in 15 cases of *P. vivax*. Majority of the cases (96%) had thrombocytopenia of which 67.16% of patients had grade 1 thrombocytopenia

Blood Indices in Malaria

50 (74.63%) of patients had normal MCV, 47 (70.15%) patients had normal MCH_and 47(70.15%) patients had normal MCH. In the present study, majority of the patients, 44 (65.67%) had reduced PCV. PCV values were normal in 23(34.33%). RDW were normal in 29 (43.28%) cases, increased in 17(25.37%) cases and rest had reduced RDW.

DISCUSSION

Diagnosing malaria is a challenge where the resources are limited and where malaria diagnostic expertise is lacking.[15,16]

Haemoglobin (g/dl)	Frequency	Percentage
>13	24	34.33%
11-12.9	25	38.81%
8-10.9	14	20.90%
<8	4	5.97%
Total	**67**	**100.00%**

Table 1. Haemoglobin Values in Malaria

Platelet Count	species			Total	Percentage
	PV	PF	Mixed		
Normal	1	0	2	3	4.48%
Grade 1	28	6	11	45	67.16%
Grade 2	4	3	1	8	11.94%
Grade 3	4	3	2	9	13.43%
Grade 4	1	0	1	2	2.99%
Total	**38**	**12**	**17**	**67**	**100.00%**

Table 2. Distribution of Cases according to Grade of Thrombocytopenia

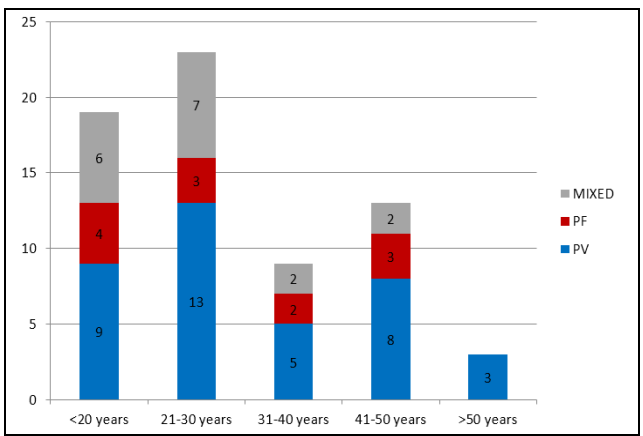

Figure 1. Age Wise Distribution of Cases

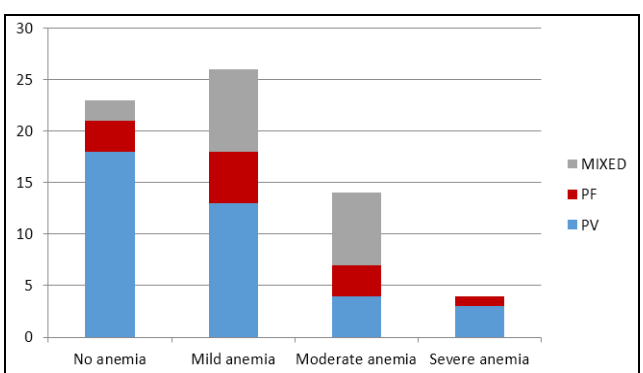

Figure 2. Grade of Anaemia in Cases

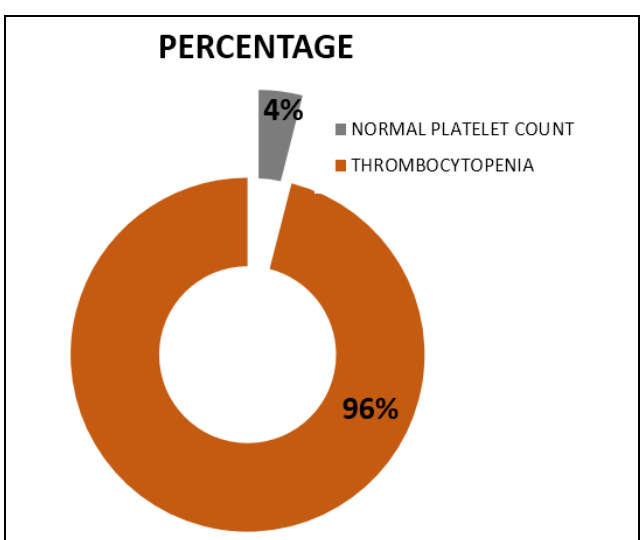

Figure 3. Distribution of Cases According to Platelet Counts

It was a South India based study conducted at department of pathology Government Medical College Thrissur in which the blood samples of febrile patients with clinical suspicion of malaria were investigated using peripheral blood smear (Thin smear and thick smear). It was a heterozygous polygenetic study due to presence of migrant labourers from different part of India seeking medical help at this institution.

The study sample was prepared as per prevailing prevalence trends and statistical methods. The primary aim was to evaluate various haematological alterations in patients infected with malaria and also to assess the presence and severity of thrombocytopenia in different species of malaria. The study duration was over a period of 18 months which included the summer and monsoon.

The haematological parameters were defined as per WHO criteria and the peripheral blood smear were examined thoroughly. The findings showed that 67 (5.2%) out of 1293 patients were diagnosed to have malaria by positive smear report.

The present study showed that out of total 67 cases of malaria investigated, 38 (57%) had *P. vivax* infection, followed by 17 (25%) mixed infection (both *P. vivax* and *P. falciparum*) and 12 (18%) had *P. falciparum* infection. The study by Sajna M.V et al [4] reported a total of 204 cases of which maximum proportion of the cases (92%) were due to *P. vivax* which was consistent with the findings of our study. In the study done by Agrawal. N was almost consistent with our study indicating high incidence of *P. vivax* in India.[17]The study done by Malik and Zaffer showed a higher frequency of *P. vivax* (52%) infection[18] and study done by Faseela and Ronald et al also reported an incidence of 51.6% for *Plasmodium* vivax.[19] In contrast, study done by Ali Hassan Abro and Abdulla Mahmood Ustadi et al in Dubai, UAE showed *P. falciparum* malaria 72 (54%) was commoner than *P. vivax* 59 (45%) while *P. malariae* represented a minority 2 (2%).[11]

The study included dichotomous and categorical variables of malaria infection. Present study showed that the majority of patients (34.33%) were of age group 21-30 years followed by 28.36 % in the age group of 12-20 years. In this study the mean age of the patients infected with *Plasmodium* was 30.6 years. Study of Malik and Zaffer et al have also reported higher incidence in adults (59%).[17] In the study of Jairajpuri ZS et al in 2014, around 81% of the malaria positive cases were seen among the adults.[20]

In this study, the number of males (92.54%) outnumbered the number of females (7.46%). The study by Sajna M.V et al[4] in Thrissur also observed that the proportion of cases in females were less as compared to males accounting for only 11%. Yasinzai and Kakar Sulemankhel et al[21] showed a male to female ratio of 2.6:1. The finding was in concordance with the finding of our study.

According to Yohannes and Petros et al, the maximum number of cases of malaria occurs in the rainy season.[22] Similar trends is observed in our study too.

Haematological Alterations in Malaria

Anaemia and thrombocytopenia are the most frequently found in patients suffering from malaria. Other than anaemia and thrombocytopenia, leukocytosis or leucopenia, atypical lymphocytosis, neutropenia, neutrophilia, monocytosis and rarely DIC have also been reported in cases of malaria.[21,23,24]

Anaemia is known to be associated with malaria in endemic areas, although malaria may not be the prime cause of it.[25] In our study mean Hb level was 12.03 ± 2.38 g/dl in males and 9.88 ± 0.64 g/dl in females. Anaemia was seen in 65.67% of total patients, of which 38.81% had mild anaemia, 20.90% had moderate anaemia and 5.97% had severe anaemia. In Nutan Agrawal et al study, anaemia was present in 94% of cases and in majority of these cases, anaemia was normocytic normochromic type.[18] There was no significant difference in Haemoglobin values between *P. vivax* and *P. falciparum* (p value>0.05). According to Tanomsri Srichaikul, anaemia is one of the most frequent finding in malaria. The incidence of anaemia in malaria was reported to be as high as 80% in their study.[26] C. Igbeneghu et al in 2013 studied 671 patients with malaria. Anaemia was present in 426 patients (63.5%).[27] These studies are in concordance with our study. 75% of the patients infected with *P. falciparum* had anaemia. Of the 4 patients with severe anaemia, 3 cases were of *P. vivax* infection and one had *P. falciparum* infection.

The peripheral smear showed the majority of cases, the anaemia was normocytic normochromic type (49.25%) a finding which is in parallel with the reports of Facer and Beals et al[7] and Nutan Agrawal et al.[18] 8(11.94%) patients had microcytic hypochromic anaemia, 1 (1.49%) had macrocytic anaemia and there were 2 cases of sickle cell anaemia.

Haematocrit runs in parallel to haemoglobin values. In the present study, PCV values were normal in 23 (34.33%) and majority, 44 (65.67%) had a decreased PCV. Agravat. A. H. and Dhruva et al study in 2009, 91% had low haematocrit and only 9% had normal haematocrit.[28] P. Senthikumar et al conducted a study in 2013 they too confirmed a significant difference in haematocrit among patients infected with malaria.[29]These results are similar to our study.

Out of 67 patients, MCV were normal in 50 (74.63%) patients MCH were normal in 47 (70.15%) patients and MCHC were normal in 47 (70.15%) patients. Blood indices including mean cell volume (MCV), mean cell haemoglobin (MCH), and mean cell haemoglobin concentration (MCHC) were reduced in 16(23.88%), 18(26.87%) and 10(14.93%) and ranging 61.0-106 fl, 20-34 pg and 30-36 g/dl with mean of 82.6, 27.4 and 33.02 respectively.

Nutan Agrawal, Kshitiz Nath et al studied 200 malaria cases and 100 cases as control and they observed 52% patients had MCV in normal range and 40% had raised MCV. MCH was reduced in 26% of the cases and MCHC was lowered in 15% of the patients and they found these values to be statistically significant compared to the control group.[18] This was consistent with our study. The finding of Pradhan M. Pagaro et al also showed similar results.[30]

Koltas et al suggested mean corpuscular volume (MCV) along with red cell distribution width (RDW) as a new parameter in the diagnosis of malaria. RDW is the range of changes in the size of red blood cells. Red cells infected with malaria enlarges and hence RDW increases. In the study conducted by Jairajpuri ZS et al, RDW expressed high sensitivity and poor specificity in diagnosis of malaria. RDW values were found to be higher in patients infected with malaria compared to the non-malaria cases.

Koltas et al demonstrated that red cells infected by *P. vivax* becomes noticeably enlarged and pale as the trophozoites grow to approximately half the size of the red cells. The

increase in size continues for 24 hours and at the end of 48 hours these red cells rupture releasing the merozoites.

According to a study by Robert N Maina et. al in the year 2010, there was no significant difference in RDW between the parasitaemic and the nonparasitaemic groups.[31] Bunyaratvej et al also observed a high RDW in their study group and those cases with high RDW showed macrocytes in the smear.[32] Lathia et al also considered RDW as a poor marker in diagnosis of malaria. However, the role of RDW as a parameter in the diagnosis of malaria is always debatable

In our study RDW were normal in 29 (43.28%) cases, increased in 17 (25.37%) cases and rest had reduced RDW. of the 17 patients with a raised RDW 12 (70.59%) had *P. vivax* infection indicating the enlargement of red cells following *P. vivax* infection, which is consistent with the previous studies.

Of total 67 cases of malaria the total leucocyte count was normal in 39 (58.21%) cases. Leucopenia was observed in 24 (35.82%) and Leukocytosis in 4 (5.97%). (Total leucocyte count ranged from 1300 cells/cumm to 52,592 cells/cumm). Leucopenia is a common finding in malaria although occasional leucocytosis can also be seen. Mckenzie FE et al,[33] Jadhav Um et al[34] suggested leucopenia to be due to the localization of leucocytes away from the peripheral circulation, splenic sequestration and other marginal pools rather than actual stasis or depletion. Our study showed leucopenia is not a consistent finding in malaria, as majority showed normal leucocyte count and leukocytosis was seen in some cases with the highest TLC value of 52,592 cells/cumm. 58.33% of patients infected with *P. falciparum* showed leucopenia whereas only 23.68% of patients infected with *P. vivax* showed leucopenia. There was no statistically significant difference between the total leukocyte counts among falciparum, vivax and mixed infection patients ($p>0.05$).

Nutan Agrawal et al observed normal WBC count in 64.5%, leucopoenia in 26% of the patients and leucocytosis in 9% with the highest TLC value of 20,000 cells/cumm. They also observed leucopenia was present more frequently in *P. falciparum* infected patients (25.6%) than in *P. vivax* infected patients (22.1%). Results of these studies are in concordance with our study.

Jadhav UM et al in 2003 studied 264 patients in tropical endemic areas of India and reported incidence of leucopenia more in *P. vivax* (15.2% of 118) than in *P. falciparum* (10.7% of 112 infected patients. This was in discordant with the findings of our study.

Differential leucocyte count showed normal neutrophil count in 46 (68.66%), Neutropenia were observed in 16 (23.88%) and Neutrophilia in 5 (7.46%). Normal lymphocytes were observed in 46 (68.66%), Lymphopenia in 15 (23.39%) and Lymphocytosis in 6 (8.96%) cases. In all cases, the monocytes, basophils and eosinophils were normal. None of the cases showed monocytosis. The study by Ali Hassan Abro et al showed 10% of their cases had monocytosis which was discordant with our study.[11]

In 6 (8.96%) cases, toxic granules were observed in the neutrophils and reactive lymphocytes (Atypical lymphocytes) were observed in 19 (28.36%) cases with their predominance in *P. vivax* infection. A shift to left in neutrophils with prevalent band forms were observed in 7 (10.45%) cases.

The reduction in circulating platelet count is consistently reported in the different types of malaria. In our study thrombocytopenia emerged as a strong predictor of malaria as 64 (96%) of the cases had thrombocytopenia and only 4% had normal platelet count. The mean platelet count was 91.8×10^9/l and platelet count ranged from 10 to 210×10^9/l. All cases of *P. falciparum* infection, 97% of *P. vivax* infection and 88% of the patients who had mixed infection showed thrombocytopenia. There was no significant difference in the incidence of thrombocytopaenia between *P. falciparum* (100%) and *P. vivax* (97%), ($p>0.05$).In the study conducted by Ali Hassan Abro and Abdulla Mahmood Ustadi et al also found no significant difference in the incidence of thrombocytopenia between *P. falciparum* (91%) and *P. vivax* (84.62%) cases which was concordant with our study.[11]

Sethi Bhawna et al in 2013 studied 200 patients of malaria and they found thrombocytopenia in 62% cases and the platelet count ranged from 10.1 to 530×10^9/l with mean of 90.3×10^9/l. 5.5% cases revealed severe thrombocytopenia out of which one had bleeding manifestation.[35]

Nutan Agrawal et al[18] study, 85.5% of patients with malaria developed thrombocytopenia. According to the study conducted by Manmeet K Gill et al in a total of 120 patients with malaria in which the platelet count was done on a fully automated, quantitative, haematology analyser, observed thrombocytopenia in 63.33% cases.[36] Results of all these studies are in concordance with our study.

Dhungat et al. concluded that although a reliable diagnostic marker, there is no prognostic significance of thrombocytopenia in malarial fevers.[37]

Peripheral destruction of platelets caused by the parasite is said to be a cause for thrombocytopenia in which the malarial antigens generate immune complexes that lead to sequestration of platelets by macrophages in spleen Another mechanism suggested for thrombocytopenia is decreased thrombopoiesis. Some authors have suggested disseminated intravascular coagulation (DIC) as a major mechanism for thrombocytopenia in malaria.[17,38]

Ladhani S et al postulated that in acute malaria infection, platelets are found to be hypersensitive and there is increased concentrations of platelet-specific proteins such as beta thromboglobulin (βTG) and platelet factor 4 (PF4).[39] Production of thromboxane A2 and prostacyclin also found to be increased. The hypersensitive (Hyperactive) platelets may enhance haemostatic responses and this may be the reason why bleeding episodes are rare in acute malarial infections, despite the significant thrombocytopenia.

In our study majority of the patients had grade 1 thrombocytopenia (67.16%). 2.99% had grade 4 (severe) thrombocytopenia. When severity of thrombocytopenia was compared between the two groups, in *P. falciparum* cases; 6 (50.00%) had grade 1, 3 (25.00%) grade 2 and 3 (25.00%) had grade 3 thrombocytopenia. In patient with *P. vivax* infection, 28(73.68%) had grade 1, 4 (10.53%) had grade 2, 4 (10.53%) had grade 3 and 1(2.63%) had grade 4 thrombocytopenia. However, severe thrombocytopenia was observed only in patients infected with *P. vivax* (2.63%). Rajesh Chetiwal et al in 2011 in his study found 6.9% of the patients had severe thrombocytopenia (<20,000 cells/ cumm)[38] which was almost consistent with the findings of our study.

CONCLUSIONS

This study concluded that both *P. vivax* and *P. falciparum* can cause significant haematological changes like anaemia and thrombocytopenia. The diagnosis of malaria should be considered with existence of above findings in patients with acute febrile illness. There was no significant difference in incidence of thrombocytopenia between *P. vivax* and *P. falciparum* infection.

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