Original Article

Haematological Parameters Including Platelet Indices in Vivax and Falciparum Malaria

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Abstract

Introduction - In India, malaria is still one the main diseases causing morbidity and mortality after HIV/AIDS. This study has been done to note the changes in haematological parameters like leucopenia, relative neutropenia, lymphocytosis, eosinopenia and presence of reactive lymphocytes in cases of malaria with special reference to platelet indices. The platelet indices include plateletcrit(Pct), platelet distribution width(PDW) and mean platelet volume(MPV).

Materials and methods - In this retrospective study, the haematological parameters in 110 patients with smear positive malaria cases were analysed with an equal number of healthy controls. Cell counts were done using haematology analysers. The haemoglobin, haematocrit, RBC count, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, total and differential leucocyte count, platelet count, mean platelet volume, platelet distribution width and plateletcrit were recorded. Malarial parasites were detected, species identified, parasite density assessed on stained smears.

Results - There was statistically significant leucopenia,relative neutropenia, lymphocytosis, monocytosis, eosinopenia. The platelet count and plateletcrit showed a statistically significant reduction, while the mean platelet volume and platelet distribution width showed an increase.

Conclusion - A history of fever with chills and rigor are sensitive indicators of malaria, but lack specificity. The identification of additional criteria would be helpful in diagnosing malarial infections. Low platelet count had a higher predictive value for malarial infection in addition to leucopenia, relative neutropenia, monocytosis, reactive lymphocytes and eosinopenia as was seen in our study. In addition a low MPV, high Pct and PDW were predictive of malarial infections.

Key Words: Low WBC, Leucopenia, Eosinopenia, Thrombocytopenia, Platelet indices.

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Introduction

In India, malaria is still one the main diseases causing morbidity and mortality after HIV/AIDS. The case load, averaging around 2 million cases annually in the late nineties, has shown a declining trend since 2002. Malaria cases have consistently declined from 2.08 million to 1.06 million during 2001 to 2012. The Slide Positivity Rate (SPR) has also shown gradual decline from 3.50 in 1995 to 0.98 in 2012. The reported *Plasmodium falciparum* cases have declined from 1.14 million in 1995 to 0.53 million cases in 2012. However, the percentage of *Plasmodium falciparum* infections has gradually increased from 39% in 1995 to 50.01% in 2012[1].

According to the National Vector Borne Disease Control Program, in 2013(upto May) the total malaria cases were 190150; there were 115672 cases of falciparum malaria and 51 deaths due to malaria[1].

The number of reported deaths has been levelling around 1000 per year. The Annual Parasite Incidence (API) rate has consistently come down from 2.12 per thousand in 2001 to 0.88 per thousand in 2012 but confirmed deaths due to malaria have been fluctuating during this period between 1707 and 519[1].

The various treatment and preventive strategies adopted by India has helped reduce the falciparum malaria from 0.734 million cases in 2010, a reduction from 1.14 million cases reported in 2000[2]. India, Myanmar and Indonesia still account for approximately 94% of the reported malaria cases in South East Asia in 2008, with India still reporting 65% of the cases. So, India still carries a high burden of the disease[3].

The haematologic changes associated with malaria, namely anaemia, thrombocytopenia and monocytosis are well known[4,5,6,7]. Other parameters are also affected, the values of which may affect the diagnosis and treatment of the disease. This study has been done

on 110 malaria positive cases and 110 healthy controls,to study the changes in other haematological parameters like low normal white blood cell (WBC) count, relative neutropenia, lymphocytosis, eosinopenia and presence of reactive lymphocytes with special reference to platelet indices. The platelet indices include plateletcrit(Pct), platelet distribution width(PDW) and mean platelet volume(MPV). In our study, the MPV and PDW were increased, while the Pct was reduced indicating thrombocytopenia and presence of giant platelets and platelet aggregates. These can be added as flagging parameters in haematology analysers and further refine our search for malarial parasite in the peripheral blood.

Materials and methods

In this retrospective study, the haematological parameters in 110 consecutive patients with smear positive malaria cases in a semi-urban area of Tamil Nadu were analysed between Jun 2010 to Dec 2010. 220 patient samples, 110 being positive for malaria were used as positive cases and 110 healthy patients negative for malaria were used as control for the study.The control population included the patients coming for'Master Health Check-up'to the hospital during the same period.

The inclusion criteria included any patient with smear positive malaria. The demographic criteria including age and sex were noted.The age of the patients ranged from three years to 62 years and 101 patients were males and nine patients were females.

Venous blood samples were collected in EDTA vacutainers. Cell counts were done using the AcT 5 Diff (Coulter) and HMX (Coulter)Cell Count haematology analysers. Daily controls were run on the counters to ensure consistent results. The haemoglobin, haematocrit, RBC count, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, total and differential leukocyte count, platelet count, mean platelet volume, platelet distribution width and plateletcrit were recorded. Thick and thin smears were made and stained with Giemsa and Leishman's stain respectively. Malarial parasites were detected, species identified, parasite density assessed. The microscopic findings were confirmed by another pathologist. The differential WBC count, presence of reactive lymphocytes, toxic granulation in neutrophils, eosinopenia and monocytosis was assessed manually. Platelet count, giant platelets and the presence of platelet aggregates were also noted on smear.

IBM SPSS statistical software version 21 was used for statistical analysis. Red blood cell parameters like hemoglobin, packed cell volume, RBC count, mean corpuscular volume, Mean Corpuscular hemoglobin, Mean Corpuscular hemoglobin concentration, white blood cell parameters like Total count, DC-Polymorphs, Lymphocytes, monocytes, eosinophils, platelet parameters like platelet count, mean platelet volume,plateletcrit, platelet distribution width were taken as explanatory parameters. Malaria status and type of malaria were taken as outcome variables. Descriptive analysis of all the explanatory and outcome parameters was done. All the categorical variables were presented in frequencies and percentages & the numerical variables presented in Means and Standard deviations. The association between explanatory and outcome parameters was assessed by calculating Mean, Mean difference and their 95% CI and p-value by Independent T-test or Paired T-test analysis.

Results

In our study of 110 positive malaria cases, 94 were positive for vivax malaria, 10 cases were positive for falciparum and 6 cases were positive for dual infection, i.e, vivax and falciparum malaria. An equal number of healthy controls, 110 patients, were enrolled for the study.

Table 1 shows haemoglobin and red cell parameters in the malaria and control groups. The haemoglobin level, with a mean of 12.24g/dl in the malaria group and 12.56g/dl in the control group showed no statistical difference(p value = 0.157,mean difference 0.32). The packed cell volume, with a mean of 37.40% in the malaria group and 36.71% in the control group did not show any statistical difference(p-value 0.349, mean difference 0.32). The red blood cell count (RBC count) with a mean of 4.31×10^{12} in the malaria group and 4.32×10^{12} did not show any statistical difference(p-value =0.265). The mean corpuscular volume, with a mean of 85.92 fl in the malaria group and 85.05 fl in the control group, did not show any statistical difference(p-value 0.009). The mean corpuscular haemoglobin with a mean of 28.49 pg in the malaria group and 29.32 pg in the control group did not show any statistical difference(p-value=0.967). The mean corpuscular haemoglobin concentration with a mean of 33.11g/l in the malaria group and 34.31g/l in the control group showed statistical difference with a 95% confidence interval(CI) of -1.47 to-0.94(p-value=0.000) and a mean difference of -1.21. Overall, the RBC parameters except MCH & MCHC, did not show any statistical difference between the malaria and control groups.

Table 2 shows white cell parameters in the malaria and control groups. The total leucocyte count was significantly reduced in malaria cases with a mean of 5.17×10^3/cu mm of blood versus 8.22×10^3/cu mm of blood in the control group and a mean difference of -3.05, with a 95%CI of -3.50 to -2.61 and a p-value of 0.000 indicating that there is a significant low normal WBC count in the malaria group. The differential count showed a reduction in neutrophils with a mean of 51.07% of blood in the malaria group compared with 61.38% in the control group and a mean difference of -10.31, with 95% CI of -13.84 to-6.78 (p value=0.000) indicating that there is a significant neutropenia in the malaria group. There was lymphocytosis with 36.65% in the malaria group versus 28.55% in the control group and a mean difference of 8.10, with a 95% CI of 4.63 to 11.57 and a p-value of 0.000. There was monocytosis with a mean of 9.98% in the malaria group compared with 2.82% in the control group and a mean difference of 7.16, with a 95% CI of 6.09 to 8.24 and a p-value of 0.000.There was a significant eosinopenia with a mean value of 2.37% in the malaria group and 7.26% in the control group and a mean difference of -4.89 with a 95% CI between -5.26 and -4.51 and a p-value of

0.000.Overall,there was a significant low normal WBC count, relative neutropenia, lymphocytosis, monocytosis, and eosinopenia. Reactive lymphocytes and toxic granulation of neutrophils was also seen in the peripheral smear examination of some patients with malaria.

Table 3 shows a comparison of the platelet parameters in the malaria and control groups.The platelet count showed a statistical difference in the platelet count (p-value=0.000) and a mean of 65.98 x 10^3/cu mm in the malaria group and 271.38 x 10^3/cu mm in the control group with a mean difference of -205.40 and a 95% confidence interval (CI) of -215.78 to -195.03. However, the platelet count did not correlate with the parasite density. The mean platelet volume(MPV) was higher in the malaria group(mean 9.31fl) than in the control group(mean 7.47fl) with a mean difference of 1.85,which was statistically significant (p-value=0.000) with a 95%CI of 1.53 to 2.16.The plateletcrit (Pct) was lower in the malaria group(mean 0.07%) than in the control group(mean 0.21%) with a mean difference of -0.15 which was statistically significant(p-value 0.000) with a 95%CI between -0.16 and -0.13.The platelet distribution width(PDW) was higher in the malaria group, (mean 18.48) than in the control group (mean 12.10) which was statistically significant(p-value 0.000) and a mean difference of 6.37, with a 95%CI between 5.45 and 7.30. Overall, the platelet count and plateletcrit showed a statistically significant reduction indicating thrombocytopenia, while the mean platelet volume and platelet distribution width showed a significant increase which indicated the presence of larger platelets together with normal sized platelets and platelet clumps in cases of malaria.

S. No	Parameters	Malaria status	Mean	Mean Difference	95% CI		p-value
					Lower	Upper	
1	Haemoglobin(g/dl)	Malaria	12.24	-0.32	-.76	.12	.157
		No Malaria	12.56				
2	Packed cell volume(%)	Malaria	37.40	0.70	-.76	2.15.	.349
		No Malaria	36.71				
3	RBC count (10^{12})	Malaria	4.31	0.00	-.15	14	.967
		No Malaria	4.32				
4	Mean Corpuscular Volume(fl)	Malaria	85.92	0.87	-.66	2.41	.265
		No Malaria	85.05				
5	Mean corpuscular Haemoglobin (pg)	Malaria	28.49	-0.83	-1.46	-.21	.009
		No Malaria	29.32				
6	Mean corpuscular haemoglobin concentration (g/l)	Malaria	33.11	-1.21	-1.47	-.94	.000
		No Malaria	34.31				

Table 1: Comparison of Red blood cell parameters in malaria patients and control group

S. No	Parameters	Malaria status	Mean	Mean Difference	95% CI		p-value
1	Total count x 10^3/cu mm	Malaria	5.17	-3.05	-3.50	-2.61	.000
		No Malaria	8.22				
2	DC-Polymorphs(%)	Malaria	51.07	-10.31	-13.84	-6.78	.000
		No malaria	61.38				
3	Lymphocytes(%)	Malaria	36.65	8.10	4.63	11.57	.000
		No Malaria	28.55				
4	Monocytes(%)	Malaria	9.98	7.16	6.09	8.24	.000
		No Malaria	2.82				
5	Eosinophils(%)	Malaria	2.37	-4.89	-5.26	-4.51	.000
		No malaria	7.26				

Table 2: Comparison of white blood cell parameters in malaria patients and control group

S. No	Parameter	Malaria status	Mean	Mean Difference	95% CI		p-value
1	Platelet count (10^3/cu mm)	Malaria	65.98	-205.40	-215.78	-195.03	.000
		No Malaria	271.38				
2	Mean Platelet volume(fl)	Malaria	9.31	1.85	1.53	2.16	.000
		No Malaria	7.47				
3	PCT(%)	Malaria	0.07	-0.15	-.16	-.13	.000
		No Malaria	0.21				
4	Platelet distribution Width	Malaria	18.48	6.37	5.45	7.30	.000
		No Malaria	12.10				

Table 3: Comparison of platelet parameters in malaria patients and control group

S. No	Parameters	Malaria parasite	Mean	Mean Difference	95% CI		p-value
1	Platelet count ($x10^3$/cu mm)	PF	65.18	-.929	-20.877	19.019	.927
		PV	66.11				
2	Mean Platelet volume(fl)	PF	8.947	-.4272	-1.2679	.4135	.316
		PV	9.374				
3	PCT(%)	PF	0.058	-.00968	-.0494	.030101 5	.631
		PV	0.068				
4	Platelet distribution Width	PF	18.853	.4391	-2.0960	2.9742	.732
		PV	18.414				

Table 4: Comparison of platelet parameters between *Plasmodium vivax* (PV) and *Plasmodium falciparum* (PF)patients

Discussion

In our retrospective study of 110 patients with malaria infection and an equal number of healthy control patients we noted no significant changes in the RBC parameters except mean corpuscular haemoglobin concentration (MCHC). There was low normal white cell count, relative neutropenia, lymphocytosis, monocytosis, the presence of reactive lymphocytes, eosinopenia and thrombocytopenia. The platelet parameters-the mean platelet volume and platelet distribution width were increased while the platelet count and plateletcrit was reduced. All these changes were similar in the vivax and falciparum infection.Mixed infections(vivax and falciparum) were not analysed as the numbers were small (6 out of 110 patients) and no statistical difference could be arrived at.

Anemia has been documented to occur in malaria because of RBC destruction of both parasitized and unparasitised RBCs, decreased RBC production due to tumour necrosis factor, anaemia of chronic disease and splenic pooling, though in our study we did not find any significant lowering of haemoglobin and the other RBC parameters except MCHC[4]. In sub-Saharan African children and pregnant women infected with *P.falciparum*, it was seen that they had severe anaemia. This is in contrast to our study, where there was no decrease in haemoglobin levels. The anaemia in other studies could be attributed to nutritional status of the patients and co-existing haemoglobinopathy[5,6] .Two studies have also noted a poor correlation between parasite counts and anaemia. They also attribute the anaemia to haemoglobinopathies and red cell enzyme defects[6,7]. Our study was also confined to an older age group with three patients less than 16 years of age. The MCHC was reduced in the malaria group(33.11g/l versus 34.31g/l, mean difference -1.21,p-value 0.000). This parameter has not been discussed in most studies.MCHC is defined as haemoglobin in gms /L x 1000 divided by MCV in femtolitres x RBC count in millions/L and maybe lowered as cells become hypochromic. Tables 4 shows a comparison of the platelet count, mean platelet volume, plateletcrit, platelet distribution width between the vivax and falciparum malaria groups and showed no statistical difference. Thus, the platelet count, mean platelet volume, plateletcrit, platelet distribution width did not differ in the vivax and falciparum infections. This denotes the nutritional status of the patient, which could be low in patients infected with malaria.

Total WBC counts have varied in different studies, some showing a leucocytosis while others have shown leucopenia. Our study shows low normal white cell count in contrast to other studies where no difference in total leucocyte counts was seen and they attribute the difference in total WBC counts to immunological status, environmental factors or socioeconomic status[4]. An increase in total WBC count has been seen though it was not statistically significant (p-value 0.27)[6].White blood cell (WBC) counts during malaria were low to normal, as was noted in our study. It is hypothesized that the leucopenia could be because of localization of leukocytes away from the peripheral circulation and to the spleen and other marginal pools, rather than actual depletion or stasis[8]. A study analyzed and compared the WBC counts of 1,310 inpatients presenting with uncomplicated *P. falciparum* and *P. vivax* malaria. Before-treatment, a statistically significant negative correlation was found between initial WBC count and highest temperature on admission. Before and during treatment, WBC counts were significantly lower in P. *falciparum* than *P. vivax* infection on days 0 and 7[9].This is in contrast to our study where we found low normal white cell count with both vivax and falciparum infections.

Contrary to our study, a decrease in lymphocyte count was seen[5]. A difference in granulocyte, lymphocyte, monocyte, eosinophil and basophil count was not seen which is in contrast to our study where we noted neutropenia, lymphocytosis, reactive lymphocytes, monocytosis and eosinopenia[4]. An increase in neutrophils, monocyte counts and a reduction in lymphocyte and eosinophil counts in patients with falciparum infections has been noted[6]. This is partly in concordance with our study where we noted monocytosis, lymphocytosis, with the presence of reactive lymphocytes and eosinopenia in malaria patients. However, we noted a decrease in neutrophil

counts. A study of thirty-eight patients with *P. vivax* malaria compared with 20, apparently healthy controls noted that at diagnosis, the patients had lymphopenia, marked eosinopenia (the eosinophil count being correlated with the platelet count) and thrombocytopenia which is partly in concordance with our study as our patients had lymphocytosis, eosinopenia and thrombocytopenia[10].

A higher number of band forms in both vivax and falciparum infections though more with falciparum infections was seen. Toxic granulation of neutrophils was seen in falciparum infections which was associated with severity of the disease[11].

Thrombocytopenia has been consistently noted in all studies of malarial infection[4,5,6,7]. In our study too we noted thrombocytopenia, the levels of which were not different in vivax and falciparum infections. Profound thrombocytopenia (6,000/cu mm of blood) was seen in 4 patients with vivax infections and one patient with falciparum infection. The degree of parasitemia did not correlate with the platelet counts. A positive correlation between the degree of parasitaemia and platelet counts has been noted[5].They hypothesize a peripheral platelet destruction and consumption leading to thrombocytopenia. Immune complexes formed between malarial antigen and platelets leading to sequestration of the injured platelets by macrophages in the spleen. Another postulated cause for thrombocytopenia was platelet consumption due to disseminated intravascular coagulation seen in complicated *P. falciparum* malaria, which we did not see in our patients. Platelets could be destroyed due to activation of platelets by adhesion to parasitized RBCs leading to their destruction[5]. An inverse relationship was seen between parasite density and platelet counts- the platelet counts being low with increased parasite density which is in contrast to our study[4,6]. But platelet counts returned to normal with treatment which is in concordance to ours' as well as other studies.

Our study showed platelet dysfunction resulting in platelet aggregates leading to increased MPV and PDW. The MPV (mean platelet volume) increased as the platelet count decreased which has also been seen in other studies which could be because of platelet aggregates and giant platelets[5,6]. Abnormalities in platelet structure and function with invasion by malarial parasites have been reported in some cases. Thrombopoietin (TPO) is the main growth factor for platelet production and is elevated in states of platelet depletion. TPO serum levels have been shown to be significantly higher in subjects with severe malaria, normalizing within 14-21 days of therapy[8]. Two types of changes in platelet dysfunction are seen in malaria. Initially there is platelet hyperactivity, this is followed by platelet hypoactivity. Platelet hyperactivity results from various aggregating agents like immune complexes, surface contact of platelet membrane to malarial red cells and damage to endothelial cells. The injured platelets undergo lysis intravascularly. The release of platelet contents can activate the coagulation cascade and can contribute to disseminated intravascular coagulation[12].Platelet production is not decreased as the megakaryocytes in the marrow are found to be usually normal or increased[13,14].

An increase in MPV with decrease in platelet counts irrespective of whether or not the patients were infected with malaria has been seen[6]. This could be because of the presence of giant platelets which are released by the bone marrow because of platelet destruction.

Larger platelets are metabolically and enzymatically more active. In severe sepsis large numbers of platelets are released by the spleen and bone-marrow leading to increased MPV. Studies in humans and rats showed that large platelets are functionally more active and have a lower threshold for aggregation and activity[15]. In all of these studies, the platelet activation was considered the main mechanism inducing the elevation of MPV and PDW. The PDW (platelet distribution width) was increased, which could be due to variation in size of platelets, some giant platelets and the other normal sized and due to platelet aggregates[15]. PDW has been seen to be linearly correlated with MPV in normal individuals[16].

Thrombocytopenia (<150x109/l) and leucopenia may be used as probable indicator for malaria. Higher MPV (>8 fl) and PDW of 6-10 also show considerable sensitivity for malarial infection. In addition, thrombocytopenia (<150x109/l) and higher MPV (>8 fl) was more sensitive for vivax infection while PDW 6-10 was more sensitive for falciparum infection[17].

A history of fever with chills and rigor are sensitive indicators of malaria, but lack specificity or positive predictive value. "Positional parameters" like the standard deviation (SD), volume of lymphocytes and monocytes would help in screening patients for malarial infection in the laboratory using Coulter GEN.S haematology analyser[18].

Conclusion

A history of fever with chills and rigor are sensitive indicators of malaria, but lack specificity or positive predictive value. The identification of additional criteria would be helpful in diagnosing malarial infections. Low platelet count(<65.98X10*3/cu mm) has a higher predictive value for malarial infection in addition to low MCHC(<33.11 g/l), low normal WBC count (<5.17 X10*3/cu mm,relative neutropenia (<51.07%), lymphocytosis (>36.65%), monocytosis (>9.98%), reactive lymphocytes and eosinopenia(<2.37%) which was seen in our study. Also, low platelet count (<65.98 cells/cu mm of blood), a low MPV(<9.31fl), high Pct(>0.07%) and PDW(>18.48) were predictive of malarial infections. There were no differences in the platelet parameters in falciparum and vivax infections. These parameters could be added as flagging parameters in haematology analysers for review of slides to detect malaria parasite.

Conflict of Interest

The authors declare no conflict of interest.

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