A Clinicopathological Study of Thrombocytopenia in Malaria Cases with Its Evaluation in Different Types of Malaria

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ABSTRACT

BACKGROUND

Malaria is a global health problem, caused by the protozoa plasmodium and is characterized by haematological abnormalities, with thrombocytopenia being the most common. Microscopic examination of thick and thin blood films is the gold standard in diagnosis of malaria. This study was conducted to assess the severity of thrombocytopenia in malaria patients and to correlate it with the type of malaria.

METHODS

A retrospective study was conducted in Yenepoya Medical College, Hospital, Mangalore for a period of 1.5 years. Patients of all ages who were hospitalized or attending OPD were included. Patients with dengue fever and drug-induced thrombocytopenia were excluded. Complete blood cell count was done using an automated cell count analyser. Thrombocytopenia was defined as a platelet count < 150,000 / µl. It was graded as severe: platelet count < 50,000/ µl, moderate: 50,000-100,000/ µl and mild: 100,000-150,000 /µl.

RESULTS

Our study included 120 malaria positive cases with 102 (85 %) males and 18 (15 %) females. 90.8 % cases presented with thrombocytopenia, predominantly moderate to severe thrombocytopenia (80.7 %). *Plasmodium vivax* (Pv) was the most common species found in our study. Ninety-nine (82.5 %) cases were positive for *Plasmodium vivax* (Pv), 8 (6.6 %) cases for *Plasmodium falciparum* (Pf) and 13 (10.8 %) cases had mixed infection with both *Plasmodium vivax* and *Plasmodium falciparum*. Out of 99 cases which had vivax malaria, 88 (88.9 %) cases had thrombocytopenia. All 8 cases detected with falciparum malaria and 13 cases with mixed infection had thrombocytopenia.

CONCLUSIONS

The above findings can have therapeutic implications in avoiding unnecessary platelet infusion in malaria patients. Presence of thrombocytopenia in a patient with acute febrile illness can heighten suspicion of malaria, and initiate prompt treatment.

KEY WORDS

Thrombocytopenia, Malaria, Severity

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BACKGROUND

Malaria is a global health problem with increased morbidity and mortality and an annual incidence of about 216 million cases and an estimated 6,55,000 deaths in 2010.[1,2] It is endemic in several countries and India contributes about 77% of the total malaria cases in Southeast Asia.[2,3] Malaria is caused by infection with plasmodium species and transmitted to people by infected female Anopheles mosquito. Five species of plasmodium which cause malaria in humans are *Plasmodium* vivax, *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale,* and *Plasmodium knowlesi.*[1,2,3,4] In India about 27 % population live in malaria high transmission area and 58 % in low transmission area. Among the overall 1.52 million cases of malaria, 0.76 million cases were due to *Plasmodium falciparum*, accounting to 50 % of the cases and 924 deaths from malaria.[4,5,6,7] Three distinct clinical stages in malarial infection are cold stage, hot stage, and sweating stage. The clinical features of malaria vary from mild to severe, and complicated, according to the patient's immunity state, the intensity of infection and also the presence of other co-morbid conditions.[4] Since malaria parasite affects multiple organs of the body like spleen, liver, brain, gastrointestinal tract and blood vessels, there is wide spectrum of clinical picture ranging from simple malaise to life threatening central nervous system complications like coma.[4,8,9]

The gold standard in the diagnosis of malaria is examination of thick and thin blood films under the light microscope.[2] Malarial antigen-based rapid diagnostic tests are a valid alternative to microscopy, but they are expensive. Haematological abnormalities like anaemia and thrombocytopenia, have been observed in malaria patients with thrombocytopenia (TP) being the most common.[2,4,8,9] Although thrombocytopenia is a reliable diagnostic marker, prognostic implications could vary in different types of malaria. A finding of thrombocytopenia should raise the suspicion of malaria thus prompting a more diligent search for the malaria parasite and perform more specific tests, including multiple peripheral blood smears and ELISA for parasite-specific antigen.[2,4,6] Various immunopathological studies have shown that platelets are an important component of the host innate immune responses against malaria infection.[10,11,12] A number of observational studies also have confirmed the association of thrombocytopenia to malaria, with both non-immunological as well as immunological destruction of platelets being implicated in causing thrombocytopenia.[13] Low platelet counts are commonly encountered in malaria types, and platelet values less than 60,000 / µL have been reported in 29 – 46 % of patients affected with *Plasmodium vivax* malaria. However, thrombocytopenia is not considered as a severity biomarker in *Plasmodium falciparum* malaria, and it has not yet been validated as an independent severity parameter in *Plasmodium vivax* malaria. Numerous studies and case reports have shown that severe thrombocytopenia was described as the most important severity sign of vivax malaria. Therefore, it cannot be excluded that the use of such an indicator may lead to an overestimation of *Plasmodium vivax* malaria severity.[14] The speculated mechanisms which can cause thrombocytopenia are sequestration in spleen, coagulation disorders, oxidative stress and antibody mediated platelet destruction.[4,15,16] Since there is a paucity of data in studies done on correlation of presence and severity of thrombocytopenia with the type of malaria in Indian studies, this study was conducted to assess the severity of thrombocytopenia in malaria patients and to correlate it with the type of malaria.

METHODS

A retrospective study was conducted for a period of one year and five months from August 2017 to December 2018 in a tertiary care hospital attached to a medical college, Dakshina Kannada district. A total of 120 patients who were positive for malaria were included in the study. Malaria test was carried out by thin peripheral blood smear examination and stained by Leishman stain. Patients who were diagnosed with dengue fever and drug-induced thrombocytopenia were excluded from the study. Complete blood cell count was done using an automated cell count analyser (SysmexXN1000). Platelet count of less than 150,000 / µl was used to define thrombocytopenia. Patients were divided into three subgroups based on the platelet count. Thrombocytopenia was graded as severe if platelet count was less than 50,000 / µl, moderate if 50,000 - 100,000 / µl and mild if 100,000-150,000 / µl.[2] Data was entered into an Excel sheet and statistical analysis was performed using SPSS version 23.

RESULTS

In our study, 120 patients with malaria positivity were investigated with platelet count. Almost all cases 120 (100 %) presented with fever as the chief complaint associated with chills and rigors, followed by fatigue (90 %), myalgia (65 %), vomiting (60 %), anorexia (70 %) and headache (35 %). On clinical examination, splenomegaly was seen in about 20 % cases and hepatomegaly in 1 % cases. The age of the patients ranged from 9 years to 69 years with majority of the patients in the age group of 21-30 years (31.6 %). Among the 120 cases, 102 (85 %) patients were males and 18 (15 %) patients were females with male to female ratio of 5:1. Distribution of cases for different age groups is given in table 1.

Age	Distribution	Percentage (%)
1-10 years	3	2.5
11-20 years	24	20
21-30 years	38	31.6
31-40 years	18	15
41-50 years	26	21.6
51-60 years	7	5.8
61-70 years	4	3.3
Total no of Cases	**120**	

Table 1. Distribution of Cases in Different Age Groups

Of the 120 malaria cases, thrombocytopenia was noted in 109 (90.8 %) cases and platelet count was normal in 11 (9.2 %) cases. Mild thrombocytopenia was noted in 21 (19.3 %) cases, moderate in 36 (33 %) cases and severe thrombocytopenia in 52 (47.7 %) cases. Ninety-nine (82.5 %) cases were positive for *Plasmodium vivax* (Pv), 8 (6.6 %)

cases for *Plasmodium falciparum* (Pf) and 13 (10.8 %) cases had mixed infection. Thus, *Plasmodium vivax* was the most common malaria species found in our area of study. While analysing the severity of malaria, out of 99 cases of *Plasmodium vivax* infection, majority of 48 cases had severe (3 + and 4 +) infection and 35 cases had moderate infection (2 +) and 16 cases had mild (1 +) infection. Whereas out of 8 cases of *Plasmodium falciparum*, 5 cases had mild infection, 2 had moderate infection and only 1 case had severe infection. Out of 13 cases with mixed infection, 8 cases showed only mild (1 +) infection and 5 cases showed moderate to severe (2 +, 3 +) infection.

The mean platelet count in *Plasmodium vivax* malaria was 57,124 / µl with a range of 13,000 to 4, 40,000 / µl. Out of the 99 cases which had vivax malaria, 88 (88.9 %) cases had thrombocytopenia, 11 (11.1 %) cases had normal platelet count. Of these 88 cases, 29 (32.9 %) cases had severe thrombocytopenia, 41 (46.6 %) cases had moderate thrombocytopenia and 18 (20.5 %) cases had mild thrombocytopenia.

The mean platelet count of *Plasmodium falciparum* was 59,074 / µl with a range of 27,000 to 108000 / µl. All 8 cases detected with falciparum malaria, had thrombocytopenia. Out of these 8 cases, 3 (37.5 %) cases had severe, 4 (50 %) cases had moderate, and one (12.5 %) case had mild thrombocytopenia respectively.

In mixed infection, mean platelet count was 56,205/µl and range being 27,000 to 116000 / µl. Among the 13 cases of mixed infection, all cases had thrombocytopenia, out of which 4 (30.8 %) cases had severe thrombocytopenia, 7 (53.8 %) cases had moderate thrombocytopenia and 2 (15.4 %) cases had mild thrombocytopenia. Distribution of platelet count in different types of malaria is shown in table 2.

Platelet Count	< 50,000 / µl	51,000-99,000/µl	100,000-149,000/µl.	> 1.5 lakhs	Total
P. vivax	29 (29.3 %)	41 (41.4 %)	18 (18.2 %)	11 (11.1 %)	99 (82.5 %)
P. falciparum	3 (37.5 %)	4 (50 %)	1 (12.5)	-	8 (6.7 %)
Mixed infection	4 (30.8 %)	7 (53.8 %)	2(15.4 %)	-	13 (10.8 %)
Total	**36**	**52**	**21**	**11**	**120**

Table 2. Distribution of Platelet Count in Different Types of Malaria

DISCUSSION

Malaria is a disease of global importance and World Health Organization (WHO) has reported a worldwide annual incidence of 247 million cases and malarial mortality of one million per year.[17] Malaria is a common protozoal disease caused by infection with parasite genus plasmodium and remains one of the major health problems in the tropics and associated with increased morbidity and mortality.[2,4] Malaria affects almost all the blood components with thrombocytopenia and anaemia being often associated with it.[4] Thrombocytopenia in malaria is usually of mild to moderate degree and rarely accompanied by clinical bleeding or disseminated intravascular coagulation (DIC).[2,4,18] Malaria is a true haematological infectious disease with anaemia and thrombocytopenia being the most frequent malaria-associated haematological complications, and these have received more attention in the scientific literature due to their associated mortality.[10,11,12] The mechanism of thrombocytopenia in malaria is not fully understood and it is thought to be a multifactorial phenomenon.[10,11]

However various studies have hypothesized the possible pathoimmunological mechanisms of thrombocytopenia in malaria. Immunoglobulin G binding to platelet-bound malaria antigens, oxidative stress, macrophage colony stimulating factor, spleen pooling, platelet phagocytosis and increased plasma cell free circulating nucleic acid levels in *Plasmodium vivax* are possible mechanisms resulting in damage to thrombocytes or resulting in excessive removal of platelets.[10]

Recently, Coelho et al. in their study demonstrated that macrophage-driven phagocytosis of platelets may be an important contributory mechanism and that the mean platelet volume was greater in thrombocytopenic patients with *Plasmodium vivax* malaria than in controls. The latter finding is particularly important and interesting because the presence of large circulating platelets may be viewed as compensatory mechanism in order to preserve primary haemostasis. Accordingly, bleeding is less commonly seen in the course of malaria even among patients with severe thrombocytopenia.[14]

Thrombocytopenia is a feature commonly seen in *Plasmodium vivax* and *Plasmodium falciparum*, regardless of the severity of infection.[2,4] Studies have also shown that thrombocytopenia is so characteristic of malaria that in some places it is used as an indicator of malaria in patients presenting with fever.[4,18,19,20] Hence patients with acute febrile illness with anaemia and thrombocytopenia without localizing signs should always alert the treating doctor about the possibility of malaria infection.[2]

In the present study, majority of the patients belonged to age group of 21 - 30 years (31.6 %) similar to the study done by Gupta et al. who found about 56 % of the patients in the age group of 15 - 40 years.[4] Whereas, in the study done by Gill et al. the maximum number of patients (43.33 %) were under the age of 20 years.[2]

Male preponderance was observed in our present study with a male to female ratio of 5:1, comparable to the study done by Gill et al. who found that 76 (63.33 %) were males and 44 (36.66 %) patients were females.[2] A study of 230 patients by Gupta et al. also showed that, 150 cases (65.22 %) were males and 80 cases (34.78 %) were females.[4]

The commonest presenting clinical feature in our study was fever with chills and rigors followed by fatigue and myalgia. Similar observation was also seen in study done by Gill et al. who found that among 120 patients with malaria positivity investigated with platelet count, fever with chills and rigors was the most common presenting manifestation followed by headache and myalgia.[2] Gupta et al. in his study also showed that all 230 cases (100 %) presented with fever, followed by weakness, nausea, vomiting, anorexia and diarrhoea.[4] In our study, 90.8 % patients with malaria presented with thrombocytopenia which is comparable with studies done by Kumar et al. and George et al. who found 88.8 % and 93.3 % patients with thrombocytopenia respectively.[21,22] (Table 3). *Plasmodium vivax* was the common malaria species seen in our study, similar to the finding in a study done by Gill et al. who found that 92 patients were positive for *Plasmodium vivax* malaria among the total 120 cases.[2]

In the study done by Gupta et al. also showed that 56.51 % of patients were positive for *Plasmodium vivax* malaria.[4] Similar observations was also seen in majority of the studies done by Faseela et al. Mohapatra et al. and Jadhav et al. [15,23,24,25,26] However in the studies done by Prasad et al. and Murthy et al. found, *Plasmodium falciparum* as the common malaria species.[27,28]

In the present study, 109 cases showed thrombocytopenia, out of which, mild thrombocytopenia was noted in 19.3 % cases, moderate in 33 % and severe thrombocytopenia in 47.7 % cases respectively. Out of the 88 vivax cases, 32.9 % cases had severe thrombocytopenia, 46.6 % cases had moderate thrombocytopenia and 20.5 % cases had mild thrombocytopenia. Among the eight cases detected with falciparum malaria, 37.5 % cases had severe, 50 % cases had moderate and 12.5 % cases had mild thrombocytopenia respectively. In the 13 cases of mixed infection, 30.8 % cases had severe thrombocytopenia, 53.8 % cases had moderate thrombocytopenia and 15.4 % cases had mild thrombocytopenia. Similar observations were also seen in the study done by Gupta et al. who found that among 130 cases detected with vivax malaria, 8.69 % cases had Grade I , 10.86 % cases had Grade II, 17.39 % cases had Grade III and 6.51 % cases had Grade IV thrombocytopenia respectively and out of the 90 falciparum malaria cases, 15 (6.51 %) cases had Grade I thrombocytopenia, 20 (8.69 %) cases had Grade II, 35 (15.17 %) cases had Grade III and no patient was detected with Grade IV thrombocytopenia. Among 10 cases of mixed infection, 3 (1.30%) cases had Grade I thrombocytopenia, 2 cases had Grade II, 3 (1.30 %) cases had Grade III and 1 (0.43 %) case had Grade IV thrombocytopenia.[4]

Numerous studies have shown that thrombocytopenia is a common manifestation equally observed in both *Plasmodium vivax* and falciparum malaria infections. A study review restricted to Brazil reported that the mortality rate in *Plasmodium vivax* malaria with severe thrombocytopenia alone was comparable to that of *Plasmodium falciparum* malaria. Study done by Naing C et al. suggested that magnitude of severe thrombocytopenia and mortality risks are similar in both *Plasmodium vivax* and *Plasmodium falciparum* malaria.[10]

The mean platelet count in *Plasmodium vivax* malaria in our study was 57,124 / µl with a range of 13,000 to 4,40,000 /µl and the mean platelet count of *Plasmodium falciparum* was 59,074 / µl with a range of 27,000 to 108000 / µl. Whereas study done by Gill et al. found the mean platelet count in *Plasmodium vivax* malaria as 1,27,652 / µl with a range of 8000-3,50,000 / µl as against *Plasmodium falciparum* malaria where the mean platelet count was 78,500 / µl with a range of 9000 -1,90,000 / µl.[2]

In our study group of 120 patients with malaria infection, platelet count ranging from 50,000 / µl – 1,50000/µl was noted in 88.9 % cases of plasmodium vivax malaria as against 100 % of cases of *Plasmodium falciparum*. Platelet count less than 50,000 / µl was noted in 29.3 % cases of *Plasmodium vivax* as against 37.5 % cases of *Plasmodium falciparum* malaria. Study done by Gill et al. showed that platelet count ranging from 50,000 / µl – 1,50000 / µl was noted in 37 % cases of *Plasmodium vivax* malaria as against 55.5 % cases of *Plasmodium falciparum*. Platelet count less than 50,000 / µl was noted in only 17.4 % cases of *Plasmodium vivax* malaria as against 33.3 % cases of *Plasmodium falciparum* malaria.[2]

Presence of thrombocytopenia is not a distinguishing feature between falciparum and vivax malaria.[2] It is usually believed that thrombocytopenia is more common in *Plasmodium falciparum* malaria, but contrary to the popular belief, *Plasmodium vivax* can also give rise to thrombocytopenia as seen in our study.

Similar observations were also seen in studies done by Gill et al. and Gupta et al.[2,4] Recent studies from the Indian subcontinent, Qatar and Venezuela have found significant thrombocytopenia in *Plasmodium vivax* malaria than *Plasmodium falciparum*.[4,23,24,29,30]

Various Studies	Common Malaria Species	Number of Cases	Thrombocytopenia (%)
Kumar et al.[21]	*P. vivax*	27	88.8
George et al.[22]	*P. vivax*	30	93.3
Gill et al.[2]	*P. vivax*	120	63.3
Prasad et al.[27]	*P. falciparum*	40	85
Present study	*P. vivax*	120	90.8

Table 3: Review of Various Studies, Estimating the Common Species and Thrombocytopenia in Malaria Patients

The mechanism of thrombocytopenia in malaria is not known clearly. Immune-mediated lysis, sequestration in spleen and dyspoietic process in the bone marrow with diminished platelet production, have been postulated as mechanisms of thrombocytopenia in malaria.[2,9] Platelet structural and functional abnormality have been demonstrated as a consequence of malaria.[2] In the study done by Fajardo and Tallent in 1974 demonstrated the presence of *Plasmodium vivax* within platelets by electron microscopy and suggested a direct lytic effect of the parasite on the platelets.[2,31]

In the study done by Makkar RP et al. showed both non-immunological destruction and immune mechanism are involving specific platelet-associated IgG antibodies that bind directly to the malarial antigen in the platelets that have been recently reported to play a role in the lysis of platelets and the development of thrombocytopenia.[4,15,32]

CONCLUSIONS

Patients with acute febrile illness and presence of thrombocytopenia, increases the possibility of malaria. In patients diagnosed with malaria, higher frequency of moderate to severe thrombocytopenia was observed. Thrombocytopenia is a most important feature in the laboratory diagnosis of malaria and its presence cannot distinguish between *Plasmodium falciparum* and *Plasmodium vivax* malaria.

Malaria infection has to be ruled out, if thrombocytopenia is present in any febrile illness, so as to avoid unnecessary expensive tests, and also correct diagnosis can be made to initiate prompt treatment.

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