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Research Article

A study of thrombocytopenia in malaria and its prognostic significance

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ABSTRACT

Background: Malaria is one of the most common infectious diseases of tropics, affecting 300-500 million people and causing over 1 million deaths each year in the world. Malaria is a multisystem infection and can be associated with many complications. Thrombocytopenia is the most common hematological complication of malaria, but association of thrombocytopenia with different types of malaria and its prognostic implications in context with severity of low platelet count has not been evaluated in many of previous studies. Objectives of the study was to study the incidence, correlation of severity and prognostic significance of thrombocytopenia in malaria.
Methods: A total of 100 cases were included in the study and identified positive for malaria parasites on peripheral smear examination with conventional microscopy and /or by rapid diagnostic test.
Results: Present study includes 100 patient with malaria from which 78% were males and 22% were females. Most of the patients were suffering from *P. vivax* malaria (65%), and rest suffered from *P. falciparum* malaria (32%) and mixed infection (03%). Incidence of thrombocytopenia was 79%, of which mild, moderate and severe thrombocytopenia was 35.44%, 41.77% and 22.78% respectively. Complicated and uncomplicated malaria cases were 22.79% and 77.21% respectively.
Conclusion: Clinical bleeding in severe malaria is not a common feature and occurred in 5.5% of individuals with severe disease. Unnecessary platelet transfusion is not required for mild to moderate degree of thrombocytopenia in malaria patients which further avoids an unnecessary cost burden in the poor group of patients.

Keywords: Malaria, *P. falciparum*, *P. vivax*, Thrombocytopenia

INTRODUCTION

Malaria is an entirely preventable and treatable mosquito-borne illness. Globally~3.2 billion people are at risk of malaria. As per World Health Organization report malaria caused 214 million (range: 149-303 million), infections and 438000 deaths (range: 236 000-635 000), worldwide in 2015. The African Region accounted for most global cases of malaria (88%), followed by the South East Asia Region (10%) and the Eastern Mediterranean Region (2%).[1] Among South East Asian Region, India shares two third of the burden (66%), followed by Myanmar (18%) and Indonesia (10%).[2] Malaria continues to be one of the important public health problem in India. In India the total numbers of confirmed cases of malaria in 2014 were 1.07 million out of which 0.7 million were due to *P. Falciparum* and total 535 deaths were reported due to malaria.[3]

Thrombocytopenia is a well-recognized complication of malaria due to *Plasmodium falciparum* infection but

recently it has also been documented with *Plasmodium vivax* infection from almost every part of world, including India.[4-8] In malarial hematopathy, thrombocytopenia is attributed to excessive platelet pooling and a shortened platelet life span. Thrombocytopenia appears to be associated with elevated serum concentrations of both pro- and anti-inflammatory cytokines.[9]

Immune processes leading to lysis of platelets, sequestration in spleen and impaired thrombopoiesis in bone marrow are all thought to be responsible for the thrombocytopenia in malaria.[10] The presence of thrombocytopenia with high grade fever should increase our suspicion of the probability of the diagnosis of malaria.[11] Malaria can cause simple asymptomatic thrombocytopenia to fulminant disseminated intravascular coagulation (DIC).[12] Previous studies largely reported the major coagulation abnormality as an important abnormality in malaria, but in recent years clinicians have observed that thrombocytopenia is a common and early manifestation of malaria infection, whereas the DIC is rare.[13] It has also been reported that 80% patients of either *P. vivax* or *P. falciparum* malaria develop thrombocytopenia during their infection.[14] The association of thrombocytopenia with different types of malaria and its prognostic implications in context with severity of low platelet count has not been evaluated in many of previous studies. This study determines the incidence of thrombocytopenia in malaria, correlation of severity of thrombocytopenia with type of malaria and its prognostic significance.

METHODS

A total of 100 patients diagnosed to have malaria, admitted at medicine wards in department of medicine, New Medical College Hospital, Govt. Medical College Kota, from January 2015 to December 2015 included in the study. Patient selection and prequalification were done by simple random sampling. This is a prospective study, which satisfying inclusion and exclusion criteria.

All study subjects were identified positive for malaria parasite by peripheral smear examination with conventional microscopy and / or by rapid diagnostic test (SD Bioline malaria antigen P.f HRP-II for *P. Falciparum* and p-LDH for *P. vivax*). Platelet count was done on a fully automated quantitative analyzer (5 part differential cell counter, SYSMEX XS- 800 i, Transasia, Japan). Platelet was counter checked by microscopic examination of thin blood smear.

Platelet count was the number of thrombocytes derived from directly measured platelet pulses, multiplied by a calibration constant and expressed in thousands of thrombocytes per microliter of whole blood. Repeat platelet counts were done daily for 6 days from admission. Very low platelet counts were re-evaluated by manual method as it is a routine practice in our hospital.

Patients with thrombocytopenia were divided into three subgroups based on the platelet count as per reference of Memon AR et al, Kochar DK et al.[15,16] Mild thrombocytopenia (Platelet counts 50,000 to less than 1,50,000 cells/µl), moderate thrombocytopenia (Platelet counts 20,000 to less than 50000 cells/µl) and severe thrombocytopenia (Platelet counts less than 20000 cells/µl).

A written informed consent was taken from each case included in the study after through proper counseling. A detailed history and complete general and systemic examination was done for cases recruited in the study as per performa. Following investigation was done-complete blood count, thick and thin blood smear for malaria parasite and parasite count, specific malarial antigen test, dengue serology, random blood sugar, urine examination, liver function test, renal function test, blood and urine culture and sensitivity, chest X-ray, ultrasonography of abdomen, if necessary: coagulation profile, FDP, G6PD, ABG and CSF analysis and NCCT head was also performed. All patients of *P. Falciparum* and *P.Vivaxmalaria* and mixed infection were treated with either Artesunateor or Quinine sulphate with Doxycycline or Clindamycin, depending upon the clinical severity. Primaquine was given for radical treatment as per malaria species.

Statistical analysis was performed with the statistical package for the social science system version SPSS.[17] Continuous variables are presented as mean±SD, and categorical variables are presented as absolute numbers and percentage. Nominal categorical data between the groups were compared using Chi-squared test. P-Value < 0.05 was considered statistically significance.

RESULTS

Total of 100 patients were eligible and randomized in the study and following characteristic were seen. Demographic characteristics of the study population showed in table 1. Maximum cases (38%) were in 21-30 years of age group. The mean age of cases was 37.9±12.67 years. Out of these 100 cases of malaria, 78 cases (78%) were males and 22 (22%), were females.

Out of 100 cases, 32% were *P. falciparum* malaria, 65% were *P. vivax* malaria and 03% were mixed infection.

Incidence of thrombocytopenia was 79%, out of which mild, moderate and severe degree of thrombocytopenia was seen 35.44%, 41.77% and 22.78% respectively (Table 2). Association of thrombocytopenia with malaria species showed in table 3. Mild thrombocytopenia was commonly associated with *P. vivax* (52.08%) as compared with P. Falciparum (10.71%) whereas severe thrombocytopenia was commonly associated with *P. falciparum* (46.43%) as compared with *P. vivax* (08.34%) and this was statistically significant (P=0.001).

Table 1: Demographic characteristics of the study participant.

Characteristic	Number of cases	Percentage
Age groups (years)		
21-30	38	38%
31-40	25	25%
41-50	21	21%
51-60	10	10%
61-70	06	6%
Sex		
Male	78	78%
Female	22	22%

Association of malaria species with severity of malaria showed in table 4. Uncomplicated and complicated cases were 77.21% and 22.79% respectively. Uncomplicated malaria cases were more associated with *P. vivax* (73.77%) as compared to *P. falciparum* (22.95%) ,whereas complicated malaria cases were more associated with *P. falciparum* (77.77%)as compared to *P. vivax* (16.67%) and this was statistically significant (P=0.001). Association of thrombocytopenia with severity of malaria showed in Table 5, in which mild thrombocytopenia was more common in uncomplicated than complicated malaria (45.90%/0.0%) whereas severe thrombocytopenia was more common in complicated malaria (83.34%/4.92%). This was statistically significant (P=0.001).

Table 2: Incidence of degree of thrombocytopenia in study population.

Degree of thrombocytopenia (platelet counts in lacs/µl)	Number of cases (n=79)	Percentage
Mild (0.50 to <1.5)	28	35.44%
Moderate (0.20 to < 0.50)	33	41.77%
Severe (< 0.20)	18	22.78%

Table 3: Association of thrombocytopenia with malaria species.

Thrombocytopenia	Species			Total
	P. falciparum	*P. vivax*	Mixed	
Mild	03 (10.71%)	25 (52.08%)	00 (00%)	28
Moderate	12 (42.86%)	19 (39.58%)	02 (66.67%)	33
Severe	13 (46.43%)	04 (8.34%)	01 (33.33%)	18
Total	28 (100%)	48 (100%)	03 (100%)	79

χ^2 = 21.568, df=4, P=0.001

Table 4: Association of malaria species with severity of malaria.

Species	Severity of malaria		Total
	Uncomplicated	**Complicated**	
P. falciparum	14 (22.95%)	14 (77.77%)	28
P. vivax	45 (73.77%)	03 (16.67%)	48
Mixed	02 (3.28%)	01 (5.56%)	03
Total	61 (100%)	18 (100%)	79

χ 2 = 19.43, df=2, P=0.001.

Table 5: Association of thrombocytopenia with severity of malaria.

Thrombocytopenia	Severity of malaria		Total
	Uncomplicated	Complicated	
Mild	28 (45.90%)	00 (00%)	28(35.44%)
Moderate	30 (49.18%)	03 (16.66%)	33 (41.78%)
Severe	03 (4.92%)	15 (83.34%)	18 (22.78%)
Total	61(100%)	18 (100%)	79 (100%)

χ2 = 49.288,df= 2, P=0.001

Platelet counts were done daily for 6 days from admission. On day one 79 (100%), on day two 66 (83.54%), on day three 60 (75.94%), on day four 40 (50.63%), on day five 21 (26.58%) and on day six 04 (5.06%) patients had low platelet counts. Four cases were persisted to have low platelet count beyond 6th day despite of adequate therapy among which 03 recovered and 01 died. Association of malaria species with outcome showed in table 6, in which out of 79 cases of thrombocytopenia, 78 cases (98.73%) were recovered and 01 case (1.27%) was died which was infected with *P. Falciparum*. 100% were recovered in *P. Vivax* and Mixed infection.

Table 6: Association of malaria species with outcome.

Species	Outcome		Number of patients
	Died	Recovered	
P. falciparum	1 (3.57%)	27(96.43%)	28
P. vivax	0 (00%)	48 (100%)	48
Mixed	0 (00%)	03 (100%)	03
Total	1 (1.27 %)	78(98.73%)	79

DISCUSSION

This was a prospective study including 100 cases, admitted in the medicine wards at New Medical College Hospital, Govt. Medical College, Kota. The results obtained were discussed as below.

In present study, a total of 100 malaria cases were studied, in which maximum cases were 38% between age group 21-30 years. The mean age of cases was 37.9±12.67 years. Similar study was done by Estacio RH et al who reported that most of their patients (30%) were in between 19-35 years of age, G. Vijaya Kumar et al reported 33% cases were in the age group of 21-30 years of age.[17,18] In present study and other similar study, there was mostly young adult were affected. This may be due to young adults are being more active outside from the home.

In the present study, 78 (78%) were males and 22 (22%) were females. This was similar to Dash SC et al had males 77.77% and females 22.23%, Maddhu et al had males 80.5% and females 19.5% and Sudhir Babu et al had males 75.6% and females 24.4% in their study.[19-21] In present and other study showed that the incidence of malaria is more common in males than females this is because males are more frequently exposed to the risk of acquiring malaria than females because of their outdoor life which they lead. Further, female in India are usually better clothed than males, hence they are less exposed.

In present study, 65% were *P.Vivax* malaria, 32% were *P. Falciparum* malaria and 03% were mixed infection. The commonest species was *P. Vivax* (65%). Similar study was done by Madhu Muddaiah et al reported that *P.Vivax*, *P. Falciparum* and mixed malaria infection were 52.54 %, 33.75 % and 13.69% respectively.[20] Maya PaiDhungat et al also reported 54% cases were *P.Vivax*, 26% were *P. Falciparum* and 20% were mixed infection in their study.[22] Later in 2015 Bezwada Srinivasa Rao et al also supported the present study with similar results showing 61% cases suffering from *P.Vivax* malaria, 35% cases had *P. Falciparum* malaria and 4% had mixed infection.[23] Present and above mentioned studies showed that *P.Vivax* malaria was more common among all malaria cases. Prevalence of *P.Vivax* malaria is common in India because of variations in climatic condition and breeding places of mosquito and genetic resistance of *P. Falciparum.*

In present study incidence of thrombocytopenia was noted 79%. Similarly incidence of thrombocytopenia noted in Jadhav UM et al 79.4%, Patel U et al 78.4%, Mumtaz et al 85.5%, Maya PaiDhungat et al 85%, and Sudheer Babu Devineniet al 81%.[10,11,22,24] Present and other similar studies indicating thrombocytopenia is a common association in malaria.[21]

In present study thrombocytopenia was observed in 79% of cases, among these mild, moderate and severe degree of thrombocytopenia were 35.45%, 41.77% and 22.78% respectively. This was nearly similar to Dhanpat Kochar et al mild ,moderate and severe degree of thrombocytopenia were 33.96%, 51.15% and 14.89% respectively16 and Sudheer Babu Devineni et al mild, moderate and severe degree of thrombocytopenia were 37.03%, 38.27% and 24.70% respectively, means majority of cases had mild to moderate degree of thrombocytopenia.[21]

In present study mild thrombocytopenia was commonly associated with *P. Vivax* (52.08%) as compared to *P. Falciparum* (10.71%), moderate thrombocytopenia was associated with both *P. Falciparum* (42%) and *P. Vivax* (40%) whereas severe thrombocytopenia was commonly associated with *P. Falciparum* (46.43%) as compared to *P. Vivax* (8.34%). Present study was similar to study done by Sudheer Babu Devineniet al.[21]

These figures are also comparable to the study done by Abdul Rauf Memom et al, they found that mild to severe degree thrombocytopenia was observed in hospitalized malaria patients, in which falciparum was found to be the most commonly associated with severe thrombocytopenia.[15] Another study conducted by Jadhav UM et al, in their study they found that absence of thrombocytopenia is uncommon in malaria; its presence is not a distinguishing feature between the two types. Severe thrombocytopenia can occur in both but more commonly in falciparum malaria, Ranjan solanki et al also reported severe thrombocytopenia more associated with *P. Falciparum* (13%) as compared to *P. Vivax* (9%) infection.[10] Concluded that thrombocytopenia is common association with malaria and severe thrombocytopenia was commonly seen in *P. Falciparum* malaria.[25]

Platelet count < 20,000 was seen in *P. Falciparum* and *P.Vivax* both but more commonly in *P. Falciparum* malaria. In present study, statistically significant association found between thrombocytopenia and type of species of malaria parasite. The above finding can have therapeutic implication in context of avoiding unnecessary platelet transfusion with the relatively more benign course in *P. Vivax* malaria.

In present study uncomplicated and complicated cases were 61 (77.21%) and 18 (22.79%) respectively.Present study was nearly similar to study done by Bezwada SrinivasaRao et al and Sudheer Babu Devineniet al among 61 uncomplicated cases of malaria, 14 (22.95%)

were *P. Falciparum*, 45 (73.77%) were *P.Vivax* and 2 (3.28%) were mixed infection and out of 18 cases of complicated malaria 14 (77.77%) were suffering from *P.Falciparum*, 3 (16.67%) from *P.Vivax* and 1(5.56%) was suffering from mixed infection.[21,23]

These findings were comparable to the study conducted by Dharmesh Kumar N Patel et al, in which complicated malaria was more commonly caused by falciparum malaria and was rarely caused by other malarial parasites.[26] Kocher et al, Bezwada Srinivasa Rao et al,Sudheer Babu Devineni et al, they all observed that *P. Falciparum* infection was to be predominantly associated with complicated malaria and *P.Vivax* was more associated with uncomplicated malaria.[16,21,23]

In present study platelet count < 20,000 was seen in 13 cases of *P. Falciparum*, 4 cases of *P.Vivax* and in one case of mixed (P.F. and P.V.) infection means more commonly in *P. Falciparum* malaria. In present study, bleeding tendency as heavy menstrual bleeding was reported in single case (5.55%) of *P. Falciparum* complicated malaria at the time of admission and platelet transfusion was done for her management. Platelet count as low as 11000 cells/mm^3 was reported in *P. Falciparum* malaria and 14000 cells/mm^3 in *P.Vivax* malaria. The possible mechanisms leading to thrombocytopenia in malaria includes immune mechanisms, oxidative stress, alterations in splenic functions and a direct interaction between plasmodium and platelets.[10]

Platelet count improved spontaneously with anti-malarial treatment. Hence according to present study we infer that it is a benign finding in mild and moderate cases of malaria and does not warrant unnecessary platelet transfusion. Present study was supported by Patel U et al study; they reported that thrombocytopenia is rarely accompanied by clinical bleeding or biochemical evidence of DIC. Platelet counts can fall to below 25,000 /mm^3 but this is uncommon. Platelet counts rise rapidly with recovery.[11] Dhanpat Kochar et al also reported that six patients developed severe epistaxis at the time admission and required platelet transfusion.[16] Erel O et al concluded clinical bleeding in severe malaria is not a common feature and occurred in less than 5-10% of individuals with severe disease.[27] Wattana Leowattana et al study showed that platelet levels significantly lower in severe malaria cases and concluded that platelet transfusions are not required for malaria patients with thrombocytopenia who have no bleeding.[28]

In present study maximum thrombocytopenia observed on the first day and gradually returned to normal by 5th to 6th day after completion of treatment and clinical recovery of the patient but 4 patients were persisted thrombocytopenic beyond 6th day. The studies done by Sudheer Babu Devineni et al showed that maximum thrombocytopenia occurred on 3rd and 4th day of infection and gradually returned to normal by 5th to 6th day by adequate anti-malarial treatment.[20]

Present study showed out of 79cases of thrombocytopenia, 78 cases (98.73%) were recovered and 01 case (1.27%) was died which was infected with *P. Falciparum*. 100% were recovered in *P. Vivax* and Mixed infection. This was nearly similar to Sudheer Babu Devineni et al in which 95.9% cases had recovery and 4.1% cases had mortality.[21] In present and other studies in which mortality occurred only in *P. Falciparum* cases. So we can say that complication and severe thrombocytopenia more commonly occurred in *P.Falciparum* malaria.

CONCLUSION

Thrombocytopenia is a common occurrence in *Plasmodium falciparum, Plasmodium vivax* and in mixed infections. Early diagnosing and treating the complications immediately reduces the global burden of malaria. Outcome of complicated malaria is better predicted by severity of thrombocytopenia but it does not help in early diagnosis. Clinical bleeding in severe malaria is not a common feature and occurred in 5.5% of individuals with severe disease. Unnecessary platelet transfusion is not required for mild to moderate degree of thrombocytopenia in malaria patients which further avoids an unnecessary cost burden in the poor group of patients.

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