

Research Article

Incidence, severity, prognostic significance of thrombocytopenia in malaria

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ABSTRACT

Background: Malaria is an infectious disease caused by plasmodium parasite. *P. falciparum* account for majority of morbidity and mortality. Thrombocytopenia and anaemia are the most frequently associated hematological complications in malaria. The low platelet count together with acute febrile syndrome emerged as the strongest predictor of malaria a finding that is frequent and present even before anemia and splenomegaly sets in. Severe thrombocytopenia is a good predictor of poor prognosis than mild and moderate thrombocytopenia. The aim is to study the incidence, severity, prognostic significance of thrombocytopenia in malaria.

Methods: This was an observational and prospective study. The study enrolled 100 patients with thrombocytopenia and fever who were proven to have malaria either by peripheral smear or Quantitative Buffy Coat (QBC) test or malarial antigen assay were included in the study and patients with thrombocytopenia due to other causes were excluded from the study. Platelet count was estimated on a fully automated quantitative analyzer. All the 100 patients were followed during the hospital stay and upto discharge or till the outcome.

Results: The incidence of thrombocytopenia was 73% indicating a common association in malaria. Complicated malaria was observed in 58.80% of *P. falciparum* infection whereas 66% of *P. vivax* infection was associated with uncomplicated malaria. Severe thrombocytopenia showed positive correlation with severity of malaria. Thrombocytopenic patients with effective anti-malarial treatment showed 95.90% recovery and 3 patients 4.10% had mortality. Patients with severe thrombocytopenia were 8.5 times more likely to have complicated malaria with $P < 0.001$ according to student 't' test.

Conclusion: Thrombocytopenia is the most common hematological finding in malaria. Severe thrombocytopenia showed positive correlation with complicated malaria and a good predictor of poor prognosis. Patients with classical malarial fever and thrombocytopenia who were negative for malaria parasite were not included in the study.

Keywords: Complicated malaria, Mixed infections, Malarial antigen assay, Plasmodium, Quantitative buffy coat (QBC), Thrombocytopenia

INTRODUCTION

The word 'malaria' comes from the Italian, and means literally 'bad air'. Malaria remains today as it has been for centuries, a heavy burden on tropical communities, a threat to non-endemic countries, and a danger to

travelers. Malaria ranks third among the major infectious diseases in causing death. Malaria is an infectious disease caused by plasmodium parasite. *Plasmodium vivax*, *P. falciparum*, *P. ovale*, *P. malariae* and *P. knowlesi*.¹ are the different species. *P. falciparum* account for majority of morbidity and is most lethal.² Populations living in sub-

Saharan Africa have the highest risk of acquiring malaria. India contributes 2/3rd burden of malaria among South East countries.³ Infants, young children and pregnant women are malaria high risk groups. Anemia and thrombocytopenia are the most frequent malaria associated hematological complications.⁴ The sensitivity of thrombocytopenia together with acute febrile syndrome was 100% for malaria diagnosis. The presence of thrombocytopenia in acute febrile travelers returning from tropical areas has become a highly sensitive clinical marker for malarial diagnosis.⁵

Malaria parasites are transmitted to humans by the bite of infected female mosquito in which sexual phase of parasite occurs. Asexual phase in the humans starts with tissue schizogony (pre-erythrocytic) in liver followed by erythrocytic schizogony with stages of rings, trophozoites and mature schizonts. Mature schizonts ruptures with release of merozoites which invade uninfected red cells. A female anopheles during its blood meal ingests the sexual forms of parasites male and female gametocytes and the cycle repeats. Clinical relapse occur in *P. vivax* and *P. ovale* due to reactivation of dormant hypnozoites. Red cell antigen (Duffy factor) is necessary for invasion by *P. vivax* parasites. The different modes of transmission of malaria can be either by blood transfusion, intraintravenous drug users, congenital or by travelers.

Malaria is a febrile illness with physical findings like anemia, jaundice and hepatosplenomegaly. *Plasmodium falciparum* is responsible for the fatal forms of the disease. Each species of plasmodium has a characteristic periodicity of fever which depends on the length of the asexual erythrocyte cycle. Cytoadherence, rosette formation and agglutination are central in pathogenesis of cerebral malaria which results due to obstruction of the microcirculation leading to hypoxia and increased lactate production.

The hematological complications in malaria include anemia, leucopenia or leukocytosis, thrombocytopenia and DIC. Anemia in malaria can be due to intravascular haemolysis⁶ Thrombocytopenia is the common along with anemia in malarial infection. Anemia and thrombocytopenia subside gradually with therapy and with clearance of parasitemia. Factors involved in pathogenesis of thrombocytopenia⁷ include hypersplenism, destruction of platelets bound by immune complexes (PAIgG) by the reticuloendothelial system and Disseminated Intravascular Coagulation (DIC). Patients infected with malaria have inverse relationship between the platelet counts and the platelet anti body level⁸ Thrombocytopenia as an early indicator for acute malaria, a finding that is frequent and present even before anemia and splenomegaly sets in. Thrombocytopenia in *falciparum* malaria is associated with high concentrations of IL-10, suggesting that platelets may play a role in the pathophysiology of severe malaria.⁹

Diagnosis of malaria involves identification of malarial parasite in thick/or thin smears currently remains the “gold standard” for malaria diagnosis. The microscopic tests include peripheral smear study (MP test) by thin & thick smear and Quantitative Buffy Coat (QBC) test. Immunochromatographic tests for the detection of malaria antigens using either monoclonal or polyclonal antibodies have opened a new and exciting avenue in malaria diagnosis. Polymerase Chain Reaction (PCR) have been found to be highly sensitive and specific for detecting malarial species than microscopy,

The WHO recommends¹⁰ intravenous artesunate, artemether or quinine as the treatment of choice for severe malaria in adults and children. The WHO recommends artesunate or quinine during the first trimester and artesunate as the first-line therapy during the second and third trimesters¹¹ Artemisinin-based combination therapies (ACT) are highly efficacious, and they are first-line therapies for uncomplicated malaria in most countries where malaria is endemic. A single dose of oral primaquine 0.75 mg/kg should be given in all cases of *falciparum* malaria for gametocidal action. In *vivax* & *ovale* malaria 15 mg of primaquine for 2 weeks is given to prevent relapse. The modalities for prevention of malaria include chemoprophylaxis, vector control strategies and malaria vaccines.

Aim of study

The aim is to study the incidence, severity, prognostic significance of thrombocytopenia in malaria.

METHODS

This is prospective and observational study. Ethical clearance was obtained from the institution. Informed consent was taken from the patients in their own language before collecting data. The present study included 100 patients with thrombocytopenia proved to be malaria positive either by peripheral smear examination (both thick and thin smear) or QBC or by malarial antigen assay. Patients with thrombocytopenia due to other causes were excluded from the study. Lab investigations like hemogram, platelet count, blood sugar, hemoglobinuria, dengue serology, renal function tests, liver function test, arterial blood gas analysis, coagulation profile, CSF analysis, chest X ray, and Ultrasound abdomen were done whenever necessary. Platelet count was estimated on a fully automated quantitative analyzer. Platelet counts were repeated daily until normal or near normal values were reached. All the patients were followed during the hospital stay and upto discharge or till the outcome.

RESULTS

The present study enrolled 100 patients with thrombocytopenia proved to be malaria positive either by peripheral smear examination (both thick and thin smear)

or QBC or by malarial antigen assay. Platelet count was estimated on a fully automated quantitative analyzer. The results were analysed by student 'T' Test and P value <0.001 calculated which is highly significant. The results were shown in tables and figures given below.

Distribution of malarial species in the study showed P. falciparum malaria in 35 patients, P. vivax in 61 patients and 4 patients had mixed infection with a peak age 2nd decade in 29 patients. The number of males 76% outnumbered the females 24% in this study. Fever is the commonest clinical presentation with chills and rigors seen in 100% of patients followed by headache in 34% of patients. Nausea and vomiting was observed to be third most common symptom found in 20% followed by jaundice in 14% of patients.

Figure 1 given below shows various signs. Commonest sign was splenomegaly found in 85% of patients followed by anemia in 55% patients and icterus (14%). A clinical spectrum of fever, splenomegaly and pallor are always associated with malaria.

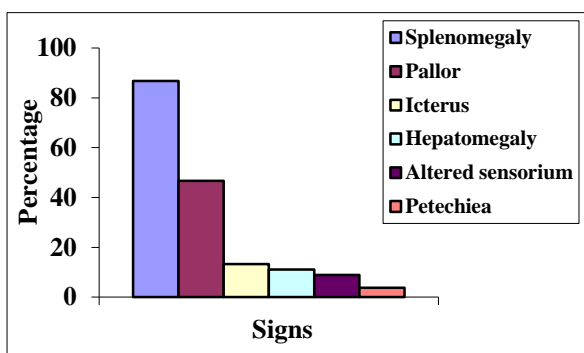


Figure 1: Showing various signs in the study.

Figure 2 given below shows incidence of thrombocytopenia in the study. Out of 100 patients, thrombocytopenia was observed in 73 (73%) of patients indicating thrombocytopenia is a common association in malaria, majority being mild (27%) and moderate (28%) thrombocytopenia and severe thrombocytopenia < 50000 in 18 patients and normal platelet count was noted in 27% of patients.

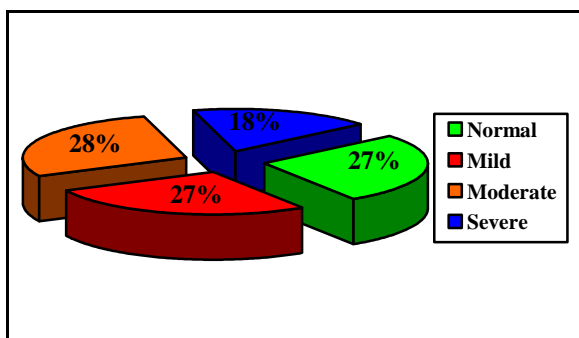


Figure 2: Showing incidence of thrombocytopenia in the study.

Table 1 below shows incidence of thrombocytopenia in different malarial species infection. Out of 73 patients with thrombocytopenia, 29 (39.72%) patients had P. falciparum infection, 42 (57.53%) had P. vivax and 2 patients with thrombocytopenia had mixed infection. Severe thrombocytopenia was commonly associated with P. falciparum (27.50%) as compared to P. vivax (19%) infection.

Table 1: Thrombocytopenia association with different species.

Thrombo-cytopenia	Species			Total
	P. falciparum	P. vivax	Mixed	
Mild	9 (31%)	18 (42.8%)	-	27
Moderate	12 (41.3%)	16 (38%)	-	28
Severe	8 (27.5%)	8 (19%)	2 (100%)	18
Total	29	42	2	73

Table 2 below shows association of different species with severity of malaria. Out of 73 patients with thrombocytopenia, 17 patients (23.30%) had complicated malaria whereas 56 patients (76.70%) had uncomplicated malaria. Among 17 cases of complicated malaria, 10 were P. falciparum, 5 were P. vivax and 2 had mixed infection. P. falciparum infection (58.8%) was associated with complicated malaria whereas P. vivax infection (66%) was associated with uncomplicated malaria.

Table 2: Association of species with severity of malaria.

Species	Type of malaria		Total
	Uncomplicated	Complicated	
P. falciparum	19 (33.9%)	10 (58.8%)	29
P. vivax	37 (66%)	5 (29.4%)	42
Mixed	-	2 (11.7%)	2
Total	56 (100%)	17 (100%)	73

In this study, the association of thrombocytopenia with severity of malaria was observed. Out of 73 patients, complicated malaria noted in 17 patients and uncomplicated malaria noted in 56 patients.

Table 3: Association of thrombocytopenia with severity of malaria.

Thrombo-cytopenia	Severity of malaria		Total
	Uncomplicated	Complicated	
Mild (1.0-1.5 lakh)	24 (42.9%)	3 (17.6%)	27
Moderate (0.5-1.0 lakh)	24 (42.9%)	4 (23.5%)	28
Severe (<0.5 lakh)	8 (14.3%)	10 (58.8%)	18
Total	56 (100.0%)	17 (100.0%)	73
Inference	Patients with severe thrombocytopenia are 8.5 times more likely to have complicated malaria with P <0.001 according to student 'T' test.		

Severe thrombocytopenia was observed in 18 patients, out of which 10 patients (58.80%) associated with complicated malaria as compared to uncomplicated malaria in 8 patients 14.3% as per Table 3 given above.

In this study it was observed that peak thrombocytopenia occurred on 2nd and 3rd day of infection and gradually returned to normal by 5th to 6th day. Those persisted to have severe thrombocytopenia beyond 6th day, their mortality and morbidity found to be high. In this study 10 patients had severe thrombocytopenia beyond 6th day, 7 recovered within 7 to 10 days, 3 died showing high mortality rate.

The outcome of patients with thrombocytopenia in relation species was shown in Table 4 given below. Out of total 73 patients with thrombocytopenia, 70 patients (95.90%) recovered and 3 patients (4.10%) had mortality. Regarding species wise outcome, out of 29 patients with falciparum infection 28(96.60%) showed recovery, one patient died. In vivax malaria, all 42 patients showed 100% mortality as shown in Table 4.

Table 4: Outcome in relation to different species.

Species	Outcome		Number of patients
	Died	Recovered	
P. falciparum	1 (3.40%)	28 (96.60%)	29
P. vivax	-	42 (100.0%)	42
Mixed	2 (100.0%)	-	2
Total	3 (4.10%)	70 (95.90%)	73

DISCUSSION

Malaria remains today as it has been for centuries, a heavy burden on tropical communities, a threat to non-endemic countries, and a danger to travelers.⁵ P. falciparum account for majority of morbidity and is most lethal.² Anemia and thrombocytopenia are the most frequent malaria associated hematological complications.⁴ The sensitivity of thrombocytopenia together with acute febrile syndrome was 100% for malarial diagnosis. The low platelet count emerged as the strongest predictor of malaria, a finding that is frequent and present even before anemia and splenomegaly sets in. In this contest, we undertook a prospective and observational study comprising of 100 thrombocytopenic patients with fever who were proven to have malaria either by peripheral smear or QBC or malarial antigen assay to assess the incidence, severity and prognostic significance of thrombocytopenia.

In this study, out of 100 patients 79% patients were in age group between 20-50 years and with a peak of 29% of patients in 2nd decade of life which correlates with the observation done by V. H. Talib et al.¹² due to increased mobility in young adults. The number of males 76% outnumbered the females 24% in our study correlating with study conducted by V. H. Talib et al.¹² due to the

increased outdoor activities and hence proximity to the vectors.

Fever is the commonest clinical presentation with chills and rigors seen in 100% of patients. Headache is the 2nd most common symptom found in 34% of patients which correlated with incidence of 33.40% in study by G. Lalitha Murthy et al.¹³ and 33.45% in S. R. Mehta et al.¹⁴ The studies conducted by S. R. Mehta et al.¹⁴ and V. H. Talib et al.¹² showed incidence of nausea and vomiting by 84.4% & 57.7% respectively though our study showed only 20% incidence. Jaundice in 14% of patients which correlated with incidence of 23.41% in study by G. Lalitha Murthy et al.¹³ In this study commonest sign was splenomegaly found in 85% of patients followed by anemia found in 55% patients. A clinical spectrum of fever, splenomegaly and pallor is always associated with malaria as per Figure 1. In this study, out of 100 patients 35 had P. falciparum malaria (35%), 61 patients had P. vivax (61%) and 4 patients had mixed infection (4%). Prevalence of P. vivax is common in India because of variation in climatic conditions, breeding places of mosquitoes and genetic resistance of P. falciparum.¹⁵

In this study out of 100 patients, thrombocytopenia was observed in 73 (73%) of patients indicating thrombocytopenia is a common association in malaria,¹⁶ majority being mild (27%) and moderate (28%) thrombocytopenia and severe thrombocytopenia <50000 in 18 patients and normal platelet count was noted in 27% of patients as per Figure 2. which correlates with studies by Kumar and Sasirekha.¹⁷ The sensitivity of thrombocytopenia together with the acute febrile syndrome was 100% for malaria diagnosis, with a specificity of 70%, a positive predictive value of 86% and a negative predictive value of 100%.

Out of 73 patients with thrombocytopenia in the study, 29 (39.72%) patients had P. falciparum infection, 42 (57.53%) had P. vivax and 2 patients had mixed infection as shown in Table 1. Severe thrombocytopenia commonly associated with P. falciparum (27%) as compared to P. vivax (19%) infection which correlates with Mahmoud and Yasir et al.¹⁸

In this study among 73 patients, 17 (23%) had complicated malaria and 56 (76.70%) had uncomplicated malaria. P. falciparum infection (58.8%) was observed to be predominantly associated with complicated malaria whereas P. vivax infection (66%) was seen in uncomplicated malaria as shown in Table 2 which correlates with Kocher et al., G. Lalitha murthy, Mohapatra et al. studies.¹⁹ In this study, the association of thrombocytopenia with severity of malaria was observed. Severe thrombocytopenia was observed in 18 patients, out of which 10 patients (58.80%) associated with complicated malaria as compared to uncomplicated malaria in 8 patients 14.3% as per Table 3.

In this study peak thrombocytopenia occurred on 2nd and 3rd day of infection and gradually returned to normal 5th to 6th day. Severe thrombocytopenia beyond 6th day showed increased mortality and morbidity despite of adequate therapy. The outcome of patients with thrombocytopenia in relation species infection was given in Table 4. In this study, out of total 73 patients with thrombocytopenia, 70 (95.90%) recovered and 3 patients (4.10%) had mortality. Regarding species wise outcome, out of 29 patients with falciparum infection 28 (96.60%) showed recovery and 1 patient died. In vivax malaria all 42 patients showed 100% mortality as shown in Table:4. Patients who had severe thrombocytopenia at the time of admission are 8.5 times more prone to develop complications when compared to mild and moderate thrombocytopenia based on student 'T' test.

CONCLUSION

Thrombocytopenia is the most frequent malaria associated hematological complication and emerged as the strongest predictor of malaria. The sensitivity of thrombocytopenia together with acute febrile syndrome was 100% for malarial diagnosis. Severe thrombocytopenia commonly associated with *P. falciparum* and showed positive correlation with complicated malaria. Severe thrombocytopenia is a good predictor of poor prognosis than mild and moderate thrombocytopenia. As thrombocytopenia is strong predictor of malaria, every patient should be investigated and effective treatment should be delivered before complications arise to limit morbidity and mortality.

Limitations of the study

Patients with thrombocytopenia with classical malarial fever who were negative for malaria parasite were not included in the study.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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