Correlation of Presence and Severity of Thrombocytopenia with Types and Severity of Malaria: A study from tertiary care center of North India

Manoj Kumar¹, Ajay Kumar¹, Parshika Panwar², Ravi Kant²

¹Department of General Medicine, UPUMS, Saifai, Etawah, Uttar Pradesh, ²Department of General Medicine, AIIMS Rishikesh, Uttarakhand, India

ABSTRACT

Background: Malaria is a major public health problem in India. Malaria is commonly associated with thrombocytopenia, but its significance is not well established. A prospective study was conducted to correlate the presence and severity of thrombocytopenia with types and severity of malaria. Material and Methods: This prospective observational study was performed in the Department of General Medicine at a tertiary care center of north India from January 2019 to June 2020. A total of 100 adult patients found positive for malaria parasites on peripheral smear examination were enrolled for the analysis. Results: The incidence of thrombocytopenia was seen in 80% of total malaria patients. There was a significant \( P = 0.0001 \) association of severity of thrombocytopenia with symptoms and signs of malaria except for rigor. There was no significant \( P > 0.05 \) association of severity of thrombocytopenia with age. There was a significant \( P = 0.003 \) association of severity of thrombocytopenia with M antigen. The analysis of variance showed that there was a significant \( P = 0.0001 \) difference in Lung Function Test (LFT) and Kidney Function Test (KFT) parameters with severity of thrombocytopenia; whereas in blood parameters, only red blood cell counts were associated significantly with the severity of thrombocytopenia. Conclusion: Thrombocytopenia is a frequent overall manifestation of both falciparum and vivax malaria. Severe thrombocytopenia is identified in all age groups, commonly in males, and increases the risk of death from falciparum or vivax malaria, particularly in those with concurrent severe anemia. Early diagnosis and prompt treatment of malaria reduces the complications and adverse outcomes of the disease.

Keywords: Anemia, malaria, P. falciparum, P. vivax, thrombocytopenia

Introduction

Malaria is one of the major public health problems for people living in tropical and subtropical areas associated with significant morbidity and large economic impact. Despite intensive control efforts during the twentieth century, approximately 40% of the world's population remains at risk of infection. The Malaria disease is a parasitic infection caused by Plasmodium species, especially falciparum, vivax, malarialae, and ovale.

Malaria is an endemic problem in 91 countries, and India is a major contributor for malaria cases in Southeast Asia, with 89% of total cases as per records of 2015. In India, about 27% population lives in malaria high-transmission zone (more than 1 case per 1000 population) and 58% in low-transmission zone.

Malaria is commonly associated with various degrees of hematological complications like anemia and thrombocytopenia. The anemia is usually due to varied reasons ranging from...
hemolysis to comorbidities like parasitic infections, folate, iron, and vitamin B12 deficiencies in endemic areas, antimalarials, and further complicated by the coexistence of thalassemia and other haemoglobinopathies. Although anemia associated with malaria has received widespread attention from the scientific community due to its associated mortality, thrombocytopenia remains neglected to a greater extent. The presence of thrombocytopenia can act as a guide to clinical diagnosis for primary care physicians where other tests may not be available.

The exact mechanism responsible for thrombocytopenia is yet to be understood. Some researchers hypothesize that the malaria parasite produces factors that reduce the platelet production from the megakaryocytes. This saves the parasite from the platelet-mediated clearance as a survival mechanism. The speculated mechanisms leading to thrombocytopenia are coagulation disturbances, sequestering of platelets in the spleen during acute infection, bone marrow alterations, antibody-mediated platelet destruction, oxidative stress, and the role of platelets as cofactors in triggering severe malaria.

According to the World Health Organization, thrombocytopenia is not included in the disease severity criteria for malaria, but this is a highly sensitive clinical marker for diagnosis of malaria during acute febrile illness in travelers returning from tropical areas. There are contradictory reports regarding the prognostic significance and the true incidence of thrombocytopenia in different types of malaria.

The correlation of thrombocytopenia with the type of malaria and prognostic implications in context with the severity of the low platelet count has not been evaluated in extensive studies. Because of the paucity of data from Indian studies, we have attempted to correlate the presence and severity of thrombocytopenia with the types and severity of malaria.

**Materials and Methods**

This prospective observational study was performed in the Department of General Medicine at a tertiary care center of north India from January 2019 to June 2020. A total of 100 adult patients positive for malaria parasites on peripheral smear examination were enrolled for the analysis after approval from the institutional ethics committee. Patients fulfilling inclusion criteria (age group of 18–60 years admitted with smear positive for malaria) were included after taking written informed consent.

Patients of acute febrile illness with a clinical feature and/or diagnosis of associated dengue, leptospirosis, and typhoid fever as well as patients with immunocompromised status, receiving immunosuppressive treatment; known cases of chronic liver disease; and pregnant women were excluded from the analysis.

A detailed history and complete general and systemic examination was done for cases recruited in the study as per proforma. All the patients were examined by an expert doctor; and after that, routine and specific blood investigations were done to evaluate falciparum/vivax malaria. Local and English language was preferred to ask the screening questions during the initial screening of patients and data were recorded in an excel sheet.

A total of 119 patients were screened; nine patients refused to participate in the study; ten were not fit according to inclusion criteria; and finally, 100 patients with smear positive for falciparum/vivax malaria were included for analysis.

All subjects were identified positive for malaria parasite by peripheral smear examination with conventional microscopy and/or by rapid diagnostic test (SD Bioline malaria antigen Pf HRP-II for P. Falciparum and p-LDH for P. vivax). Platelet counts were recorded on a fully automated quantitative analyzer. Platelets were counter-checked by microscopic examination of thin blood smear in cases of very low counts. Platelets were counted as 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 during admission. Very low platelet counts were re-evaluated by manual methods 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. and Kochar DK et al. Mild thrombocytopenia (Platelet counts 50,000 to 1,50,000 cells/µl), moderate thrombocytopenia (Platelet counts 20,000 to 50,000 cells/µl), and severe thrombocytopenia (Platelet counts less than 20,000 cells/µl). All patients of P. falciparum and P. vivax malaria and mixed infections were treated with either Artesunate or Quinine sulfate with Doxycycline or Clindamycin, depending upon the clinical severity. Primaquine was given for radical treatment as per malaria species.

**Statistical analysis**

Microsoft Excel was used in creating the database, while the data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23 for Windows. For the continuous quantitative variables, mean and standard deviation was calculated. The inter-group continuous variables were compared using suitable tools of statistics like unpaired student’s t-test. Two quantitative variables within a group were compared using student’s paired t-test. The categorical data were expressed in terms of rates, ratios, and percentages. The associations between the outcome, clinical, and demographic characteristics were tested using Chi-square test or Fisher’s exact test. For all the tests, the value of P less than 5% (0.05) was considered significant.

**Results**

In the present study, malaria was observed commonly in males (64%), and thrombocytopenia was seen in 80% of patients. The demographic relationship of incidence and severity of thrombocytopenia is shown in Table 1. More than one-third of patients (40.0%) had moderate thrombocytopenia followed by mild (36.2%) and severe (23.8%).
The mild thrombocytopenia was most common among patients aged 41–50 years (55.6%). Moderate thrombocytopenia was most common in ages 30–40 years (50%) and severe thrombocytopenia was most common in ages >50 years (28.6%). However, there was no significant ($P > 0.05$) association of severity of thrombocytopenia with age. The mild thrombocytopenia was higher among males (41.2%) than females (36.2%). The moderate thrombocytopenia was higher among females (48.3%) than males (35.3%) and severe thrombocytopenia was also higher among females (24.1%) than males (23.5%) [Table 1].

There was a significant ($P = 0.0001$) association of severity of thrombocytopenia with symptoms except for rigor. Splenomegaly was seen in 38.8% of patients and hepatomegaly was present in 18.8% of patients. Dyspnea was present in 23.7% and CNS manifestations were present in 22.5% patients. ($P < 0.01$) [Table 2].

$P.$ vivax was present in 62.5% of the patients. Mild thrombocytopenia was more commonly associated with $P.$ vivax malaria (50%). There was a significant ($P = 0.003$) association of severity of thrombocytopenia with M antigen [Table 3]. The analysis of variance showed that there was a significant ($P = 0.0001$) difference in LFT, and KFT parameters with the severity of thrombocytopenia, whereas in blood parameters, only red blood cell counts were associated significantly with severity of thrombocytopenia [Table 4].

### Table 1: Demographic Distribution of incidence and severity of Thrombocytopenia

| Parameters          | Thrombocytopenia (n=80) % | Mild (n=29) % | Moderate (n=32) % | Severe (n=19) % | $P$  |
|---------------------|---------------------------|---------------|-------------------|-----------------|------|
| Age in years        |                           |               |                   |                 |      |
| <30                 | 43 (53.7)                 | 14 (48.3)     | 18 (56.3)         | 11 (57.9)       | 0.74 |
| 30-40               | 14 (17.5)                 | 4 (13.8)      | 7 (21.9)          | 3 (15.8)        |      |
| 41-50               | 9 (11.3)                  | 5 (17.2)      | 3 (9.3)           | 1 (5.3)         |      |
| >50                 | 14 (17.5)                 | 6 (20.7)      | 4 (12.5)          | 4 (21.0)        |      |
| Mean age (years)    | 33.09±13.53               | 36.04±14.12   | 31.36±12.41       | 32.22±15.16     | 0.38 |
| Gender              |                           |               |                   |                 |      |
| Male                | 51 (63.8)                 | 21 (72.4)     | 18 (56.3)         | 11 (57.9)       | 0.52 |
| Female              | 29 (36.2)                 | 8 (27.6)      | 14 (43.7)         | 8 (42.1)        |      |

### Table 2: Association of clinical findings with severity of thrombocytopenia

| Signs and Symptoms  | Thrombocytopenia (n=80) % | Mild (n=29)% | Moderate (n=32)% | Severe (n=19)% | $P$ |
|---------------------|---------------------------|-------------|------------------|---------------|-----|
| Signs               |                           |             |                  |               |     |
| Splenomegaly        | 31 (38.8)                 | 7 (24.1)    | 8 (25.0)         | 16 (84.2)     | 0.008 |
| Hepatomegaly        | 15 (18.8)                 | 1 (3.4)     | 0 (0.0)          | 14 (73.7)     | 0.001 |
| Dyspnea             | 19 (23.7)                 | 0 (0.0)     | 1 (3.1)          | 18 (94.7)     | 0.001 |
| CNS                 | 18 (22.5)                 | 0 (0.0)     | 1 (3.1)          | 17 (89.5)     | 0.001 |
| Symptoms            |                           |             |                  |               |     |
| Rigor               | 65 (81.25)                | 22 (75.9)   | 27 (84.4)        | 16 (84.2)     | 0.59 |
| Headache            | 80 (100.0)                | 29 (100.0)  | 32 (100.0)       | 19 (100.0)    | <0.01 |
| Pallor              | 18 (22.5)                 | 0 (0.0)     | 1 (3.1)          | 17 (89.5)     | <0.01 |
| Icterus             | 18 (22.5)                 | 0 (0.0)     | 1 (3.1)          | 17 (89.5)     | <0.01 |
| Low Fever           | 8 (10.0)                  | 4 (13.8)    | 4 (12.5)         | 0 (0.0)       | <0.01 |
| Moderate Fever      | 47 (58.75)                | 22 (75.9)   | 24 (75.0)        | 1 (5.3)       |     |
| High Fever          | 25 (31.25)                | 3 (10.3)    | 4 (12.5)         | 18 (94.7)     |     |

### Discussion

Malarial fever remains a major health problem in tropical regions, including India. Sporozoites from the salivary gland of infected mosquitoes are transferred into the human host, where they invade the liver parenchyma and mature into schizonts which release merozoites. These merozoites infect the red blood cells and can further mature into gametocyte or erythrocytic schizonts. Thrombocytopenia is a common associated finding in acute malaria, and it can occur in both P. falciparum and P. vivax infections. Thrombocytopenia is also seen in patients with acute febrile illness due to viral causes, but its presence is considered as a diagnostic clue for malaria in endemic areas.$^{[10]}$

Thrombocytopenia was seen in 80.0% of the cases in our series and highlights the fact that normal platelet count is unlikely in the laboratory findings of malaria. Out of these cases, 29 (36.25%) were having mild, 32 (40.0%) moderate, and 19 (23.75%) were having severe thrombocytopenia. Thrombocytopenia in malaria was found in 78.4% of cases in a study by Jadhav U M, et al.$^{[13]}$ similarly Shetty G, et al.$^{[12]}$ from Mangalore also reported thrombocytopenia in 72.0% cases of malarial infection. According to Meenai F J, et al.$^{[13]}$ overall 103 (85.83%) patients were found to have low platelet count. The mechanism of thrombocytopenia in malaria could be attributed to peripheral destruction and consumption by disseminated intravascular coagulation (DIC), sequestration of platelets by the spleen,
Kumar, et al.: Correlation of thrombocytopenia with types and severity of malaria

Table 3: Association of M antigen with severity of thrombocytopenia

| M. Antigen | Thrombocytopenia (n=80) % | Mild (n=29)% | Moderate (n=32)% | Severe (n=19)% | P |
|------------|--------------------------|--------------|------------------|---------------|---|
| P. Vivax   | 50 (62.5)                | 25 (82.6)    | 20 (62.5)        | 5 (62.3)      | 0.003 |
| P. Falciparum | 27 (33.8)              | 4 (13.8)     | 10 (31.3)        | 13 (68.4)     |     |
| Mixed      | 3 (3.7)                  | 0 (0.0)      | 2 (6.2)          | 1 (5.3)       |     |

Table 4: Association of blood parameters with severity of Thrombocytopenia

| Blood Parameters | Severity of Thrombocytopenia | P | Mild vs Moderate | Mild vs Severe | Moderate vs Severe |
|------------------|------------------------------|---|------------------|----------------|--------------------|
|                  | Mild | Moderate | Severe |              |                   |                   |
| C                | WBC  | 6819.64±16 | 5453.64±110 | 4450.12±394 | 0.002             |                   |
|                  | RBC  | 3.49±0.35  | 3.06±0.34   | 2.12±0.34   | <0.01             |                   |
| L                | STB  | 0.88±0.17  | 1.38±0.78   | 4.73±1.18   | <0.01             | <0.01             | <0.01             |
|                  | SIB  | 0.61±0.15  | 1.05±0.59   | 3.62±0.97   | <0.01             | <0.01             | <0.01             |
| T                | SGOT | 29.04±5.75 | 39.91±23.5  | 136.94±34.4 | <0.01             | <0.01             | <0.01             |
|                  | SGPT | 45.96±6.47 | 50.52±24.87 | 155.89±35.1 | <0.01             | <0.01             | <0.01             |
| S. Albumin       | 4.01±0.45 | 3.44±0.18 | 2.70±0.19   | <0.01         | <0.01             | <0.01             |
| K                | Urea | 30.12±5.6  | 31.97±53    | 66.6±12.12  | 0.01              | 0.01              | <0.01             |
| FT               | Creatinine | 0.83±0.18 | 0.84±0.47   | 2.66±0.68   | <0.01             | <0.01             | <0.01             |

Immune mediated destruction, or oxygen free radicals induced damage to platelets.

In our study, the majority of patients were between 18 to 30 years of age (54%), followed by 30–40 years, 41-50 years (12%), and more than 50 years (17%). The mean age of the studied patients was 33.09 ± 13.53 years like in other reported series in literature (Jadhav U M, et al. 37.4 ± 14.2 years) young adults were mostly affected. This may be due to young adults being more active outside of the home. There was no significant (P > 0.05) association of severity of thrombocytopenia with age.

In the present study, there was a male predominance, as 64 (64.0%) patients were males and 36 (36.0%) patients were females. Our findings are in accordance with studies conducted by Murthy GL., Trampuz A., Patel U., and Patel U., who found that males were more commonly involved than females. This may be attributed to more frequent exposure of males to the risk of acquiring malaria than females because they mostly spend their time outdoors, which increases the risk of exposure to malarial infection.

On statistical analysis, there was a significant (P = 0.0001) association of severity of thrombocytopenia with signs and symptoms of malaria except for rigor. Splenomegaly was present in 38.8%, hepatomegaly in 18.8%, dyspnea in 23.7%, and CNS signs were seen in 22.5% patients of malaria with thrombocytopenia. Spleen is a major site of immune response to the parasite and controlling of parasitemia by phagocytosis of red blood cells containing the parasite, leading to enlargement of the spleen.

Echoing to the findings reported in literature,[16,17] fever with chills was the most common symptom followed by atypical symptoms headache and vomiting. Common clinical signs in decreasing order are splenomegaly (86%), pallor (46.6%), Icterus (13.3%), hepatomegaly (10%), altered sensorium (8%), and petechiae (6%). A clinical spectrum of fever, splenomegaly, and pallor is most often associated with malaria.

P. vivax was the most common parasite present in 62.5% of patients, 33.18% were P. falciparum malaria, and 3.79% were a mixed infection. Devineni S B, et al.[17] in their study, reported that out of 180 cases, 114 had P. vivax malaria, 62 patients had P. falciparum, and four had mixed infection. Although uneven geographical distribution is there, the prevalence of P. vivax malaria is common in India because of variation in climatic conditions, breeding places of mosquitoes, and genetic resistance to P. Falciparum.

Mild thrombocytopenia was more common in P. vivax malaria. There was a significant (P = 0.003) association of severity of thrombocytopenia with M antigen. We observed that severe thrombocytopenia was commonly associated with P. falciparum (68.4%) as compared to P. vivax (26.3%). Memon A R, et al.[8] found that severe thrombocytopenia was observed in hospitalized malarial patients, in which falciparum was found to be the most common. Another study conducted by Jadhav U M., et al.[11] in their study, it was found that absence of thrombocytopenia is uncommon in malaria, its presence is not a distinguishing feature between the two types of malaria, and severe thrombocytopenia can occur in both but more commonly in falciparum malaria. Although in the study by Kaur D, et al.[10], severe thrombocytopenia was seen in vivax malaria.

In the present study, according to the analysis of variance, there was a significant (P = 0.0001) difference in LFT and KFT parameters with the severity of thrombocytopenia, whereas in CBC parameters, only RBCs were associated significantly with the severity of thrombocytopenia.
Key points and take-home message
Malaria is associated with different degrees of low platelet count, commonly mild or moderate, and bleeding is rare even during severe malaria. Also, other causes for thrombocytopenia should be considered because there are many normal and abnormal conditions that can lead to change in platelet numbers if malaria is associated with underlying medical conditions that may contribute to it. Blood test to see platelet counts is easily available everywhere, even at primary health centers, so the presence of thrombocytopenia can guide the health care providers regarding clinical diagnosis of malaria and its severity. In the present study, thrombocytopenia has a significant association with symptoms of malaria, M antigen, and deranged liver function tests.

Thrombocytopenia may not be a cause of mortality by itself, but it can be a marker of increased severity, and the need for aggressive management is warranted in this clinical scenario.

Conclusions
Thrombocytopenia is a frequent manifestation of both falciparum and vivax malaria. Severe thrombocytopenia can be seen in all age categories, commonly in males and falciparum malaria, particularly in those with concurrent severe anemia. Early diagnosis and prompt treatment of complications reduces the lethality of malaria. Thrombocytopenia is a key indicator for malaria in patients with acute febrile illness.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Mohammed O, Abdalla M. Determination of prothrombin time, activated partial thromboplastin time and D dimer levels among Malaria infected patients in Sinnar State, Sudan. Open Access Libr J 2019;6:e5973.
2. Faseela TS, Ronald AR, Anita KB, Chaitra SM, Rai Y. Diagnostic value of platelet count in Malaria. J Clin Diagn Res 2011;5:464-6.
3. Qayum A, Arya R, Kumar P, Lynn AM. Socio-economic, epidemiological and geographic features based on GIS-integrated mapping to identify malarial hotspots. Malaria Journal 2015 May;14:192.DOI:10.1186/s12936-015-0685-4.
4. Ghosh K, Ghosh K. Pathogenesis of anemia in malaria: A concise review. Parasitol Res 2007;101:1463-9.
5. Srivastava K, Sharma M, Mitchell WB. Malaria and thrombopoiesis: A possible mechanism for the malarial thrombocytopenia. J Immunol Infect Inflamm 2017;2:14.
6. Faseela TS, Roche, Anita KB, Malli CS, Rai Y. Diagnostic value of platelet count in malaria. J Clin Diagn Res 2011;5:464-6.
7. Gebreweld A, Erkahun Y, Feleke DG, Hailu G, Fiseha T. Thrombocytopenia as a diagnostic marker for Malaria in patients with acute febrile illness. J Trop Med 2021;2021:5585272.
8. Memon AR, Afsar S. Thrombocytopenia in hospitalized malaria patients. Pak J Med Sci 2006;22:141-3.
9. Kochar DK, Das A, Kochar A. Thrombocytopenia in plasmodium falciparum, plasmodium vivax and mixed infection malaria: A study from Bikaner (Northwestern India). Platelets 2010;21:623-7.
10. Patel U, Ghandi G, Friedman S, Niranjan S. Thrombocytopenia in malaria. J Nati Med Assoc 2004;96:1212-4.
11. Jadhav UM, Patkar VS, Kadam NN. Thrombocytopenia in malaria--correlation with type and severity of malaria. J Assoc Physicians India 2004;52:615-8.
12. Shetty G, Shreedhara K. Thrombocytopenia in children with malaria – A Study from Coastal Karnataka, India. Asia Pacific J Trop Dis 2012;2:2107-9.
13. Meenai FJ, Jalaly T, Khairkar P, Narkhede V, Sawke GK, Sawke N. Significance of thrombocytopenia in different types of malaria. Int J Med Res Rev 2016;4:52-4.
14. Murthy GL, Sahay RK, Srinivasan VR, Upadhaya AC, Shantaram V, Gayatri K. Clinical profile of falciparum malaria in a tertiary care hospital. J Indian Med Assoc 2000;98:160-9.
15. Trampuz A, Jereb M, Muzlovic I, Prabhuj RM. Clinical review: Severe Malaria. Crit Care 2003;7:315-23.
16. Giha HA, Elghazali G, A Elgadir TM, A Elbasit IE, Eltahir EM, Baraka OZ, et al. Clinical pattern of severe plasmodium falciparum malaria in Sudan in an area characterized by seasonal and unstable malaria transmission. Trans R Soc Trop Med Hyg 2005;99:243-51.
17. Devineni SB, Suneetha O, Harshavardhan N. Study of platelet count in Malaria patients and the correlation between the presence and severity of platelet count with type of Malaria. J Evol Med Dent Sci 2015;4:11734-46.
18. Kaur D, Wasir V, Gulati S. Unusual presentation of plasmodium vivax Malaria with severe thrombocytopenia and acute renal failure. J Trop Pediatr 2007;53:210-2.
19. Muley A, Lakhani J, Bhirud S, Patel A. Thrombocytopenia in plasmodium vivax Malaria: How significant? J Trop Med 2014;2014:567469.