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Original Article

Thrombocytopenia and its Comparison with *Plasmodium Vivax* and *Plasmodium Falciparum* in Malaria Patients

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Abstract

Background: Malaria in Pakistan is a serious public health problem and thrombocytopenia can serve as diagnostic predictive marker.
Objective: The objective of present study was to find out the frequency of *plasmodium vivax* and falciparum in malaria patients and to compare the frequency of thrombocytopenia in patients effected by *plasmodium falciparum* versus vivax.
Study type, settings & duration: This observational cross-sectional study was conducted at Department of Medicine, Jinnah Hospital, Lahore from February 2018 to July 2018.
Methodology: Fever more than 100°F for >3 days and >2 hours daily along with evidence of presence of >1 parasite of plasmodium on microscopic examination of thick smear of blood was labeled as malaria. Subsequently, depending on the type of parasite on microscopic examination of thin smear of blood (>1per film) the patients were labeled *plasmodium falciparum* and *plasmodium vivax*. Thrombocytopenia was defined as a platelet count <150,000 per mm^3. After taking informed written consent, 236 patients of malaria were enrolled using non-probability consecutive sampling technique. Approximately three ml of blood was taken from each patient for microscopic examination of plasmodium type and platelet count measurement. SPSS version 17.0 was used for data entry and analysis. Data was stratified and chi square test applied keeping p-value <0.05 significant.
Results: Mean age was 42.14±13.5 years with 123(52.1%) females. Seventy two (30.5%) patients had previous history of malaria. Mean duration of fever was 4.61±0.6 days. There were 88 (37.3%) patients with *plasmodium falciparum* and 148 (62.7%) had *plasmodium vivax*. Thrombocytopenia was seen in 41 (17.3%) patients. Out of the 88 patients with *plasmodium falciparum*, 11 (12.5%) patients had thrombocytopenia while it was seen in 30 (20.27%) patients out of 148 with *plasmodium vivax*.
Conclusion: *Plasmodium vivax* was more commonly seen in our population. Over all, thrombocytopenia was seen in 17.3% malaria patients while frequency of thrombocytopenia was higher in malaria patients affected by *plasmodium vivax* as compared to those affected from *plasmodium falciparum*.
Key words: Malaria, thrombocytopenia, *plasmodium vivax*, *plasmodium falciparum*.

Introduction

The clinical features of malaria differ depending on epidemiology, geography, patient age and immunity. In endemic areas, children younger than 36 months and pregnant women are at highest risk because adults and older children have partial immunity due to repeated infections.[1] Early symptoms of malaria vary and can include tachypnea, tachycardia, cough, malaise, chills, fatigue, headache, diaphoresis, nausea, vomiting, anorexia, diarrhea, abdominal pain, joint pain and body aches.[2] In severe complicated malaria patients present with hyperparasitemia [≥100,000 parasites/microL (5-10% parasitized RBCs)].[3] WHO has recommended cutoffs of 10% (in high transmission areas) and 5% (in low transmission

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MA & NIB conceptualized the project. MA, SA & AIB did the data collection. MA, MH & FA did the literature search. NIB & AIB also performed Statistical analysis. Drafting, revision & writing of manuscript were done by all authors.

areas) for hyperparasitemia to diagnose severe disease.[4] Circulatory collapse, altered consciousness, seizures, respiratory distress, renal failure, metabolic acidosis, hemoglobinuria, coagulopathy, hepatic failure, disseminated intravascular coagulation, hypoglycemia, anemia and intravascular hemolysis may complicate severe malaria.[5] *P. falciparum* is usually the cause of severe complicated malaria having a poor prognosis.[6] Coagulopathy and thrombocytopenia are frequently seen in falciparum malaria and up to 5% may develop disseminated intravascular coagulation.[5]

Malaria has no pathognomonic clinical signs or symptoms.[7] Clinical features suggesting malaria include fever with no localizing symptoms, spleenomegaly, platelet count ≤150,000 per mm^3 and bilirubin ≥1.3 mg/dL.[8] Among Canadian travelers with malaria, anemia was present in 41% and low WBC count in 48%.[9] Thrombocytopenia was reported in 83% with *P. vivax* and 62% with *P. falciparum*.[9] The presence of triad of fever, thrombocytopenia, and splenomegaly was 71% sensitive, 88% specific, 91% positive predictive value and 64% negative predictive value for malaria diagnosis.[10] The gold standard for malaria diagnosis is parasite detection by light microscopy on giemsa stained blood smears.[11] Two types of blood smears are prepared: thick smear and thin smear. Specie identification, stage of circulating parasite and measurement of parasite load is done by thin smears. Thick smears help to measure parasite density also when parasitemia is low.[12]

Malaria in Pakistan is extremely unstable and prevails to be a serious public health problem with 319,592 cases yearly including 67% with vivax malaria and 33 % with falciparum malaria and still a large number of cases remained unreported.[13] The increasing incidence of malaria in Pakistan highlights a need to address the early diagnostic markers and management. Although proper diagnostic test for malaria on serum are available in developed countries but they are usually unavailable in Pakistan. So malaria diagnosis is commonly done by blood smear examination. The presence of thrombocytopenia can serve as diagnostic predictive marker in patients of malaria considering the limitation of observer based blood smear examination. However, limited and variable existing data is available showing no statistical difference between mean platelet count between the two infection[14] to higher frequency of thrombocytopenia in *P. vivax* 18.18% as compared to *P. falciparum* 10.59%.[15] The objectives of the study were to find out the frequency of *plasmodium vivax* and falciparum among patients of malaria and to compare the frequency of thrombocytopenia in patients of malaria with infection due to *plasmodium falciparum* and vivax.

Methodology

The present observational cross-sectional study was conducted at Department of Medicine, Jinnah Hospital, Lahore from February 2018 to July 2018 with a sample size of 236 keeping 95% confidence level and 6 % margin of error.[2,5] Fever more than 100°F for ≥3 days and ≥2 hours daily along with evidence of presence of ≥1 parasite of plasmodium on microscopic examination of thick smear of blood was labeled as malaria. Subsequently, depending on the type of parasite on microscopic examination of thin smear of blood (≥1per film) the patients were labeled *plasmodium falciparum* and plasmodium vivax. Thrombocytopenia was defined as a platelet count <150,000 per mm.[3]

After taking informed consent, 236 malaria patients of both genders aged 20-60 years were enrolled by non-probability consecutive sampling. Patients with concomitant infections such as dengue fever, patients with pre-existing conditions causing thrombocytopenia such as chronic liver disease, immune thrombocytopenia, aplastic anemia; and patients on heparin or NSAIDs as determined by history and medical record were excluded. Three ml of blood was taken in an EDTA anticoagulant vial under aseptic measure from each patient for light microscopy examination of plasmodium type and platelet count measurement by automated analyzers as per operational definitions. SPSS version 17.0 was used for data entry and analysis. For quantitative variables, mean and standard deviation were calculated. Qualitative variables were presented in form of frequency and percentage. Data was stratified to reduce effect modifiers and chi-square test was applied keeping *p*-value <0.05 as significant.

The ethical approval was obtained from Ethical Review Board of Allama Iqbal Medical College/ Jinnah Hospital, Lahore.

Results

Of the 236 patients enrolled, 113 (47.9%) were male and 123 (52.1%) females. Seventy two (30.5%) patients had previous history of malaria. Minimum age was 20 years and maximum age 59 years with mean age 42.14±13.5 years. Minimum duration of fever was 3 days and maximum duration was 6 days with mean duration of disease 4.61±0.6 days. There were 88 (37.3%) patients with

plasmodium falciparum and 148 (62.7%) had *plasmodium vivax*. Minimum platelet count was 83,000 mm^3 and maximum platelet count was 196,000 mm^3 with mean platelet count 163,394.07±28,200.68 mm^3. Thrombocytopenia was present in 41 (17.3%) patients. Out of the 88 patients with *plasmodium falciparum*, 11 (12.5%) patients had thrombocytopenia while it was seen in 30 (20.27%) patients out of 148 with *plasmodium vivax*. Comparison of thrombocytopenia with demographic variables is shown in Table.

Table: Comparison of Thrombocytopenia with demographic variables.

Demographic variables	*Thrombocytopenia*		*p-value*
	Present n (%)	*Absent n (%)*	
Sex			
Male	22 (19.4)	91 (80.6)	0.415
Female	19 (15.4)	104 (84.6)	
Age group			
20 to 40 years	21 (18.9)	90 (81.1)	0.555
41 to 60 years	20 (16.0)	105 (84.0)	
Past history of malaria			
Present	12 (16.6)	60 (83.4)	0.850
Absent	29 (17.6)	135 (82.4)	
Type of malaria			
Plasmodium Vivax	30 (20.2)	118 (79.8)	0.128
Plasmodium Falciparium	11 (12.5)	77 (87.5)	

Discussion

The objective of present study was to find out the frequency of *plasmodium vivax* and falciparum among patients of malaria and to compare the frequency of thrombocytopenia in patients of malaria with infection due to *plasmodium falciparum* and vivax in a tertiary care hospital. In this regard a cross-sectional study was performed. By using non probability consecutive sampling, we collected the relevant information from two hundred and thirty six malaria patients from Jinnah Hospital Lahore. Malaria due to *plasmodium falciparum* was seen in 37.3% and 62.7% patients had vivax malaria. White et al.[16] showed that the occurrence of severe features was comparable in severe vivax and falciparum malaria but thrombocytopenia was more prevalent in *P. vivax*. Hepatic dysfunction was present in 50.0% of P. falciparum and 43.8% of *P. vivax*, and the risk of mortality in severe malaria was 7.3% in *P. falciparum* and 4.5% in *P. vivax*.[16] In the present study, out of the 88 patients having malaria due to *plasmodium falciparum* there were 12.5% patients in which thrombocytopenia was diagnosed. On the other hand thrombocytopenia was detected in 20.27% patients out of 148 patients of malaria due to *plasmodium vivax*. The frequency of thrombocytopenia was higher in *plasmodium vivax* as compared to *plasmodium falciparum*. The study by White el al.[17] with 228 patients of fever and thrombocytopenia showed 121 (53.0%) had malaria, of these falciparum malaria was seen in 68.0% and vivax malaria in 38%. Platelet counts ranged from 25,000 to 150,000/dL and mean platelet count was 101,000/dL±47,500.[17] In the study by Brooker et al.[18] 46% had *plasmodium vivax* and 54% *Plasmodium falciparum* while 18% had severe falciparum infection but thrombocytopenia was comparable in both malaria types. However, patients with severe falciparum malaria, with high parasitaemia, with renal failure and multi-organ dysfunction had significantly reduced mean platelet counts.[18]

In the present study, the mean age was 42.14±13.55 years, the mean fever duration was 4.61±0.67 days and the mean platelet count was 163394.07±28200.68 mm^3. There were 47.9% males and 30.5% patients having previous history of malaria. By using chi-square test it was observed that there was no significant association between gender and thrombocytopenia with *p*-value 0.415. No significant association was seen in age groups and thrombocytopenia having *p*-value 0.555. Significant association was not found between previous history of malaria and thrombocytopenia with *p*-value 0.85. Thrombocytopenia was not significantly associated with type of malaria (*plasmodium falciparum* and *plasmodium vivax*) having *p*-value 0.128. Thrombocytopenia was seen in 24.6% over all with 49.3% *P. falciparum* and 43.23% *P. vivax* malaria patients.[4] Severe thrombocytopenia risk was 18.1% with *P. vivax* as opposed to 10.5% with *P. falciparum*.[4] In the study conducted in Peshawar by Khan et al.[19] 228 patients presenting with fever and thrombocytopenia were evaluated to demonstrate 121 patients (53%) had malaria, and of these falciparum was seen in 82 patients (68%) while vivax in 39 patients (32%). The patients diagnosed with malaria had mean platelet count of 101,000/dL (SD ± 47, 500) as opposed to mean platelet count of 58,000/dL (SD ± 54, 000) in patients without malaria.[19] Moreover falciparum malaria was twice more common than vivax malaria in patients with thrombocytopenia.[19] In the study by Akhtar et al.[20] out of 250 samples 37 (14.8%) were malaria positive microscopically and thrombocytopenia was seen in 24 (64.8%) cases of malaria. Goel et al.[21] included 150 patients with fever to report malaria in 97 (64.6%) and of these 78 (80.4%) had thrombocytopenia. Of the malaria positive patients, 86 (88.7%) had *plasmodium vivax*, 8 (8.2%) patients *plasmodium falciparum* while 3

(3.1%) had mixed infection and thrombocytopenia was seen in 67 (77.9%) with vivax and 7 (87.5%) with falciparum.[21]

The incidence of drug-resistant falciparum malaria is a big hindrance in controlling malaria. In a region of chloroquine resistance in Malawi, return of chloroquine-susceptible malaria was demonstrated following abandonment of chloroquine use.[22] These chloroquine-susceptible parasites indicate that susceptible parasites that survived can re-expand and spread in spite of high usage of drugs. It is of vital importance that the goals of control, elimination, and malaria eradication be defined to process strategies for malaria control. Control is lowering the disease prevalence and incidence to levels which no longer pose a risk to public health.[23] Elimination is lowering incidence and transmission rate in humans to zero in a defined geographic area. Worldwide elimination of disease in humans is eradication.[23] A surveillance program which detects, responds to, and reports malaria cases and infections promptly is necessary.[24] A problem is that baseline epidemiological information for malaria (and other diseases) is woefully incomplete in most endemic countries. Subsequently, continuous rigorous monitoring is required for identification of imported cases, so that they can be diagnosed, treated, and contained promptly to limit reestablishment of endemic infection.

Malaria is an ideal candidate for disease eradication.[24] Clinical diagnosis alone has been used in most endemic African areas for recording malaria cases, contributing to imprecisions. Training and supervision of clinicians in proper diagnosis of presumed malaria remain the most important keys to effective management and surveillance.[25] Microscopic confirmation of malaria, the historic "gold standard," is frequently delayed and inaccurate; hence, the rapid diagnostic test (RDT) is being used with increasing frequency. Advantages of RDTs include improved diagnosis, rapidity, and more rational use of antimalarial drugs. The malaria eradication approach incorporates preparatory, attack, consolidation, and maintenance phases as suggested by WHO. Progression of these phases is dependent on decreasing the incidence of parasitemia and therefore need a comprehension of endogenous and exogenous components in malaria transmission. Endogenous components encompass the cycle of human, parasite, mosquito transmission while exogenous components rely on physical environment, and socio-economic context, and preventive strategies.[26] The most important epidemiological criterion for moving from the attack to the consolidation phase of malaria eradication (in which surveillance is the key) is annual incidence of <0.1 infections/1000 persons (1 case per 10,000 population).[23]

The present study showed that *plasmodium vivax* was more commonly seen in our population. Thrombocytopenia was seen in 17.3% patients and the frequency of thrombocytopenia was higher in *plasmodium vivax* as compared to *plasmodium falciparum*.

Conflict of interest: None declared.

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