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The New Spectrum of Plasmodium Vivax Malaria Severity: A Single-Center Experience

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ABSTRACT

Plasmodium vivax malaria, once considered a benign and self-limiting disease, has emerged as a significant public health concern, with increasing reports of severe and even fatal cases. **Objective:** To evaluate the clinical severity and complications associated with Plasmodium vivax malaria in patients in Peshawar. **Methods:** A descriptive cross-sectional study was conducted at Lady Reading Hospital, Peshawar, for about two months. A total of 160 patients diagnosed with Plasmodium vivax malaria were enrolled. Participants were divided into two groups based on platelet count. Laboratory tests, including complete blood count, liver function tests, and Renal Function Tests were performed. Data were analyzed using SPSS version 20.0 , An Independent sample t-test was used to assess the significant difference between the two groups with statistical significance set at $p<0.05$. **Results:** A total of 165 patients were included in the study. In the severe thrombocytopenia group (<100,000/µL), there were 23 cases of anemia, jaundice (n=25), acute renal failure (n=7), cerebral malaria (n=2), seizures (n=1) and hypoglycemia (n=1). In the less severe thrombocytopenia group (>100,000/µL), there were 14 cases of anemia, jaundice (n=17), and acute renal failure (n=2). The blood glucose level (p=0.37), systolic blood pressure (p=0.18) and pulse rate (p=0.21) revealed no significant differences between the two groups. **Conclusions:** It was concluded that severe thrombocytopenia in P. vivax malaria was associated with more severe clinical manifestations, with a few cases requiring transfusions. Patients with less severe thrombocytopenia had fewer complications.

INTRODUCTION

Malaria has impacted human populations since ancient times, causing significant morbidity and mortality in endemic regions. Malaria is caused by parasitic protozoa of the Plasmodium genus and is naturally transmitted to humans through the bite of female Anopheles mosquitoes carrying the parasites [1]. Despite advancements in medicine, malaria remains highly endemic in tropical, subtropical, and developing countries, and continues to be one of the leading causes of death globally, even though it is a treatable disease [2]. While Plasmodium falciparum is typically responsible for severe malaria cases, particularly in Africa, infections caused by Plasmodium vivax (P. vivax) have recently gained attention due to an increase in severe malaria cases linked to this species. P. vivax is widely distributed across Latin America, the Middle East, South Asia, Southeast Asia, and parts of Africa and Oceania [3]. The latest World Malaria Report documented 247 million malaria cases in 2021, a slight increase from 245 million in 2020. Malaria-related deaths decreased to 619,000 in 2021 compared to 625,000 in 2020 [4]. Malaria affects all blood components through mechanisms such as hemolysis, the host's inflammatory response, suppression of

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hematopoiesis, and sequestration of blood components in the spleen [5]. Although malaria is caused by five different Plasmodium species, P. falciparum is primarily responsible for severe complications, including acute renal failure, respiratory distress syndrome, cerebral malaria, and hematological and hemodynamic instability, occurring in about 1% of cases [1]. In 2018, Plasmodium spp. infections were estimated to result in 228 million malaria cases globally, with the African Region accounting for 213 million cases (93%), followed by the Southeast Asia Region (3.4%) and the Eastern Mediterranean Region (2.1%), leading to approximately 405,000 deaths. P. vivax infections were predominantly observed in the Southeast Asia Region, contributing to 53% of cases, with the majority (47%) occurring in India [6]. P. vivax causes an estimated 7 million cases annually [7]. Children younger than 5 years old made up 67% of the deaths, and the disease is still killing 1 child every 2 min [8]. Traditionally associated with mild tertian malaria, P. vivax has recently shown an increasing trend of life-threatening complications similar to those caused by P. falciparum [9]. Severe clinical manifestations of P. vivax malaria, such as acute kidney injury, splenic rupture, acute respiratory distress syndrome, and severe anemia, are being reported more frequently [1]. Several hypotheses have been proposed for the emergence of severe P. vivax cases, including platelet adherence to endothelial cells, triggered by tumor necrosis factor. Similar to P. falciparum, where platelets form bridges between red blood cells (RBCs) and endothelial cells, P. vivax-infected RBCs adhere to endothelial cells through mechanisms that resemble those seen in P. falciparum infections [10]. Given the high prevalence of Plasmodium vivax and the limited research on thrombocytopenia and its severe manifestations, this study was designed to explore the emerging trend of increased severity in Plasmodium vivax infections.

The study aims to explore the complications and clinical severity of Plasmodium Vivax malaria in Peshawar. By focusing on the complications associated with thrombocytopenia and other severe clinical outcomes, our study aims to fill a critical gap in the literature and provide valuable insights into the changing clinical profile of Plasmodium vivax malaria in the region. Understanding these trends is essential for improving clinical management and guiding public health strategies to address this evolving health concern.

METHODS

This descriptive longitudinal cross-sectional study was conducted at the Medical Teaching Institution (MTI), Lady Reading Hospital, Peshawar, from May to June 2024. Patients diagnosed with malaria via thick and thin smears, as well as immunochromatographic tests (ICT), were enrolled through non-probability random sampling. The sample size was calculated to be 160 using WHO's OpenEpi software, based on a prevalence rate of Plasmodium vivax in patients with severe malaria at 29.3%, with a 5% margin of error and a 95% confidence interval [1]. Informed written consent was obtained from all participants. Patients with mixed P. falciparum and P. vivax infections, as well as those with other conditions causing thrombocytopenia or severe systemic manifestations, such as sepsis, dengue fever, and chronic liver disease, were excluded. The participants were enrolled in the study after ethical approval from the Institutional Review Board of Lady Reading Hospital Peshawar (Ref. No: 131/LRH/MTI). Each patient underwent a thorough physical examination. Laboratory investigations, including complete blood count (CBC), were performed using Ruby cell-dyn Hematology analyzer, liver function tests (LFTs), blood glucose, and renal function tests were performed using Abbott Architect c4000, serum electrolytes were performed using EasyLyte Instrument, and chest X-rays, were performed. Selected patients also underwent specialized tests such as computed tomography (CT) brain scans and arterial blood gas (ABG) analysis. Thrombocytopenia was defined according to WHO criteria as a platelet count of fewer than 100,000 cells/mm^3, while anemia was defined as hemoglobin levels below 10 g/dL for women and below 12 g/dL for men. Respiratory distress was classified as an oxygen saturation of less than 94% on room air, acidotic breathing, or a respiratory rate greater than 32 breaths per minute [9]. Patients were divided into two groups based on their platelet count: Group A with a count of less than 100,000 cells/mm^3 and Group B with a count greater than 100,000 cells/mm3. Clinical history, examination findings, laboratory investigations, and complications were recorded for both groups via a performed proforma. The collected data were entered into Microsoft Excel 2020 and then imported into the Statistical Package for the Social Sciences (SPSS) version 20.0 for statistical analysis. Descriptive statistics, such as frequencies, and percentages were calculated for categorical variables such as gender, and clinical abnormalities while mean and standard deviation were used to summarize the quantitative variables such as Age, Blood glucose levels, Pulse rate and Systolic BP. For comparative analysis between the two groups (platelet count <100,000 cells/mm^3 and >100,000 cells/mm^3), an Independent sample t-test was used. Statistical significance was set at a p-value of less than 0.05. The results were presented in the form of tables and graphs, with a focus on highlighting significant clinical and laboratory differences between the two groups.

RESULTS

A total of 165 patients were enrolled in the study, patients

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were divided into two groups based on their platelet count: Group A (platelet count <100,000/µL) and Group B (platelet count >100,000/µL). Group A consisted of 67 patients (41.88%), while Group B had 83 patients (51.88%). In Group A, 39 patients (58.20%) were male, and 28 patients (41.80%) were female. Group B had 58 males (69.88%) and 25 females (30.12%). The average age of patients in Group A was 54 ± 8 years, while in Group B, it was 45 ± 6 years, indicating that patients in Group A were generally older. The mean blood glucose level was 111 ± 14 mg/dL in Group A and 116 ± 13 mg/dL in Group B, with no statistically significant difference (p=0.37) revealed by independent t-test. The average systolic blood pressure in Group A was 114 ± 11 mmHg, while in Group B, it was 118 ± 12 mmHg, also showing no significant difference (p=0.18). The average pulse rate in Group A was 100 ± 11 beats per minute, compared to 94 ± 9 beats per minute in Group B, with no significant difference between the groups (p=0.21) (Table 1).

Table 1: Demographic Characteristics of the Two Groups

Variable	Group A	Group B	p-value
Total Patients	67 (41.875%)	83 (51.875%)	–
Male	39 (58.20%)	58 (69.88%)	
Female	28 (41.80%)	25 (30.12%)	
Age (Years)	54 ± 8	45 ± 6	
Blood Glucose (gm⁄ dl)	111 ± 14	116 ± 13	0.37
BP Systolic (mmHg)	114 ± 11	118 ± 12	0.18
Pulse	100 ± 11	94 ± 9	0.21

Severe manifestations, including anemia, jaundice, renal failure, cerebral malaria, disseminated intravascular coagulation (DIC), and multi-organ failure, were more prevalent in Group-A (thrombocytopenia <100,000/µL) compared to Group B (>100,000/µL). In Group A, anemia (34.33%), jaundice (37.31%), and renal failure (10.45%) were more common, with additional cases of cerebral malaria, disseminated intravascular coagulation (DIC), and multi-organ failure, which was absent in Group-B. Group B exhibited fewer severe manifestations, with no cases of cerebral malaria, seizures, hypoglycemia, or multi-organ failure, suggesting a milder clinical course in patients with higher platelet counts (Table 2).

Table 2: Clinical Manifestations between the Two Groups

Variable	Group A	Group B
Anemia (HB<10 gm/dl)	23 (34.33%)	14 (16.86%)
Jaundice (Bilirubin>2 mg/dl)	25 (37.31%)	17 (20.48%)
Renal Failure (Creatinine>3mg/dl)	7 (10.45%)	2 (2.41%)
Cerebral Malaria (GCS<9/15)	2 (2.98%)	0 (0.00%)
Disseminated Intravascular Coagulation	1 (1.49%)	0 (0.00%)
Deranged Liver Enzymes (>3-fold elevation)	9 (13.43%)	3 (3.61%)
Leukocytosis (>11000/mm3)	3 (4.48%)	1 (1.20%)
Hypoglycemia	1 (1.49%)	0 (0.00%)
Multi-Organ Failure	3 (4.48%)	0 (0.00%)
Seizures	1 (1.49%)	0 (0.00%)

Some patients required various supportive interventions. In Group A, 4.47% (n=3) of patients needed blood transfusions, 1.49% (n=1) required platelet transfusions, 1.49% (n=1) ionotropic support, and mechanical ventilation in 1.49% (n=1). However, no patients in Group B required these interventions. Additionally, there were two deaths (2.98%) in Group A, while no deaths occurred in Group B. No patients in either group required hemodialysis. These findings highlight the more severe clinical course in Group A with lower platelet counts (Table 3).

Table 3: Supportive Care among the Participants of Both Groups

Supportive Care	Group A	Group B
Blood Transfusion	3 (4.47%)	0 (0.00%)
Platelet Transfusion	1 (1.49%)	0 (0.00%)
Ionotropic Support	1 (1.49%)	0 (0.00%)
Mechanical Ventilation	1 (1.49%)	0 (0.00%)
Hemodialysis	0 (0.00%)	0 (0.00%)
Deaths	2 (2.98%)	0 (0.00%)

DISCUSSION

Malaria presents with a wide range of signs and symptoms and its clinical course is dependent on several variables connected to both the host and the parasite. The illness spectrum advances from the stage of asymptomatic parasitemia to severe malaria, simple malaria, and in rare instances, fatal malaria [11]. With 305 million instances reported in the previous year, Pakistan too has a high illness burden. It is one of the malaria-endemic countries, meaning that practically everyone is susceptible to contracting the illness due to the extremely high risk of transmission. In Pakistan, P. vivax is more common than falciparum ranging from 71% to 80 % and other species of P. vivax are very rarely found [11]. Similar to falciparum, P. vivax was once believed to be a benign illness, but in recent years, more problematic and even fatal results have been reported. Notwithstanding minor variations, the ratio of falciparum malaria to P. vivax fell precipitously from 2.9:1 in 2010 to 0.6:1 in 2021, according to the 2022 World Malaria Report [12]. In our study, severe malarial manifestations were more common in Group A, which had more severe thrombocytopenia (<100,000/µL). This group included 23 patients (34.33%) with anemia, 25 patients (37.31%) with jaundice, 7 patients (10.45%) with acute renal failure, 2 patients (2.98%) with cerebral malaria, and 1 patient (1.49%) each with seizures and symptomatic hypoglycemia. Supportive treatments, such as blood transfusions and platelet transfusions, were required in three and one patient, respectively. Moreover, Group B (Platelets>100,000/µL), had 14 patients (16.86%) with anemia, 17 patients (20.48%) with jaundice, 2 patients (2.41%) with acute renal failure, 3 patients (3.61%) with deranged liver enzymes, and 1 patient (1.20%) with leukocytosis. No patients in this group exhibited cerebral malaria, seizures, or hypoglycemia, and none required supportive treatments. Our findings align with those of

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Humaira *et al.*, who conducted a study in the Sindh province of Pakistan, reporting severe manifestations in 54% of *P. vivax* patients, with jaundice present in 28% [13]. However, it should be noted that their study followed a major flood event. Zubairi *et al.*, reported an even higher severity rate, with severe *P. vivax* present in 79.9% of cases, a figure significantly higher than our findings [14]. Severe thrombocytopenia and neurological complications associated with *P. vivax* malaria were also noted in a study by Akhlaq *et al.*, conducted at Aga Khan University Hospital in Karachi [15]. In our study, severe anemia was the most common finding, observed in 34.33% of patients with severe thrombocytopenia and 16.86% of those with less severe thrombocytopenia. These results are comparable to those of Humaira *et al.*, who found anemia in 28% of *P. vivax* patients as the most frequent complication [13]. In New Delhi, an Indian study reported severe *P. vivax* malaria in 56% of patients [16]. Notably, jaundice (15%) and thrombocytopenia (65.5%) were also commonly observed as severe symptoms, with ARDS and renal impairment absent in that study. Doung MC and colleagues found severe *P. vivax* malaria in 10.5% of cases in Vietnam, which is lower than the severity observed in our study [17]. Similarly, in South Korea, Hyoung *et al.*, reported severe *P. vivax* in 21% of patients, a finding consistent with our results [18]. In Ethiopia, a study in children found severe *P. vivax* in 13.8% of cases [19]. This variation in severity across regions highlights the complex and evolving nature of *P. vivax* infections. Different studies from India have shown a wide range of severity, from 8.8% to 78.9% [20, 21]. We also reported two cases (2.98%) of cerebral malaria, which is unusual for *P. vivax*. These findings suggest that the clinical and biochemical spectrum of *P. vivax* has been changing, now resembling P. falciparum in its severity. This shift is concerning, particularly in countries like Pakistan and others in Asia, where *P. vivax* remains the predominant species. The mechanisms driving the increased severity of *P. vivax* infections are not fully understood, and there is a pressing need for further research into this alarming trend. A further large-scale study involving molecular and biochemical pathogenesis of the severity of the diseases is required to further elaborate on the factors leading to severity of the *P. vivax*. Every effort should be made to reduce the malaria burden. This was a single-center experience involving a small number of patients.

CONCLUSIONS

It was concluded that while uncomplicated *P. vivax* cases are still common, there is a notable rise in severe forms of the disease, characterized by complications such as anemia, jaundice, renal failure, and, in some cases, cerebral malaria. Patients with severe thrombocytopenia experienced more frequent and severe complications, including the need for blood and platelet transfusions, ionotropic support, and mechanical ventilation. Mortality was observed exclusively in this group. These findings emphasize the increasing severity of P. vivax malaria in endemic areas, highlighting the urgent need for preventive measures like mosquito control, repellents, and protective clothing to reduce transmission and severe disease outcomes.

Authors Contribution

Conceptualization: NI,
Methodology: NI, AAI, AG, SNM
Formal analysis: SNM
Writing review and editing: MH, FS, AG

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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