

Clinical spectrum and predictors of severe *Plasmodium vivax* infections at a tertiary care center in North India

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SUMMARY Traditionally attributed only to *Plasmodium falciparum*, *Plasmodium vivax* has recently been reported to cause a significant burden of complicated malaria cases. The present study aimed to delineate the clinical spectrum and identify predictors for severe disease. This was a prospective observational cohort study conducted at a tertiary care hospital in North India. Patients with acute febrile illness (AFI) aged at least 14 years were included if they were diagnosed with vivax malaria based on rapid kits or peripheral smears. Clinical data and investigations during hospital stay was recorded. 439 cases of acute febrile illness were screened, of whom 50 (11%) were diagnosed with malaria including eight *P. falciparum* infections. Forty-two vivax malaria cases, 22 (52%) of whom were severe, were followed till discharge or death. The median age of the cohort was 24.5 years (Q1-Q3, 19-36 years), including a total of 29 males (69%). Severe malaria was more frequently associated with historical complaints of oliguria or dyspnea, and examination findings of pallor, splenomegaly or altered sensorium. The following five factors were identified to predict severe disease: prolonged illness over 7 days, symptoms of oliguria or dyspnea, examination findings of pallor or crepitations on auscultation. Malaria accounts for 1 in 10 cases of AFI at our North Indian tertiary care center and approximately half of them present with severe disease. Prolonged duration of disease prior to presentation is a modifiable predictor for severe disease and should be targeted for reducing morbidity.

Keywords Malaria, acute febrile illness, disease severity, tropical infections

1. Introduction

Malaria is an endemic, vector-borne, tropical infection caused by the protozoan parasite of the genus *Plasmodium*, of which five species have been identified to infect humans. The clinical spectrum ranges from uncomplicated high-grade fever with headache and rigors to severe disease with the potential for devastating multi-organ dysfunction – cardiovascular, pulmonary, hematological, hepatic, renal, or neurological. *Plasmodium vivax* is classically considered to be benign compared to *Plasmodium falciparum*. In recent years, *P. vivax* has been reported to be the cause of many complicated malaria cases, and even deaths, in countries including Papua New Guinea (1), India (2,3), Brazil (4), and Malaysia (5). Factors predisposing to severe *P. vivax* malaria are unclear. Identification of patients at risk of severe disease and

close monitoring, with or without hospitalization, can help triage these patients appropriately to improve outcomes.

In observance of the increasing burden of severe *P. vivax* infections and its impact on the community, the present study aimed to identify these patients' clinical spectrum as well as predictors for severe disease.

2. Methodology

2.1. Study setting and design

The present study was a prospective observational cohort study conducted at a tertiary care teaching hospital situated in North India (All India Institute of Medical Sciences, Delhi, India). The recruitment period extends from September 2018 to May 2020, and the study was approved by the institute ethics committee.

2.2. Study population

Patients presenting with acute febrile illness of ≤ 14 days duration were evaluated for malaria infection. Malaria fever was diagnosed by examining a quantitative buffy coat or peripheral smear, or antigen detection by rapid diagnostic kit (Optimal, Bio-Rad, Marnes-la-Coquette, France). The species were identified by antigen detection or peripheral smear examination by microbiologists with at least ten years of experience in the field. Patients aged ≥ 14 years diagnosed with malaria were recruited after informed consent. The patients were excluded if they were infected with more than one malaria species, another cause for the febrile illness was demonstrated, or refused consent. Patients were treated following the national guidelines using oral chloroquine and primaquine if they were diagnosed with non-severe vivax malaria, and with intravenous artesunate therapy in case of severe vivax malaria (6).

2.3. Data collection

Information was obtained from the patients' medical records and collected in a uniformly structured questionnaire. Details noted include demographic characteristics, duration between onset of symptoms and diagnosis, duration of fever, headache, and complications, including active bleeding, altered sensorium, decreased urine output, or seizures. The patients were clinically examined daily till discharge or death. Routine blood investigations were performed at baseline and recorded every alternate day to identify the development of severe malaria infection. These included hemogram, renal function tests, liver function tests, blood lactate level, random plasma glucose, and blood gas analysis, including pH value and blood bicarbonate levels.

2.4. Definitions

Severe vivax malaria was defined by the presence of any one of the following World Health Organization (WHO) 2014 epidemiological and research criteria, as described for *P. falciparum* (except parasitemia) (7). The criteria include impaired consciousness (Glasgow coma score < 11), acidosis (base deficit of > 8 meq/L or plasma bicarbonate of < 15 mEq/L or venous plasma lactate > 5 mmol/L), hypoglycemia (blood glucose < 40 mg/dL), severe anemia (hemoglobin concentration < 7 gm/dL or hematocrit $< 20\%$ in adults, together with a parasite count $> 10,000/\mu\text{L}$), acute kidney injury (serum creatinine > 3 mg/dL or blood urea > 20 mg/dL), jaundice (serum bilirubin > 3 mg/dl together with a parasite count $> 100,000/\mu\text{L}$), pulmonary edema (radiologically confirmed, or oxygen saturation $< 92\%$ on room air with a respiratory rate $> 30/\text{min}$), significant bleeding (recurrent or prolonged epistaxis, hematemesis

or melena), and shock (compensated with capillary filling time ≥ 3 seconds without hypotension or decompensated with systolic blood pressure < 80 mm Hg).

2.5. Statistical analysis

All data were analysed using Stata 14.0 (StataCorp, College Station, Texas, USA). Categorical variables are presented as frequencies and percentages. The chi-square test/Fisher's exact test was used to establish the association between 2 or more groups. Data was tested for normality using the Kolmogorov-Smirnov test. Continuous variables are represented as mean \pm standard deviations (SD) or median and interquartile range (IQR). Unpaired *t*-test was used to observe the difference between the groups if normality assumed otherwise Mann-Whitney-*U* test applied. Univariate logistic regression analysis was performed. A step-wise approach was used to estimate the risk and relative 95% confidence interval for each covariate. A value of *p* less than 0.05 was considered to represent statistical significance of the study.

3. Results

Four hundred thirty-nine cases of acute febrile illness were screened, of whom fifty (11%) were diagnosed with malaria and recruited (Figure 1). After excluding eight *P. falciparum* infections, forty-two *P. vivax* malaria cases were identified and followed up till discharge or death. Twenty-two of these (52%) were classified as severe. The median age of the cohort was 24.5 years (Q1-Q3, 19-36 years), including a total of 29 males (69%). Ten patients (38%) with severe malaria had associated comorbidities.

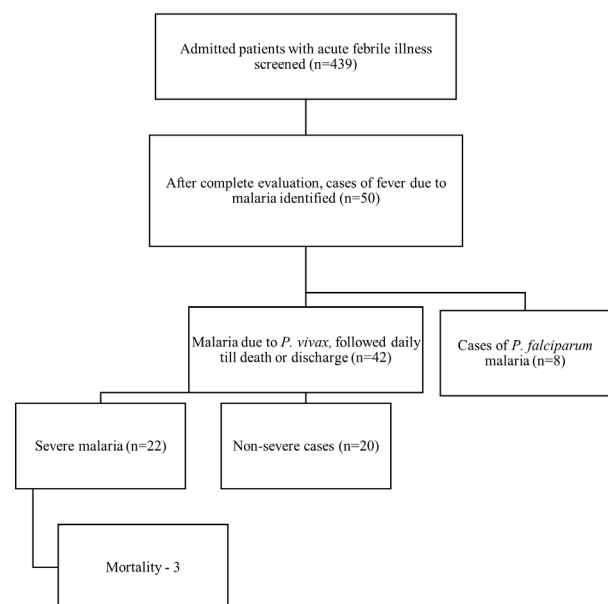


Figure 1. Study flow chart.

Table 1. Clinical profile of severe and non-severe vivax malaria (n = 42)

Clinical feature	Severe vivax n = 22	Non-severe vivax n = 20	p-value (chi-square or fishers' exact test, as appropriate)
Symptoms			
Fever	22 (100%)	20 (90.9%)	-
Headache	22 (100%)	19 (86.4%)	0.47
Prostration	19 (86.4%)	19 (86.4%)	0.60
Altered sensorium	2 (9.1%)	0 (0%)	0.48
Decreased urine output	9 (40.9%)	2 (9.1%)	0.035
Shortness of breath	9 (40.9%)	1 (4.5%)	0.009
Nausea/Vomiting	11 (50%)	5 (22.7%)	0.12
Pain abdomen	5 (22.7%)	1 (4.5%)	0.19
Examination			
Altered sensorium (Glasgow coma score < 11/15)	4 (18.2%)	0 (0%)	0.1
Hypotension (systolic blood pressure <80 mmHg)	3 (13.6%)	0 (0%)	0.23
Tachycardia (Heart rate > 100/min)	14 (63.6%)	5 (22.7%)	0.016
Tachypnea (Respiratory rate > 30/min)	6 (27.3%)	1 (4.5%)	0.09
Pallor	18 (81.8%)	10 (45.5%)	0.02
Icterus	12 (54.5%)	2 (9.1%)	0.002
Edema	4 (18.2%)	1 (4.5%)	0.34
Skin rash	7 (31.8%)	3 (13.6%)	0.28
Facial swelling	3 (13.6%)	0 (0%)	0.23
Active bleed	3 (13.6%)	0 (0%)	0.23
Hematuria	1 (4.5%)	0 (0%)	1
Epistaxis	2 (9.1%)	0 (0%)	1
Mechanically ventilated	5 (22.7%)	0 (0%)	0.02
Hepatomegaly	3 (13.6%)	1 (4.5%)	0.6
Splenomegaly	8 (36.4%)	2 (9.1%)	0.07
Ascites	5 (22.7%)	0 (0%)	0.04
Right upper quadrant tenderness	4 (18.2%)	0 (0%)	0.1
Lung crepitations	6 (27.3%)	1 (4.5%)	0.09
Bronchial breathing	3 (13.6%)	0 (0%)	0.23
Chest X-ray (CXR)			
Infiltrates on CXR	7 (31.8%)	1 (4.5%)	0.04
Effusion on CXR	6 (27.3%)	0 (0%)	0.02

3.1. Demographic characteristics and clinical presentation

Patients with severe and non-severe vivax infections had a similar median age at presentation (29 vs. 22 years, $p = 0.15$), sex distribution (73% vs. 65% males, $p = 0.74$) and mean duration of fever at presentation (8 ± 3.8 vs. 6.7 ± 3.2 days, $p = 0.2$). Patients in the severe vivax group were more likely to complain of decreased urine output (40% vs. 10%, $p = 0.035$) and shortness of breath (40% vs. 5%, $p = 0.009$). The duration of decreased urine output was over 2 days in severe vivax and up to 1 day in non-severe vivax infections. Majority of patients with severe vivax on examination demonstrated pallor ($n = 18$, 81%) and icterus ($n = 12$, 54%), splenomegaly ($n = 8$, 36%), ascites ($n = 5$, 22.7%) and altered sensorium with Glasgow Coma Score (GCS) < 11 ($n = 4$, 18%) (Table 1).

3.2. Biochemical parameters

The mean hemoglobin concentration was lower in the severe vivax group but did not reach statistical significance. Investigations that were used to classify patients were expectedly deranged in the severe vivax group: elevated leukocyte count, serum urea, creatine, total bilirubin, and lactate levels, and lower hematocrit

and bicarbonate levels (Table 2). Time trends for the measured parameters were plotted and the recovery in platelet counts was faster in the non-severe group, shown in Figure 2. There were three mortalities in the severe vivax group, all of whom developed acute kidney injury, and pulmonary infiltrates on chest X-ray and required mechanical ventilation. Those who died had decreased hemoglobin values (7.2 vs. 10 gm/dL, $p = 0.004$) and bicarbonate levels (13 vs. 22 mEq/L, $p = 0.02$), and elevated serum urea (136 vs. 55 mg/dL, $p = 0.03$) and creatinine levels (4.6 vs. 1, $p = 0.02$), compared to survivors.

3.3. Predicting severe malaria

Univariate logistic regression was used to find factors which could predict the diagnosis of severe malaria prior to the application of the diagnostic criteria (Table 3). The following findings were associated with the final diagnosis of severe vivax malaria: prolonged illness over 7 days, symptoms of decreased urine output or dyspnea, examination findings of pallor or crepitations on chest auscultation. Other findings such as icterus, elevated serum urea, lactate and bilirubin levels, and infiltrates on chest-X ray are used to diagnose as severe malaria and hence not truly predictive.

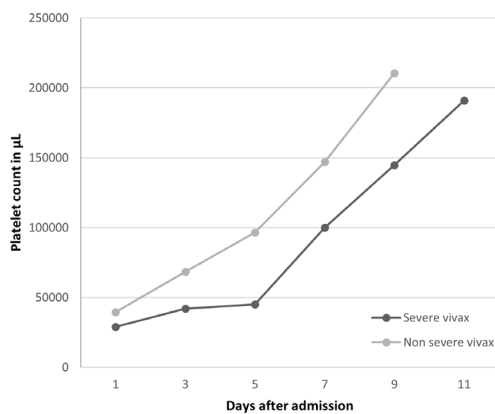


Figure 2. Trend of mean platelet count between severe and non-severe vivax groups.

4. Discussion

According to the WHO malaria report, most malaria cases in 2018 belonged to the African region (213 million, 93%), followed by the South-East Asian region (7.9 million, 3.4%) (8). The WHO South-East Asia region reports 53% of the *P. vivax* burden, with the most significant contributor being India (47%). *P. vivax* accounts for a third of all malaria cases in India, with around 380,000 confirmed cases in 2014 (9). Two-thirds of these arise in only five states: Jharkhand, Madhya Pradesh, Odisha, Uttar Pradesh, and Gujarat.

Prospective studies have shown that severe disease occurs in approximately 23% to 42% of vivax malaria infections (10,11). Thrombocytopenia is the most

Table 2. Laboratory investigations in the severe and non-severe vivax groups

	Severe vivax Median (Q1-Q3) n = 22	Non-severe vivax Median (Q1-Q3) n = 20	p Value
Hemoglobin (g/dL)	8.3 (6.7 - 11.8)	11.2 (8.9 - 12.9)	0.08
Hematocrit (%)	23.7 (20.225 - 29)	28.75 (24.15 - 36.525)	0.02
Platelet count (/µL)	29,000 (12,750 - 47,500)	39,500 (13,750 - 50,000)	0.69
Leukocyte count (/µL)	6,495 (4,290 - 9,550)	4,559.5 (3,425 - 6,095)	0.04
Urea (mg/dL)	95.5 (59.5 - 134.25)	32 (19 - 57.75)	0.0001
Creatine (mg/dL)	1.6 (1.05 - 4.575)	0.8 (0.675 - 1)	0.0006
Alanine aminotransferase (ALT, IU/mL)	34 (25.25 - 67.5)	26 (20.75 - 34.75)	0.04
Aspartate aminotransferase (AST, IU/mL)	47.5 (35 - 85.75)	36 (25.5 - 48)	0.03
Sodium (mEq/L)	136.5 (134.25 - 140.75)	138 (136 - 141)	0.75
Potassium (mEq/L)	4.85 (4.175 - 4.975)	4.15 (3.875 - 4.375)	0.004
Total Bilirubin (mg/dL)	2.8 (1.15 - 5.075)	1.05 (0.75 - 1.6)	0.007
Conjugated bilirubin (mg/dL)	2 (1.1 - 3.65)	0.8 (0.45 - 1.075)	0.1
Bicarbonate (mEq/L)	16.55 (13.325 - 20.85)	22.8 (21.925 - 23)	0.0001
Lactate (mmol/L)	1.95 (1.125 - 2.9)	1.2 (0.875 - 1.475)	0.01
International Normalized Ratio (INR)	1.2 (1.115 - 1.4)	1.18 (1.0925 - 1.285)	0.34

Table 3. Univariate logistic regression analysis to identify predictive factors for severe *P. vivax* infection

Parameter	OR	95% CI	P-Value
Clinico-Demographic details			
Female sex	0.67	0.16 - 2.73	0.58
Age > 29 years	2.78	0.77 - 10.04	0.11
Duration of illness > 7 days	4.33	1.15 - 16.32	0.02
Duration of hospitalization > 7 days	1.88	0.53 - 6.68	0.32
Signs and symptoms			
Decreased urine output	5.2	0.94 - 28.90	0.03
Shortness of breath	13.5	1.50 - 120.78	0.003
Pallor	4.72	1.14 - 19.40	0.02
Icterus*	9.35	1.71 - 51.03	0.003
Splenomegaly	4.25	0.75 - 23.81	0.07
Creptitations on auscultation	7.2	0.77 - 66.63	0.04
Investigations			
Infiltrates (on chest X-ray)*	9	0.98 - 81.92	0.01
Oxygen saturation < 92%*	1.89	0.15 - 22.75	0.6
Hemoglobin < 7g/dL*	13.5	1.50 - 120.78	0.003
Urea > 50mg/dL*	16.28	2.88 - 91.83	0.0002
Alanine aminotransferase (ALT) > 45 IU/L*	1.87	0.44 - 7.82	0.4
Bilirubin > 3 mg/dL*	15.8	1.79 - 139	0.001
Lactate > 2 mmol/L*	5.6	1.42 - 21.94	0.009

*These parameters are part of the WHO classification criteria and thus cannot be considered predictive.

common "severe" manifestation of vivax infection (12). A prolonged history of fever, dyspnea, and oliguria were more frequent in severe vivax infections in the present study. Serum bilirubin and urea levels have been shown to carry good discriminatory performance for severe vivax malaria (11), and the mean duration of fever and tachycardia at presentation predict poor outcome (13).

Patients with severe vivax malaria had significantly higher serum urea and creatinine level indicating that patients with early renal impairment had a more severe course and poor outcome than those without renal impairment. Renal impairment is multifactorial, can be prerenal or intrinsic renal damage. Renal biopsy in vivax-associated acute kidney injury (AKI) shows patchy cortical necrosis, acute tubular necrosis (14), or thrombotic microangiopathy have also been reported (15). Icterus, splenomegaly, crepitations on auscultation, consolidation on chest X-ray, and hospitalization duration over 7 days predicted severity in vivax patients in our cohort. Similarly, tachypnea, elevated bilirubin and creatinine, and falling hemoglobin have been shown to be independent predictors of disease severity (16). Even though elevations in urea over 50 mg/dL and severe anemia (hemoglobin below 7 gm/dL) were associated with severity, these were used to classify the infection as severe and cannot be used as predictors. Mortality occurred in 7% of vivax infections, much higher than reported estimates of 0.3% to 1.3% (10,11).

Severe anemia occurs at comparable rates among *P. vivax* and *P. falciparum*, despite lower rates of parasitemia in vivax (17). This is attributable to increased destruction of non-parasitized red blood cells because of increased fragility, and a toxic effect on erythroblasts precursors (18). Parasite load is frequently unavailable, owing to low parasite density, prior treatment, or slide techniques.

The present study comprehensively assessed the clinical spectrum and risk factors associated with severity in *P. vivax* infections. However, our study's limitations include referral bias- the higher rates of severity may be attributed to the study being performed in a tertiary referral center. Since pre-morbid baseline investigations are not available for most patients, biochemical parameters associated with severe disease may be affected by comorbidities resulting in confounding. The parasite load could not be detected for most patients, possibly due to empirical treatment. We could not perform polymerase chain reaction (PCR) to establish mono-infection due to non-availability.

In conclusion, severe disease is predicted by delayed presentation (beyond one week) and findings of icterus, dyspnea, oliguria, and infiltrates on chest X-ray. Faster access to healthcare and education about early initiation of therapy may help prevent delayed presentation and subsequently severe vivax malaria.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received November 25, 2020; Revised December 20, 2020; Accepted December 27, 2020.

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Released online in J-STAGE as advance publication December 31, 2020.