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Clinical Profile, Including Complications, in Patients with *Vivax* Malaria Mono-Infection

Neelabh Pratap, Esha Singhal**, Anamika Chaudhary*, Ajai Kumar Garg*****, AK Agarwal***, Suparna Dubey*****

Abstract

***Background and objectives:** Vivax malaria was long considered to have a benign course. However, in recent times there has been a remarkable increase in case studies describing complicated disease with vivax malaria. We report findings from a study conducted at a tertiary care hospital aiming at analysing the clinical manifestations, complications, and outcome of patients infected with P. vivax malaria.*

***Methodology:** This hospital-based cross-sectional observational study was carried-out on 100 patients diagnosed with P. vivax infection from January 2019 to June 2020. Detailed history, clinical findings, and relevant investigations were recorded and analysed.*

***Results:** 100 patients with malarial parasite rapid diagnostic test and peripheral smear positive for P. vivax were selected. Mean age was 30.59 ± 13.35 years, 62% were in age group of 20 - 30 years, 55% were males. Clinical features seen were fever (100%), vomiting (53%), abdominal pain (44%), headache (44%), cough (18%), breathlessness (12%) and altered sensorium (1%).*

***Pallor** was seen in 53% of cases, icterus in 32%, pedal oedema in 7%, splenomegaly in 61%, hepatomegaly in 36% and chest crepitations in 12%. Severe anaemia was seen in 11% of cases, thrombocytopenia in 85%, azotaemia in 29%, hyperbilirubinaemia in 76%, altered liver transaminases in 50%, and ARDS in 2%. 5% patients required dialysis support. All patients recovered and were discharged without residual features.*

***Conclusion:** P. vivax malaria may be a potentially life-threatening disease which has excellent prognosis if diagnosed early and treated appropriately. Parameters like severe anaemia, thrombocytopenia and hepato-renal dysfunction serve as early indicators for progression into rather severe disease.*

Introduction

Malaria is a major public health problem, endemic in over a hundred countries across the world[1]. *P. vivax* malaria currently has the widest geographical distribution among all malaria parasites with about 35% of the world population living at risk of this physically debilitating infection[2-4]. A total of 130 - 435 million people are estimated to get *P. vivax* infection annually[5].

During recent years, many surveillance studies[6-9], case series[10-13] and reviews[14-16] have linked *vivax* malaria with severe manifestations similar to those seen in *P. falciparum* infection; observations that conflict the notion that *vivax* malaria is a benign disease.

This observational study was conducted with the aim of exploring varied clinical features of *vivax* malaria. Comparison of clinical profile of patients with *vivax* malaria with regards to demographic, clinical, haematological, and biochemical features was done in this study.

Material and methods

This was a cross-sectional, observational study conducted at the Department of Medicine in a tertiary care teaching institute in Greater Noida, Uttar Pradesh, over a period of one year and six months from January 2019 to June 2020. The study was approved by the institutional ethics committee.

Inclusion criteria

1. Patients admitted in hospital having fever (≥ 38.5° C) with peripheral smear and rapid malaria diagnostic test positive for *P. vivax* malaria.
2. Patients willing to give written consent.
3. All patients >20 years of age.

Exclusion criteria

1. Patients with co-existent *falciparum* infection or dengue virus infection.

**Post-Graduate Resident, **Assistant Professor, ***Professor Emeritus, Department of Medicine, ****Professor, Department of Pathology, Sharda School of Medical Sciences and Research, *****Associate Professor, Department of Medicine, Government Institute of Medical Sciences, Greater Noida - 201 308, Uttar Pradesh.*

***Corresponding Author:** Dr Ajai Kumar Garg, Associate Professor, Department of Medicine, Government Institute of Medical Sciences, Greater Noida - 201 308, Uttar Pradesh. Tel: 9871862300, E-mail: drajaigarg@yahoo.co.in.*

2. History of chronic HBV and/or HCV infection.
3. Patients with advanced stage of HIV or AIDS.
4. Patient with history of hepatotoxic drug, toxic herbal medicine, alcohol consumption.
5. Chronic liver disease/renal failure patients.

Detailed medical history was taken and a thorough clinical examination was performed on all patients. Light microscopy Giemsa-stained peripheral blood smear examination and malarial antigen based rapid diagnostic testing (RDT) were used to diagnose *P. vivax* malaria. The malaria card lactate dehydrogenase/histidine-rich protein 2 (pLDH/HRP2) combo (Pf/Pv) test was used. A complete blood count, liver function test, kidney function test, random plasma glucose estimation, ABG, CXR PA view, HEPACARD for HBsAg, HCV TRI-DOT, HIV TRI-DOT, Dengue serology (IgG, IgM) were done for all the patients.

Patients were also evaluated for severe malaria as per WHO criteria[17]. The parameters taken into consideration for identifying severe malaria were: Impaired consciousness, severe anaemia (Hb <7 gm/dl), pulmonary oedema, jaundice (serum bilirubin >3 mg/dl), acute renal failure (serum creatinine >3 mg/dl), convulsions, hypoglycaemia (plasma glucose <40 mg/dl), acute respiratory distress syndrome, bleeding manifestations, hypotension (systolic blood pressure <80 mm of Hg), and metabolic acidosis.

Patients were treated as per standard practice, in accordance with the national malarial management protocol. Patients were observed from the time of admission up to discharge from the hospital.

Statistical analysis

Data was collected in a predetermined proforma and entered in Microsoft excel sheet. The data was analysed using the SPSS version 21 operating on windows 10. All the data represented in tables as frequency, percentage, mean, standard deviation and diagrammatic representation using the pie-chart and bar charts as applicable. P value less than 0.05 was considered significant.

Results

Total of 100 consecutive patients attending the medicine department and diagnosed with *P. vivax* malaria were included in the present study after obtaining informed consent from all patients.

Maximum patients belonged to the age group of 20 - 30 years (62%) (Fig. 1). 55% were males, whereas 45% were females (Fig. 2). The most common symptom was fever, found in all patients. Vomiting, abdominal pain and

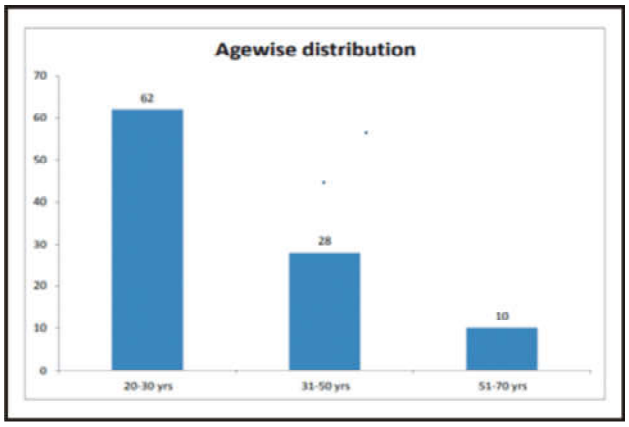

Fig. 1: *Agewise distribution of patients.*

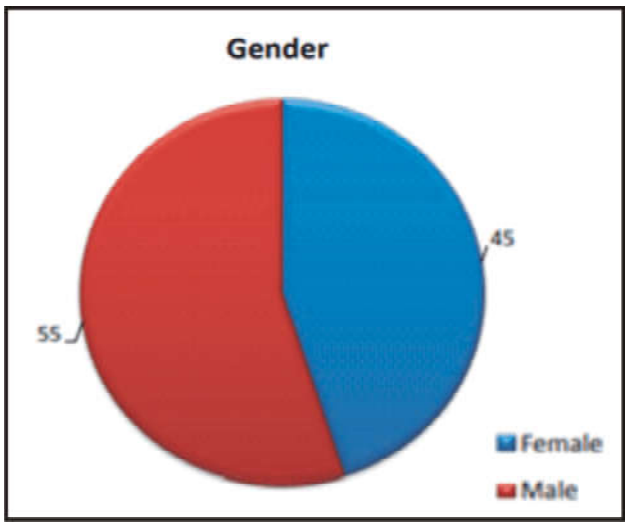

Fig. 2: *Gender distribution of patients.*

headache were next in frequency, being found in 53%, 44% and 44%, respectively. 18% patients had cough, 12% patients had breathlessness, and 1 patient presented with altered sensorium (Fig. 3).

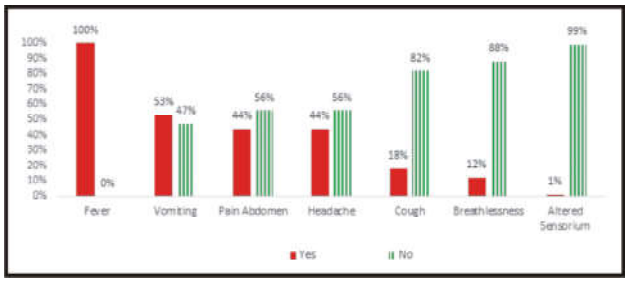

Fig. 3: *Symptoms among patients of vivax malaria.*

On examination, 53% patients had pallor, 32% patients had icterus, 61% patients had splenomegaly, and 36% patients

had hepatomegaly. On respiratory examination, 12% patients had bilateral crepitations and 3% had wheezing. One patient with severe anaemia was found to have a murmur (Fig. 4).

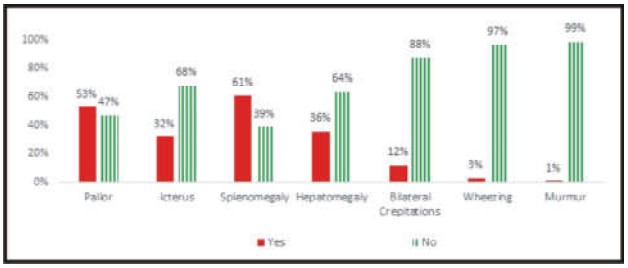

Fig. 4: *Signs among patients of vivax malaria.*

On laboratory investigations, 11 patients had severe anaemia with Hb lower than 7 gm%, 35% were in range of 7.1 - 10 gm%, 34% patients in range of 10.1 - 13 gm% and 20% were in range of 13.1 - 18 gm% (Fig. 5).

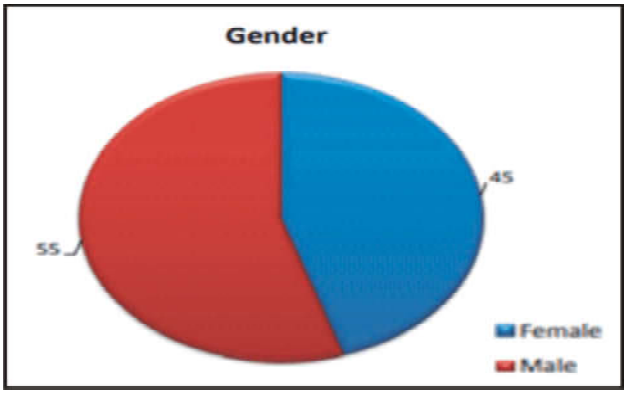

Fig. 5: *Haemoglobin distribution among the patients with malaria.*

38% of patients were found to have thrombocytopenia with platelet counts lower than 50,000/cmm followed by 33% patients in range of 50,000 - 1,00,000/cmm. Only 12% of patients with *P. vivax* were with platelet count more than 1.5 lakh (Fig. 6).

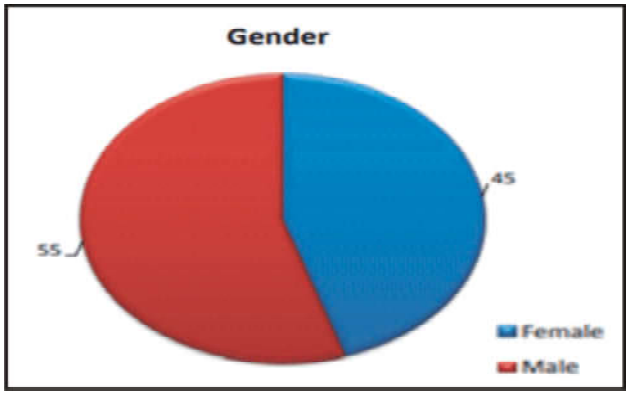

Fig. 6: *Platelet distribution in patients with malaria.*

76% of patients had elevated bilirubin more than 1 mg/dl. Only 24% were with bilirubin lower than 1 mg/dl. Majority of the patients who had elevated bilirubin were in the range group of 1.01 - 3 mg/dl of serum bilirubin (48%), and the remaining 28% patients had bilirubin more than 3 mg/dl. Serum AST level was more than 41 IU/L in 70% of the patients and serum ALT was more than 40 IU/L in 64% of the patients. The mean level of AST and ALT was 62.2 IU/L and 62.5 IU/L in our patients (Fig. 7).

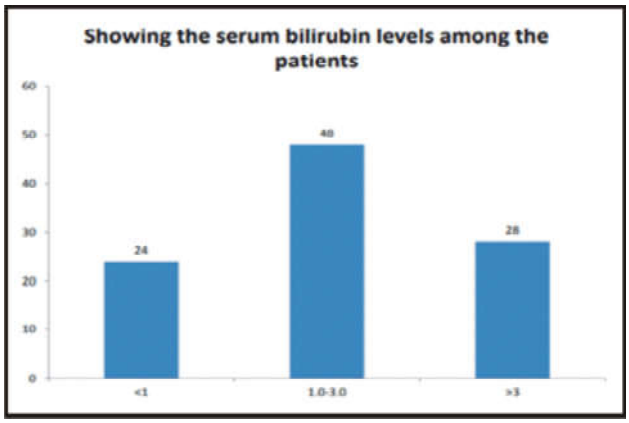

Fig. 7: *Serum billirubin level among patients of malaria.*

The serum creatinine was elevated among the 33% of patients and blood urea was elevated in 29% of patients. 5% of the patients required dialysis support (Fig. 8).

CXR suggestive of ARDS was seen in 2% of cases. Cerebral malaria was seen in 1% of cases. All 100 patients improved and were discharged.

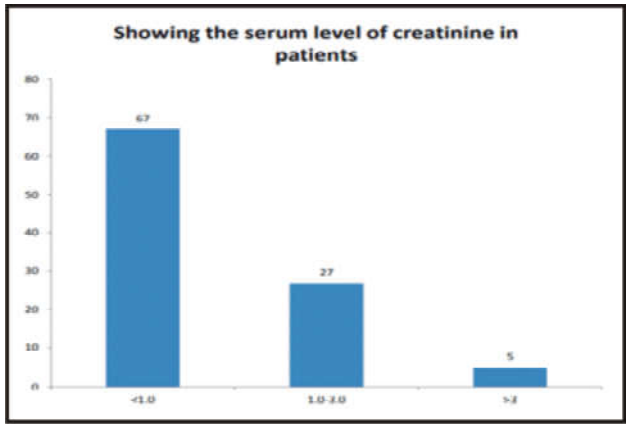

Fig. 8: *Serum creatinine level among patients of malaria.*

Discussion

Total of 100 patients diagnosed with *P. vivax* fulfilling the inclusion and exclusion criteria were included in this study.

Among 100 patients, 55 were males and 45 were female

patients (with male preponderance). Similar results have been reported by various studies conducted across India[18-20]. The mean age of all the participants was 30.59 ± 13.35 years. The majority of the patients in the present study were in the age group of 20 - 30 years (62%) followed with patients in age group of 31 - 50 years (28%) and 51 - 70 years with 10%.

In the present study, all patients presented with fever at presentation. 53% patients also had vomiting, 44% patients presented with pain abdomen, 44% patients with headache, 18% patients with cough, 12% patients with breathlessness, and 1 patient with altered sensorium. No patient in the present study had history of convulsion at presentation. Similar findings have been reported by many others authors such as Mathews *et al* (fever 100%, vomiting 36%)[20], Manikyamba *et al* (fever 80%, headache 40%, vomiting 30%)[21], and Yadav *et al* (fever 98.2%, vomiting 42.8%)[22] (Table I).

Table I:

Clinical features	Present study	Manikyamba *et al*	Mathews *et al*	Yadav *et al*
Fever	100.0%	80.0%	100.0%	98.2%
Vomiting	53.0%	30.0%	36.0%	42.8%
Pain abdomen	44.0%	–	24.7%	28.5%
Cough	18.0%	–	13.3%	12.3%
Headache	44.0%	40.0%	20.0%	24.2%
Breathlessness	12.0%	14.0%	10.0%	–
Altered sensorium	1.0%	–	3.3%	20.2%

Severe anaemia (Hb < 7 gm%) was seen in 11% of patients, moderate anaemia (Hb 7.1 - 10 gm%) was seen in 35% of patients. Many previous studies have also documented severe anaemia in *vivax* malaria[23-25]. The pathophysiology of malarial anaemia is multifactorial. In developing tropical countries, pre-existing anaemia – most commonly due to malnutrition and helminthiasis – compounds the problem. *Vivax*-associated anaemia is an important public health concern that underscores the importance of reducing global transmission of *P. vivax*.

Thrombocytopenia was seen in 88% of our patients (platelet count <1,50,000/mm^3) (Table II). Thrombocytopenia was the most common complication seen in the present study. Naha *et al*[26] reported thrombocytopenia in 86.4%, George *et al*[27] and Singh *et al*[28] reported thrombocytopenia in 93.3% and 96% of patients respectively. Increased splenic sequestration, immune-mediated degradation, and shortened platelet survival are known to cause thrombocytopenia.

Table II:

Lab feature/ Result	Present study	Manikyamba *et al*	Mathews *et al*	Yadav *et al*
Anaemia	11.0%	37.5%	4.0%	17.4%
Thrombocytopenia	85.0%	12.5%	86.7%	81.2%
Raised ESR	47.0%	–	36.0%	–
Deranged KFT	29.0%	6.3%	–	–
Hyperbilirubinaemia	76.0%	10.0%	36.0%	13.5%
Altered liver transaminases	50.0%	4.9%	–	–

Hepatic dysfunction was the second most common complication noted in the present study. Majority of patients had elevated bilirubin ranging from 1.01 - 3 mg/dl (48%) and the remaining 28% patients had bilirubin more than 3 mg/dl. Serum AST and ALT levels were more than 40 IU/L in 70% and 64% of the patients respectively. The mean level of AST and ALT was 62.2 and 62.5 IU/L in our patients respectively. Serum ALP was also elevated in 28% of patients. Kochar *et al*[29] and George *et al*[27] reported hepatic dysfunction in 57.5% and 43.3% of patients respectively. Jaundice in malaria results from haemolysis of both parasitised and non-parasitised red cells as well as malarial hepatitis. Raised liver enzymes occur because of injury to hepatocyte and cholestasis. Hepatic dysfunction is reversible in acute malaria and patients respond favourably to antimalarial therapy without any residual effects.

Renal dysfunction was seen in 33% of patients in the present study. 5% of patients required dialysis support. Kochar *et al*[29], Naha *et al*[26], George *et al*[27], and Singh *et al*[28] reported renal dysfunction in 57.5%, 27.5%, 26.7% and 26% patients of *vivax* malaria. In a retrospective study on 93 patients of malarial ARF, 19 (20.4%) were found due to *P. vivax* infection[30]. Aetiology of renal failure in malaria is multifactorial – volume depletion, intravascular haemolysis, and hyperbilirubinaemia are factors considered responsible for renal injury[31].

Two patients in the present study developed ARDS. Indian studies described above have also observed occurrence of ARDS in their study groups[27]. Mathews *et al*[20], and Yadav *et al*[22], found ARDS IN 12.7% and 2.2% of patients, respectively.

In the present study, cerebral malaria was seen in 1 patient. Cerebral malaria due to *P. vivax* infection has been documented in various case reports[32,33], Hazra *et al*[34], and Singh *et al*[28], found cerebral malaria in 1.3%, and 13%, respectively. Cerebral dysfunction in vivax malaria may occur through the generation of nitric oxide[32].

Atypical presentation encountered in the present study was hyperglycaemia which was found in 3% of our patients, which could be explained as stress-induced. Stress-induced

hyperglycaemia usually occurs in children during serious illness, including in those with previously normal homoeostasis of glucose[35].

In the present study, 5% patients required dialysis support and no patients were put on the ventilator. All the 100 patients recovered and were discharged with no significant adverse events.

Limitations

1. Molecular diagnosis (by PCR assay) which has emerged as the most sensitive method for malaria diagnosis was not used in our study. However, despite the high negative predictive value of molecular testing, the majority of laboratories in non-endemic settings do not use PCR as a first-line diagnosis for all their malaria suspected cases. The major reason for not fully replacing existing conventional methods with this real-time PCR is the longer "time to results" period of the PCR.
2. The number of patients included in our study was not very large.

Conclusion

P. vivax infection has a varying clinical profile. Though previously called as benign tertian malaria, it is actually not a benign disease. It has immense potential to cause life-threatening complications – and even death – if not detected early and treated appropriately. This study highlights that certain clinical characteristics such as vomiting, abdominal pain, headache, altered consciousness, breathlessness, cough, hepatosplenomegaly, and laboratory parameters such as extreme thrombocytopenia, leucopenia, increased total bilirubin, elevated serum creatinine and blood urea may serve as indicators of the onset of severe malaria.

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