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Research Article

Hospital Based Study of Vivax Malaria - How Benign is it?

Sangita Kamath[1]* and Manish Kumar[2]

[1]*Consultant, Department of Medicine, Tata Main Hospital, Jharkhand, India*

[2]*Specialist, Department of Medicine, Tata Main Hospital, Jharkhand, India*

***Corresponding Author:** Sangita Kamath, Consultant, Department of Medicine, Tata Main Hospital, Jharkhand, India.

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Abstract

Introduction: In South and Southeast Asia, where the majority of vivax malaria occurs, *P. vivax* accounts for up to 50% of malaria cases with prevalence rates between 1% and 6% of the population. Although once regarded as a benign disease, it is proven to be the sole cause for severe complicated malaria including death.

Aim: To study the clinical profile and outcomes of *Plasmodium vivax* mono infections among adults.

Methods: A retrospective study carried out in a tertiary care hospital, Tata Main Hospital, Jamshedpur from January 2016 to December 2016. Severe *Plasmodium vivax* malaria was categorized as per WHO guidelines. Clinical presentations and laboratory parameters were noted from the medical records.

Results: Out of the total 95 cases of vivax malaria, 27 (28.4%) were due to severe vivax malaria. The most common haematological complication was thrombocytopenia (73.1%). Severe anaemia was seen in 14.8% cases while 27.3% of patients had jaundice. Transaminitis was detected in 44.4%, polysynovitis in 7.4%, and renal failure in 18.5% of cases. Hyponatremia was encountered in 22.2% of patients. Shock, adult respiratory distress syndrome and cerebral malaria were found in 11.1%, 11.1% and 7.4% of patients respectively. 40.7% of the cases had organ failure, 5 patients (18.5%) had single organ, 4 patients (14.8%) had two organ and 2 patients (7.4%) had three organ failures. Mortality rate was 3.7%.

Conclusions: *P. vivax* malaria is a potentially severe disease with morbidity and mortality. Despite this, with early diagnosis and timely intervention, outcome can be significantly better.

Keywords: Malaria; Vivax; Complications; Organs; Failure

Introduction

An estimated 2.8 billion people globally live in one of the 95 countries endemic for *P. vivax* of which India constitutes nearly half (46%) [1]. India accounts for 77% of the total malaria in south-east Asia with Plasmodium vivax being responsible for more than 50% of the cases [2]. Traditionally, vivax malaria was considered to run a benign clinical course, although death in *P.vivax* infections was recognized for over a century [3]. It was known for recurrences; but the typical complications seen with falciparum malaria were unknown with vivax monoinfection. In past, whenever complications were detected among *P. vivax* infections, they were attributed to undetected associated *P. falciparum* infections or underlying comorbidity. However, the past few years have witnessed a changing trend in the clinical manifestations of vivax malaria.

Cases of severe or complicated disease, sometimes even causing death due to sole *P. vivax* infection have come to light. *P. vivax* malaria has been reported to cause to cerebral malaria with convulsions and status epilepticus [4-7], acute renal failure [5,6,8-10], severe thrombocytopenia with or without bleeding [6,11-14], acute respiratory syndrome (ARDS) [6,15-19], shock [16,20,21], acute liver failure with jaundice [5,6,22-24], splenic rupture [25], severe anemia [5,6,13,21], and Multi Organ Dysfunction Syndrome (MODS) [26]. Despite this, it still remains a neglected tropical disease.

Jharkhand (Figure 1), with a population of 35.7 million as per 2016 statistics, is a malaria-endemic state with perennial transmission. As per the annual report 2014-15 provided by the Directorate of National Vector Borne Disease Control Programme (NVBDCP), it is a high disease burden state with annual parasite index (API) of 5 to 10. Further, the incidence of disease is on rise due to various factors like overpopulation, construction works, migration, water stagnation, insecticide resistance, and inadequate surveillance. The escalating burden of the disease and the changing scenario prompted us to undertake this study to provide a status report of vivax malaria in Tata Main Hospital (TMH), a tertiary care hospital in Jamshedpur which is in south-east of Jharkhand. For the purpose of this study, the catchment area of this hospital corresponds to the district of East Singhbum, adjoining districts of West Singhbum, Dhanbad, Ranchi and Purulia in West Bengal.

Figure 1: Map of Jharkhand showing the location of Jamshedpur.

Aim

To evaluate the clinical profile, response to treatment and outcome of the patients admitted with severe vivax malaria.

Inclusion Criteria

Patients > 12 years of age with acute febrile illness and severe clinical manifestations (as defined by WHO) with evidence of *Plasmodium vivax* infection by peripheral smear and or rapid diagnostic test.

Patients with one or more of the following were defined as having severe malaria as per the WHO criteria:

- Cerebral involvement
- Severe anemia with hemoglobin ≤ 5g/dl
- Jaundice with serum bilirubin > 3 mg/dl
- Splenic rupture
- Acute renal failure with serum creatinine > 3 mg/dl
- Acute respiratory distress syndrome (ARDS)
- Severe thrombocytopenia with platelet count 50,000/cumm
- Pancytopenia
- Shock requiring inotropic support for correction

Exclusion Criteria

- Patients with *P. falciparum* malaria or mixed infections
- Pregnant females
- Severe co-morbid conditions

Methods and Materials

It was a retrospective study carried out in Tata Main Hospital (TMH), Jamshedpur. All the case records of confirmed vivax malaria cases admitted in the medical wards of TMH from January 2016 to December 2016 were included in the study. The data analyzed included demographic profile, clinical presentation (symptoms and signs), specific tests for diagnosis of malaria, biochemical parameters, hematological profile, treatment given and clinical outcomes (length of hospital stay, mortality and complications).

Diagnostic methods used to detect malaria parasites

The diagnosis of malaria was done by examining conventional thick and thin Peripheral Blood Flows (PBFs) stained with Giemsa under oil immersion. Slides were considered negative when there were no parasites in 100 high power fields. The Rapid Diagnostic Test (RDT) used was based on the detection of histidine rich protein-2 (HRP-2) of *Plasmodium falciparum* and Pan specific pLDH (lactate dehydrogenase) of other species of malarial parasites like *P. ovale, P. vivax* and *P. malariae*.

Biochemical profile

Parameters included liver function test - serum bilirubin (direct and indirect fraction), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), serum proteins and renal function tests (blood urea and serum creatinine).

Hematological profile

Hematological parameters evaluated were complete blood count (CBC) and absolute platelet count in all patients, Prothrombin Test (PT), Activated Partial Thromboplastin Time (APTT) in presence of bleeding manifestations. CBC and platelet count were done by autoanalyzer and also evaluated on peripheral smear simultaneously.

Other evaluation

Chest x ray and abdominal ultrasound were done in those cases where there was an indication as decided by the treating clinician. SOFA (Sequential Organ Failure Assessment) score was calculated in all patients on hospital admission (day one) to assess the organ involvement and morbidity.

Treatment

All patients received treatment based on WHO recommendations for antimalarial chemotherapy. Complicated vivax malaria was treated like falciparum malaria using artemisinin-based combination therapy (ACT) with Artesunate and Doxycycline for 7 days. This was followed by oral primaquine for 14 days in G6PD (glucose-6-phosphate dehydrogenase) normal patients. Intravenous fluids were given based on the central venous pressure after establishing a central line in all patients with hypotension. Noradrenaline was used as inotropic agent for correction of shock.

Statistical methods

Results were analyzed and presented as mean ± standard deviation (SD) for continuous variables. Frequency and percentage were calculated for qualitative variables.

Result

Total number of malaria admissions in the year 2016 was 576 of which vivax malaria cases were 95 (16.5%). Of these 27 (28.4%) were due to complicated vivax malaria. The male to female ratio was 4.4:1. Their age ranged from 15 to 80 years with the average being 40.7 years (SD ± 20.1). The age and sex distribution of cases is as follows.

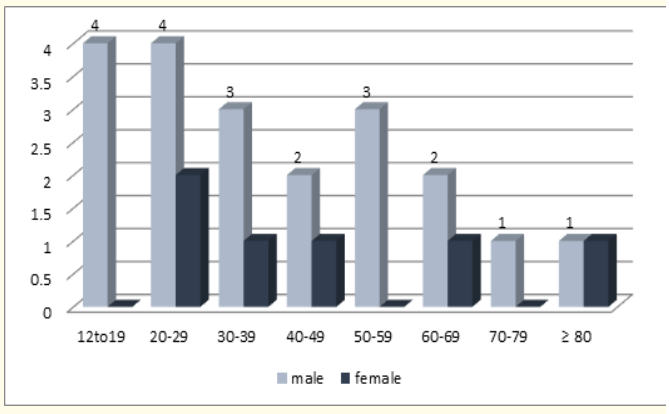

Figure 2: Bar graph showing age and sex distribution of cases.

The mean length of hospital stays (LOS) was 4.75 days (SD ± 1.1). Among the clinical manifestations fever was the most common presentation and was found in all (100%) of the patients. Mean duration of fever prior to admission was 4.2 days (SD ± 3.26) with the maximum duration being 15 days. Typical pattern of fever of once in 48 hours was seen in 10 (37.03%) of patients. Fever persisted for an average of 2.5 days after the treatment was initiated. Fever was associated with rigors in all (100%) patients, body aches (myalgias) in 11 (40.7%) patients, dry cough in 4 (14.8%) patients, breathlessness in 2 (7.4%) patients, vomiting in 3 (11.1%) patients, headache in 5 (18.5%) patients, decreased urine output in 3 (10.7%) patients, loose stools for 5 days before the onset of fever in 1 (3.7%) patient, abdominal pain in 1 (3.7%) patient, jaundice in 7 (25.3%) patients, and bleeding from nose in 1 patient (3.7%). Cerebral malaria was seen in 2 (7.4%) patients, one of whom had seizures (3.7%). Glasgow Coma Scale of 7 and 9 were found in these patients. Oher causes of altered sensorium

were ruled out by computerized tomography (CT) of brain, CSF examination, and serum electrolytes. Ultrasound abdomen was normal in 15 patients (55.6%). It revealed hepatomegaly in 6 (22.2%) patients, mild splenomegaly in 3 (11.1%) patients, increased renal echogenicity in 1 patient (3.7%) and evidence of polysynovitis (ascites, bilateral pleural effusions) in 2 patients (7.4%). Of the 6 patients with hepatomegaly, 2 (7.4%) were diabetics and obese. They had grade 2 fatty liver while the remaining 4 (14.8%) had non-specific hepatitis. None of the patients had splenic rupture. Chest radiograph revealed mild pleural effusion in 1 (3.7%) patient, bilateral fluffy opacities in 3 (11.1%) patients, and cardiomegaly in 2 (7.4%) patients. Shock, defined as Systolic Blood Pressure (SBP) < 90 mm Hg was detected in 3 (11.1%) patients on admission, while hypotension was found in 14 patients (51.9%). One patient (3.7%) was hypertensive and had blood pressure (BP) of 190/110 mm Hg while the remaining 9 patients (33.3%) had normal BP on admission. All patients with hypotension responded to intravenous fluids (1 to 2 liters) except one who needed inotropic support. Two out of the 3 patients with shock, needed noradrenaline @4 microgram/minute for 48 hours for correction of shock while one patient went into refractory shock despite double inotropes (Noradrenaline and adrenaline).

Laboratory Parameters

16 out of 27 patients (59.3%) were anemic (Hb ≤ 11 gm/dl). Average haemoglobin (Hb) on admission was 9.6gm/dl (SD ± 3.04), minimum being 4 gm/dl. 4 (14.8%) patients had severe anemia (Hb ≤ 5 gm/dl) while 4 (14.8%) patients had moderate anemia (Hb > 5 to 8 gm/dl) and 8 (29.6%) patients had mild anemia (Hb > 8 to 11 gm/dl). 7 out of 27 (25.9%) patients received compatible packed red blood cell (PRBC) transfusion. 4 (14.8%) patients received 5 units while the rest received 2 units each. The average total leucocyte (WBC) count was 6,285.2 /cu mm (SD ± 2,880) with the lowest WBC count being 2,100/cu mm. 2 patients (7.4%) had neutrophilic leukocytosis, 4 patients (14.8%) had leucopenia (WBC count < 3,500/cu mm) while the remaining 21 patients (77.7%) had WBC count within normal limits. Average platelet count on admission was 77,740/cu mm (SD ± 48,362.2). Mild thrombocytopenia (platelets 50,000 to 100,000/cu mm) was detected in 12 patients, (44.4%), moderate thrombocytopenia (platelets < 50,000 to 20,000/cu mm) in 6 patients (22.2%) while severe thrombocytopenia (platelets < 20,000/cu mm) was found in 2 patients (7.1%). None of the patients had very severe thrombocytopenia (platelet count < 10,000/cu mm). Bleeding manifestations were not seen in any patient except in one patient with chronic idiopathic thrombocytopenic purpura (ITP) who had platelet count of 40,000/cu mm and severe epistaxis. 2 (7.4%) patients with severe thrombocytopenia and 1 (3.7%) patient of chronic ITP who had moderate thrombocytopenia received platelet transfusions in view of epistaxis. Average platelet count at discharge was 107,333.3/cu mm (SD ± 62,133.2). The average time for the platelet count to increase (without transfusion) was 4.3 days (SD ± 2.2).

The average serum bilirubin level was 2.6 mg/dl (SD ± 1.85). A total of 7 patients (25.3%) had serum total bilirubin level of > 3 mg/dl, the highest being 7.8 mg/dl. All of them had conjugated hyperbilirubinemia. 16 patients (59.3%) had serum bilirubin of > 1 mg/dl to 3 mg/dl. Hepatic involvement in form of transaminitis was found in 12 (44.4%) patients. Serum alanine transaminase (ALT) level was increased > 3 times the upper limit of normal (ULN) -120 IU/L) in 3 patients (11.1%), maximum value being 236.2 IU/L, while values > 1.5 times the ULN were found in 7 (25.9%) patients. The average ALT level was 56.5 IU/L (SD ± 63.12). 1 patient (3.7%) had aspartate transaminase (AST) level more than 3 times the ULN, maximum value being 201.3 IU/L. 9 patients had normal AST values, while 17 patients (62.7%) had mild elevation of AST (< X3 ULN). The ratio of AST/ALT > 1.5 was found in 1 patient (3.7%) while 3 patients (11.1%) had ALT/AST > 1.5. All patients with serum bilirubin > 3 mg/dl had normal or just mild elevation of liver enzymes. Serum alkaline phosphatase (ALP) levels were normal in all patients. The average alkaline phosphatase level was 99.5 U/L (SD ± 49.58).

Average serum creatinine was 1.54 mg/dl (SD ± 1.2). Raised serum creatinine was detected in 5 (18.5%) patients with maximum being 7.2 mg/dl. Of these 4 (14.8%) patients had urine output > 1000 ml/day while 1 (3.7%) patient with serum creatinine of 7.2 mg/dl had oliguria (urine output < 400 ml/day). He underwent two haemodialysis before going into the diuretic phase. His renal function returned to normal within 15 days. Remaining 3 (11.1%) patients improved with conservative treatment. All patients with acute kidney injury (AKI) had normal serum potassium. Average serum potassium was 4.16 mmol/L (SD ± 0.48).

The average serum sodium level was 127.2 ± 5.21 mmol/L. Mild hyponatremia (serum sodium < 135 to 125 mmol/L) was found in 6 (22.2%) patients with minimum level being 124 mmol/L. However, none of the patient except one was symptomatic for hyponatremia. One patient (3.7%) with serum sodium of 124 mmol/L complained of lassitude and hiccoughs, which were corrected with correction of hyponatremia. Arterial blood gas (ABG) analysis revealed metabolic acidosis in 5 (18.5%) patients. One patient had severe metabolic acidosis with PH of 6.78 related to renal failure. 3 (11.1%) patients had metabolic acidosis related to hypotension while 1 patient (3.7%) had metabolic acidosis related to lactic acidosis due to shock.

All 27 patients showed positive card test for vivax malaria. Of these only 14 (51.9%) showed slide positivity. Ring forms were seen in 8 (28.6%) patients, schizonts were seen in 1 (3.7%) patient while mature trophozoites were found in 5 (18.5%) patients.

As per the Multi System Organ Failure criteria, 11 patients (40.7%) had organ failure, of which 5 patients (18.5%) had single organ failure, 4 patients (14.8%) had two organ failure and 2 patients (7.4%) had three organ failures. Of the 27 patients, 3 (11.1%) had respiratory failure, 3 (11.1%) had renal failure, 2 (5.3%) had hepatic failure, 6 (22.2%) had hematological failure and 3 (11.1%) had cardiovascular failure. One patient (3.7%) expired. He had three organ failures (renal, cardiovascular and hematological). There were 46 organ involvements with 3 (8.3%) renal, 15 (41.7%) hepatic, 14 (38.9%) hematological, 12 (33.3%) cardiovascular and 2 (5.6%) central nervous system involvement. 5 patients (13.9%) had single organ involvement while 10 (27.8%) had two organ involvements. As per the Severity of organ Failure Assessment (SOFA) scoring system, 16 (59.3%) patients had score of 0 to 6, 6 (25.9%) patients had score of 7 to 9 while 4 (14.8%) patients had a score of 10 to 12. One patient with SOFA score of 12 expired.

Parameters	Deranged parameters n (%)	Mean ±SD
Hemoglobin (g/dl)	16 (59.3%)	9.6 ± 3.1
TLC (cumm)	4 (21.9)	6285.2 ± 2,880
Platelet count (x 10^3/cumm)	20 (73.7)	77,740 ± 48,362.2
Serum bilirubin (> 3 mg/dl)	7 (25.3%)	2.6 ± 1.85
ALT (U/L)	10 (37)	56.5 ± 63.12
AST (U/L)	18 (66.4)	60.3 ±
Serum creatinine (mg/dl)	5 (18.5)	1.54 ± 1.2
Serum albumin (g/dl)	3 (11.7)	3.86 ± 0.78
Serum sodium (mmol/L)	6 (22.2)	127.5 ± 5.2
Serum potassium (mmol/L)	5 (18.5)	4.1 ± 0.5

Table 1: Deranged laboratory parameters encountered.

*TLC: Total Leucocyte Count; ALT: Alanine Transaminase; AST: Aspartate Transaminase.

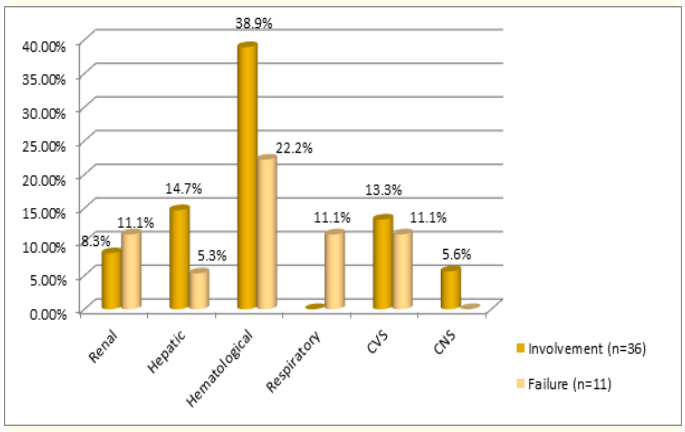

Figure 3: Organs affected in vivax malaria.

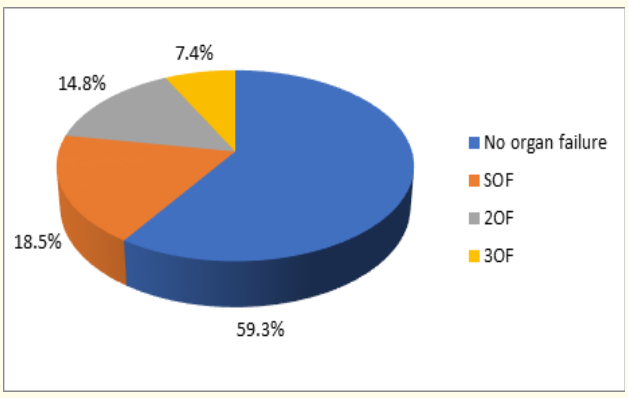

Figure 4: MOFS in patients (%) n = 27.

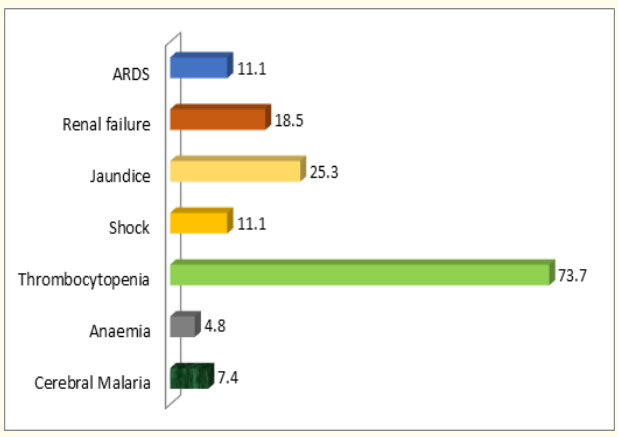

Figure 5: Complications of vivax malaria patients.

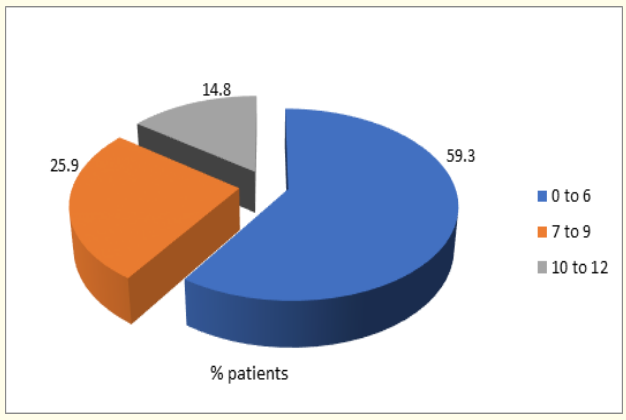

Figure 6: SOFA score of vivax malaria patients (n = 27).

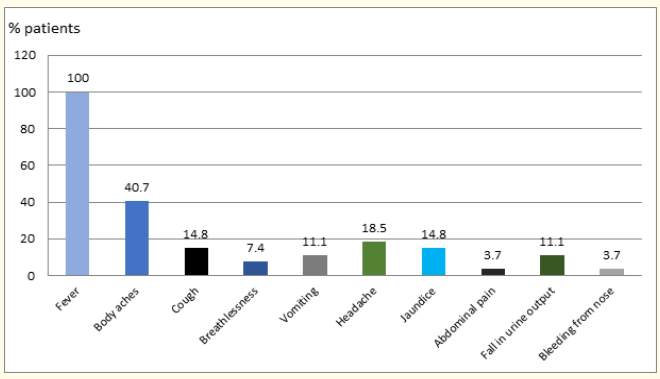

Figure 7: Symptomatology of vivax malaria patients.

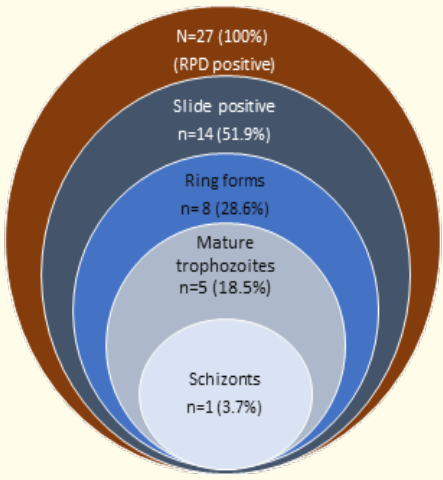

Figure 8: Positivity of diagnostic test of vivax malaria (slide and antigen detection).

Discussion

Plasmodium vivax is responsible for approximately 100 to 300 million clinical cases each year and 2.5 million persons world-wide are at risk [20]. The incidence of malaria in India is estimated at 1.5 million cases annually, of which 40% are due to vivax malaria [26]. Yet the morbidity associated with this infection and its spectrum of are less studied. *P. vivax* infection has been considered for a long time, a benign and self-limited disease [27]. Historically, cases of complicated *P. vivax* malaria have been rare and documented almost exclusively by case reports or small case series. However, in 2009 Kochar., *et al.* reported a series of severe vivax malaria from Bikaner using antigen and polymerase chain reaction (PCR) test to exclude falciparum co-infection [20]. Since then, it has been increasingly observed that vivax malaria can manifest with sequestration and non-sequestration related complications [20]. The exact causes of changes in the clinical profile of vivax malaria are uncertain and may include genetic alterations of the parasite,

change in vector and its biting habits or drug resistance. Hence, this study was carried out to study the clinical profile, various complications and outcome of vivax malaria.

The most common haematological manifestation found in the study was thrombocytopenia of varying severity (74.1%). Makkar., *et al.* [11], Kakar., *et al.* [14], also have reported cases of *P. vivax* mono-infections with thrombocytopenia as the commonest haematological abnormality. The frequency of thrombocytopenia in malaria ranges from 24% to 94% in the literature. Tanwar and Kocher., et al. detected thrombocytopenia in 22.5% of patients [28]. In this study, none of the patients except that of ITP had bleeding manifestations. This is in accordance with a one-year study by George., *et al.* from Karnataka in 2010, in which 28 patients of the total of 30 (93.3%) had thrombocytopenia, of whom none had bleeding manifestations [29]. Also, in a study by Naha K., *et al.* (2010) from a tertiary hospital in South-Western India, thrombocytopenia was the commonest complication, seen in 184 (86.4%) patients [21]. Severe thrombocytopenia below 20×10^3 /mm^3 was observed in 17 (8.3%) patients; however, none of these patients displayed bleeding tendencies. Review of the literature revealed low occurrence of bleeding even in severe illness and a conservative approach was adopted in most cases. The mechanism of thrombocytopenia in severe *P. vivax* malaria is poorly understood. Some of the postulated mechanisms of thrombocytopenia are platelet-associated IgG antibodies mediated immune destruction of platelets [29], oxidative stress, alterations in splenic functions, a direct interaction between the *plasmodium* and platelets [31,32], high platelet lipid peroxidation and platelet phagocytosis mediated by the increase in P-selectin expression in the surface of activated platelets [33]. Platelet counts usually revert to normal after effective antimalarial treatment [2]. In our study, an increase in the platelet count was noticed within 36 hours of initiating treatment. All the patients with platelet count < 50,000/cu mm had > 50% increase in platelet count at discharge.

Anaemia was the next common haematological abnormality seen in 53.3% of the patients. Given the socio-economic conditions of the population, it is difficult to associate anaemia solely with P. vivax, as other factors, such as malnutrition, menstrual blood loss in females, and worm infestation could have influenced the presence of anaemia. The incidence of anaemia was 86.4% in the Bikaner study by Kocher., *et al.* [26] and in 46% of patients by Sarkar D., *et al.* (2013) in a tertiary care centre in Kolkata [13]. In their studies, severe anaemia was found in 32.5% and 6% of the hospitalised patients respectively while in our study, it was found in 14.8% of the cases. In the study done in Papua, [34], severe anemia was the major complication seen in 87% of the severe vivax cases as against 73% of the falciparum cases unlike in the study by Limaye., et al. comparing the complications of falciparum with vivax malaria, severe anemia was significantly ($p = 0.03$) more common in falciparum 26 (12.62%) than in vivax infection 10 (2.96%) [35]. Severe anaemia is possibly due to recurrent bouts of hemolysis of predominantly uninfected erythrocytes with increased fragility [2]. Also, recurrent infections due to treatment failure and relapse from the liver stages are also responsible. Cytokine-related dyserythropoiesis also probably contributes to anaemia [2,3].

The incidence of leucopenia in our study was 14.8% while it was 19% in a study by Limaye., et al. from a tertiary care hospital in Mumbai [35]. The leukocyte count in malaria is low to normal due to the localization of leukocytes away from peripheral circulation into the spleen and other marginal pools rather than actual depletion or stasis [36]. This is a transient finding like thrombocytopenia and normalizes after antimalarial therapy [37].

Acute Respiratory Distress Syndrome (ARDS), considered to be the most severe form of lung injury, is being increasingly reported with *P. vivax* malaria. Nadkar., *et al.* (2012) study had 8 patients with vivax malaria and ARDS, out of which 5 succumbed to death [38]. It was found in 4 (1.88%) patients in a one-year study by Naha K., *et al.* (2010) [21]. Sharma and Khanduri [39] reported three cases of ARDS out of 221 patients with P. vivax malaria, while Kochar., et al. noted ARDS in four cases out of 40 patients [26]. Compromised pulmonary function has been observed in patients with vivax malaria, including small airway obstruction, reduced alveolar gas exchange and increased pulmonary phagocytic activity [17,19]. Clinically apparent lung injury in vivax malaria most commonly develops after the six hours to eight days after the initiation of anti-malarial treatment [18,19] and corresponds to the exacerbation of the post-treatment inflammatory response [15,19,41,42]. In all cases of ARDS with vivax malaria reported till 2007, the symptoms developed after starting antimalarial therapy; raising the possibility of pulmonary inflammatory response to parasite killing. Nevertheless, our patients presented with pulmonary symptoms 2 to 3 days prior to hospital admission as was observed by Mukherjee T., *et al.* suggesting that severe pulmonary involvement is not necessarily a consequence of an inflammatory response to anti-malarial treatment. The diagnosis of ARDS was confirmed by excluding cardiac disease by echocardiography. One patient had isolated pulmonary involvement, while the other 2 patients had associated two more organ involvement. Of this one patient was managed with non-invasive ventilation (NIV) for 2 days and two patients needed invasive ventilation with high PEEP (10 cm of H2O) within 2 hours of admission for an average of 5.6 days. All 3 patients had good outcome. The mechanisms underlying lung injury in vivax malaria are not well understood. Cytoadherence of *P. vivax*–infected red cells to pulmonary endothelial cells ligand chondroitin sulphate A (CSA) leading to sequestration in the pulmonary microcirculation [40], accumulation of pulmonary monocytes occurs leading to an intravascular inflammatory response [41], ultimately interfering in the gas-exchange have been proposed as some of the mechanisms.

Renal manifestations have a wide spectrum, which can cause electrolyte imbalance, urinary abnormalities and acute renal failure (ARF) [10]. Renal dysfunction was present in 8 (26.7%) out of 30 the patients in a retrospective study by Peter G., *et al.* in 2010 while raised serum creatinine (> 1.5 mg/dl) was seen in 72 patients (36%) in a study by Sarkar., *et al*. [13]. In yet another 5-year retrospective analysis of ARF, due to diverse aetiologies by Prakash J., *et al*. out of the 554 cases, 19 (20.4%) were due to severe vivax malaria [10]. Sharma and Khanduri [39] detected renal failure in 7% of their cases while Kochar., *et al*. found renal failure in 45% of their patients [26]. It was the second most common complication after hepatic dysfunction in the study by Kocher., *et al*. Renal ischemia is the dominant pathogenic mechanism which leads to acute tubular necrosis (ATN) and renal dysfunction in severe malaria [10,29]. Microrheologic abnormalities which because renal ischemia includes endothelial cytoadherence, formation of intravascular rosettes, clumps and decreased RBC deformability that impedes the renal microcirculation [43]. The various non-specific effect of infection like haemolysis, disseminated intravascular coagulation (DIC), hypovolemia, also contribute to ARF [10]. Jaundice, hemolysis, thrombocytopenia and hypotension are common associations with malarial ARF [43].

Causes of jaundice in malaria can be classified into direct causes, including malarial hepatitis due to microvascular sequestration of parasitized red cells and intravascular haemolysis of parasitized red blood cells and indirect causes which include microangiopathic haemolysis, G6PD-related haemolysis, antimalarial drug induction, septicemic hepatitis, and unrelated causes such as coexisting acute viral hepatitis. In a two-year study by Kocher., et al. from Bikaner, hepatic dysfunction with jaundice was seen in 23 (57.5%) out of the 40 cases of severe vivax malaria [20]. Hepatic involvement was also the commonest complication (85.2%) in a prospective study involving 200 patients by Nigam AK., *et al.* in 2015 from Kolkata as in our study [22]. Jaundice was found in 72 (36%) patients while serum bilirubin (> 3 mg /dl) was seen in 27% of P. vivax cases. In yet another study involving 200 cases of severe vivax malaria by Sarkar D., *et al.* 132 patients (66%) had serum total bilirubin level of > 3 mg/dl. Serum ALT level was increased > 3 fold (120 IU/l) in 48 patients (24%), whereas 76 patients (38%) had AST level more 3 x ULN [13]. Guha., *et al.* proposed malarial infection induced generation of reactive hydroxyl radicals (OH) in liver, which causes oxidative stress and apoptosis in the mitochondrial pathway as the pathophysiology of hepatic dysfunction in malaria [22,44]. The study by Fabrri., *et al*. demonstrated P. vivax infection increases the oxidative stress (OS) by lipid peroxidation of erythrocytes and hepatocytes membranes and alters profile of antioxidant enzymes resulting in hepatocyte injury and hyperbilirubinemia. Higher levels of bilirubin further compound the oxidative damage [45]. Liver biopsy in such cases has demonstrated brown malarial pigments in Kupffer's cells, granulomatous lesions with mononuclear infiltration and hepatocyte necrosis [44]. Hepatomegaly present in 20% of cases by Sarkar., *et al* [13], while Echeverri., *et al.* [46] reported 17%. This was close to our observation of 22.2%. Kochar., et al. noted that jaundice due to malarial hepatitis regressed in 1 - 2 weeks whereas that due to acute viral hepatitis required 3 - 4 weeks to regress [47].

Neurological involvement in the form of cerebral malaria is commonly encountered in *P. falciparum* malaria, but unusual with *P. vivax* [21]. Kochar., *et al.* [20] diagnosed cerebral malaria in five cases (12.5%). There were three cases of cerebral malaria out of the 213 patients (1.4%) in the study by Naha K., *et al.* [21] while two patients (7.5%) had cerebral malaria in our study. 12 cases of cerebral malaria (3.5%) were described by Limaye., *et al.* in 2012 [35]. In yet another study by Mahapatra., *et al.* on the typical manifestations of Plasmodium vivax malaria, 0.9% of the 110 vivax malaria patients had cerebral malaria [5]. Our patient presented with convulsions and impaired consciousness like in other studies. Other reported neurologic manifestations include acute inflammatory demyelinating polyneuropathy [48] and post-malaria neurologic syndrome causing bilateral facial paralysis [49]. Numerous pathologic processes have been proposed including adherence of parasitized red cells to the cerebral vascular endothelium, fibrin microthrombi, agglutination of parasitized red cells and dysregulated local nitric oxide production [21].

Hypotension was observed in 10 (4.69%) patients in our study while it was detected in 9.4% cases in the study by Naha K., *et al.* [21]. Kochar., *et al*. noted hypotension in three cases (7.5%) [20]. Various mechanisms for hypotension in malaria include metabolic acidosis, gastrointestinal bleeding, splenic rupture, dehydration and secondary bacterial septicaemia. In our study, hypotension was secondary to insensible water loss due to fever, vomiting and diarrhoea. Bacterial sepsis was ruled out by sterile aerobic and anaerobic blood cultures of all the affected patients.

As per the WHO guidelines, all patients were treated like complicated falciparum malaria with Artemisinin based combination therapy (ACT) for one week followed by primaquine except one patient who did not receive primaquine due to its non- availability then. That patient relapsed after 4 weeks and presented with fever and hypotension. Of note, certain complications known to occur with severe malarial infection were not seen at all in our study. These included hypoglycemia, splenic rupture and DIC. There was only one death in our series, mortality rate being 3.7% probably due to the smaller numbers. In a study by Kochar et al. (2009) from Bikaner, the mortality was 5% [20] while it was 20% in a study by Sarkar D., *et al.* [13]. There has been an increased incidence of *Plasmodium vivax* producing complications in the last five years [50] and a large-scale study examining the clinical spectrum of severe vivax malaria, outcome and the burden of the disease is needed.

Conclusion

The clinical picture of vivax malaria has undergone a sea change from that of a benign one to a more severe, life - threatening one and hence the term "benign" tertian malaria is a misnomer in the present context. Although earlier regarded as causing a benign infection, there is increasing evidence that the overall burden, economic impact, and severity of *P. vivax* have been underestimated. It can affect all the organ systems like falciparum malaria. Vivax malaria can present with atypical and protean manifestations. Hence, patients of vivax malaria should be monitored for early complications as their detection and treatment can be life-saving. Despite significant morbidity, with timely and appropriate treatment *P. vivax* malaria has an excellent outcome.

Limitations

1. As this is a hospital-based study with a small sample size, the incidence of various complications may be higher than the incidence in the community.
2. Data retrieved from case records.
3. Polymerase Chain Reaction was not done for species identification as the test is not available in our hospital.

Conflict of Interest

None.

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None.

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