

Biochemical and clinical variations among severe Plasmodium Vivax malaria cases: A prospective study

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Abstract

Context: Plasmodium vivax is geographically widely distributed with up to 2.5 billion people at risk and an estimated 70-80 million cases every year. India contributes 77% of the total malaria in Southeast Asia. Retrospective analysis of burden of malaria showed that disability adjusted life years due to malaria were 1.86 million years. According to recent study, West Bengal contributes 11% of total malaria cases in country and is one of states where falciparum resistance to chloroquine has been confirmed. **Aims:** The aim of this study was to evaluate the biochemical and clinical profile of severe and non-severe Plasmodium vivax malaria and the complications and outcome of P. vivax malaria infections as there is very limited information on age and sex specific seasonal prevalence of malaria in different paradigms in the country. **Materials and Methods:** A hospital based prospective study was conducted in Medical College, Kolkata comprising of 138 patients with fever ($\geq 37.5^{\circ}\text{C}$), peripheral smear and/or rapid diagnostic tests positive for P. vivax. Previously established cases of CKD, hematological abnormalities, chronic liver diseases and neuro-psychiatric disorders were excluded from our study. Demographical, clinical and laboratory parameters including liver function test, renal function test were documented and were presented in tabular and statistical means. **Results:** Jaundice was present in 22% of patients and vomiting in 32% of the patients. Hepatomegaly was seen in 16 % cases and 33% cases had splenomegaly. ARDS was seen in 16% of severe malaria cases. Acute kidney injury was seen in 8% and cerebral malaria was seen in 12% of severe malaria cases. Multi organ dysfunction was seen in 12 %cases. There was 1 death in the study due to multi organ dysfunction. **Conclusion:** Life threatening complications such as ARDS, AKI, cerebral malaria and MODS can be seen in P. vivax mono infections.

Keywords: Malaria, Plasmodium vivax, Biochemical profile, Complicated malaria

Introduction

William Osler has said that-Humanity has but 3 great enemies; fever, famine, and war; of these by far the greatest, by far the most terrible is fever. Malaria has plagued mankind since long. For centuries it prevented any economic development in vast regions of the world. It continues to be a huge social, economical and health problem in many parts of the world. Incidence of malaria worldwide is estimated to be 300-500 million clinical cases per year causing more than one to three million deaths every year [1]. Malaria is a febrile illness transmitted by infected female Anopheles mosquito and

caused by protozoa of genus plasmodium. Four species of the Plasmodium cause nearly all malarial infections in humans. These are Plasmodium falciparum, Plasmodium vivax (P. vivax), Plasmodium ovale and Plasmodium malariae. Plasmodium knowlesi, a fifth species previously confined to monkeys, is now implicated in human disease [2].

Malaria continues to be one of the major public health problems of India with around 1.5 to 2 million confirmed cases per year with approximately 1000 reported malarial deaths every year, but according to WHO, SEARO, this figure could be 20 million cases with 15000-20000 deaths annually [2]. Among South

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East Asia region India shares two thirds of burden (66%) [3]. *P. vivax* contributes to >40% and *P. malariae* and *P. ovale* contributing to <10% of the burden [2]. *P. vivax* threatens almost 40% of the world's population causing an estimated 400 million clinical infections each year representing the widest spread plasmodium species [4].

Studies from India, Indonesia, Papua New Guinea and Thailand have shown that 21-27% patients with severe malaria had *P. vivax* mono infection. Overall mortality is around 0.8-1.6% [3]. Of the 1.6 million confirmed cases in India in 2010 almost half were caused by *P. vivax* illustrating that *vivax* remains a major public health issue in country. Although *P. vivax* malaria has a huge burden on the health, longevity and general prosperity of the people, research on *vivax* malaria and its complications are grossly overlooked and left in the shadow of the enormous problem caused by *P. falciparum* [4].

Recent studies have shown that complications associated with *P. vivax* are on the rise and outcomes are similar to that of *P. falciparum* malaria [3]. The trend of disease with *P. vivax* malaria is changing globally. It is increasingly recognized that serious and life-threatening complications can occur with *P. vivax* malaria due to evolution of *P. vivax* or due to some unexplored host factors or both [5]. Decreases in the incidence of *P. falciparum* are, on average, larger than those of *P. vivax*, suggesting that *P. vivax* responds more slowly to control measures, possibly because of its biological characteristics [6]. Hence a study on the complications of *P. vivax* malaria and comparative analysis of in patients with severe and non-severe *P. vivax* malaria would help gather information on the morbidity caused by the disease and help reduce the burden and unexpected mortality due to the disease.

Material & Methods

This study was a prospective study and consent was obtained from subjects. A total of 138 patients who attended to the hospital with fever of $\geq 37.5^{\circ}\text{C}$ and

Results & Analysis

One hundred and thirty-eight cases of *P. vivax* malaria were studied out of which 25 (18%) were classified to be severe *vivax* malaria on the basis of WHO criteria while the remaining 113 (82%) were non-severe *vivax* malaria. Out of the 25 cases of severe *P. vivax* malaria, 16 were males and 9 females (M: F ratio = 1.8). The majority of patients were in 21-30 and 31-40 years age groups. Mean age of distribution of severe *vivax* malaria (39 ± 4.5) was compared with that of non-severe *vivax* malaria (37 ± 7.4) which showed no significant association ($p=1.012$).

Fever, jaundice and vomiting were the commonest presenting symptoms (Table 1). Fever was the commonest symptom in both severe and non-severe malaria, occurring in 88% and 87% of patients respectively. 28% of patients with severe

peripheral smear and/or Rapid diagnostic test (immunochromatographic) positive for *P. vivax* were selected using purposive sampling techniques. They were followed from admission till recovery, discharge or death whichever was earlier. The following investigations were done in all cases: Haemoglobin estimation by cyanmethemoglobin method, Total and differential leucocyte count, Platelet count, ESR estimation by Westergren method, Peripheral smear for malarial parasite-both thick and thin smears stained with JSB stain and seen under oil immersion and Rapid diagnostic test (immunochromatographic) for *P. vivax*, Histidine rich protein-2 test to rule out *P. falciparum*, Random blood sugar, Urine analysis, Liver function test – Total and Direct Bilirubin, SGOT, SGPT, Serum protein and albumin, Renal function test– Serum urea and creatinine, Coagulation profile– Bleeding time, Clotting time, activated partial thromboplastin time, Prothrombin time. In selected cases, chest X ray, blood culture, cerebrospinal fluid analysis, and arterial blood gas analysis were done.

Those patients of age more than 18 years and less than 60 years who attended Medical College hospital having fever ($\geq 37.5^{\circ}\text{C}$) and peripheral smear and/or Rapid diagnostic test positive for *P. vivax* were included in the study. Patients with *P. falciparum*, *P. ovale*, *P. malariae* co-infection, age less than 18 years and more than 60 years, pregnant female patient of any age group, previously established cases of chronic kidney disease, previously established case of hematological abnormalities, previously established case of chronic liver disease, previously established case of neuropsychiatric disorders were excluded from the study.

Data collected was analyzed by frequency, percentage, mean, standard deviation and Chi-square test. Once the patient was diagnosed to have malaria, they were started on antimalarial drugs according to the new WHO guidelines for treatment of malaria [7]. Other supportive treatment was given according to the patients conditions.

vivax malaria and 8% of patients with non-severe vivax malaria had hyperpyrexia. The association of fever between severe and non-severe vivax was statistically significant with hyperpyrexia seen more with cases of severe vivax [1]. Nausea and vomiting were seen in 36% of severe plasmodium vivax malaria and 31% of non-severe vivax malaria. Abdominal pain was presenting complaint in 16 % of severe malaria and 12% of non-severe vivax malaria. Headache was seen in 28% of severe plasmodium vivax malaria and 23% of non-severe vivax malaria.

Breathlessness was seen in 12% patients with severe vivax malaria. Altered sensorium ($GCS \leq 10$) was present in 12% of the patients with severe vivax malaria. The association was statistically significant with altered sensorium present in severe vivax cases only ($P < 0.0002$). Jaundice was presenting complaint in 52% of severe vivax and 16% of non-severe malaria. The association was statistically significant with jaundice being commoner in severe vivax malaria ($P (\chi^2 > 15.292) = 0.0001$).

Petechiae were seen in 12% of patients with severe plasmodium vivax malaria and 6% of patients with non-severe vivax malaria. Petechiae did not show any significant association with severe and non-severe vivax malaria ($P (\chi^2 > 1.026) = 0.3110$). Oliguria was seen in 8% of patients with severe vivax malaria. Oliguria is defined as urinary output between 100-400 ml/day. Oliguria showed significant association with vivax malaria ($P (\chi^2 > 4.873) = 0.0273$).

Table-1: Presenting symptoms in patients with vivax malaria.

Symptoms	Severe vivax malaria (n=25) n (%)	Non-severe vivax malaria (n=113)
Fever	22(88%)	99(87%)
Vomiting	9(36%)	36(31%)
Pain abdomen	4(16%)	14(12%)
Headache	7(28%)	27(23%)
Breathlessness	3(12%)	--
Altered sensorium	3(12%)	--
Bleeding	3(12%)	--
Jaundice	13(52%)	18(16%)
Petechiae	3(12%)	7(6%)
Oliguria	2(8%)	1(0.9%)

Pallor was seen in 32% of the patients with severe vivax malaria and 20% of patients with non-severe vivax malaria. Icterus was seen in 72% of patients with severe vivax malaria and 5% of patients with non-severe vivax malaria. Splenomegaly was present in 56% patients with severe vivax malaria and 30% of patients with non-severe vivax malaria. Respiratory system involvement was seen in 16% of patients with severe vivax malaria. Respiratory manifestation included bronchitis, rhonchi, crepitations and ARDS. Central nervous system abnormality was seen in 12% of patients with severe plasmodium vivax malaria.

Table-2: Clinical signs in patients with vivax malaria.

	Severe vivax malaria (n=25)	Non severe vivax malaria (n=113)
Pallor	8(32%)	23(20%)
Icterus	18(72%)	6(5%)
Splenomegaly	14(56%)	34(30%)
Hepatomegaly	8(32%)	15(13%)
Respiratory signs	4(16%)	--
CNS manifestation	3(12%)	--

Table-3: Severe malaria patients with icterus.

Groups	A	B
Serum Bilirubin (mg %)	<3	≥3
No. of patients	5	8
Significant hyperbilirubinaemia		
Conjugated	1	7
Unconjugated	4	1
	Fisher exact test A with B, p value equals=.0319	
Hemoglobin Level		
<5	2	0
>5	3	8
	Fisher exact test A with B, p VALUE=0.1282	
Alt Level (IU)		
<40	4	1
40-100	1	5
>100	-	2
	X ² A with B 8.454 p=.0474	

Table-4: Manifestations of severe vivax malaria among the study subjects

Manifestations of severe malaria	Present study (%)	Kochar (%) [11]	Naha (%) [15]
Cerebral malaria	12	12.5	1.41
Severe anemia (Hb<5g/dl)	8	32.5	.47
Leucocytosis (>12,000/μl)	4	-	-
Thrombocytopenia (<50,000/μl)	8	22.5	31.92
Hyperbilirubinemia (> 3 mg/dl)	40	57.5	13.62
Acute kidney injury	8	45	.94
Metabolic acidosis	8	-	-
ARDS	16	10	1.88
Mods	8	47.5	-
Bleeding/dic	12	5	-
Mortality	4	5	-

Out of 13 patients with icterus 5 (28%) patients had bilirubin <3 mg% with 4 patients having unconjugated hyperbilirubinaemia while .8 (%) patients had bilirubin >3 mg% with 7 patients having conjugated hyperbilirubinaemia (See Table-3). The association of ALT with bilirubin is significant with ALT level increasing with increasing bilirubin level ($P(\chi^2 > 6.099) = 0.0474$). Total serum protein and Albumin: Globulin ratios in this study were within normal range. Majority of patients with severe vivax malaria had hemoglobin (Hb) levels between 8-10.9 gm% and greater than 11gm%. Two Patients had Hb level less than 5 gm%. There is significant association between anemia and splenomegaly in severe vivax ($P(\chi^2 > 4.573) = 0.0325$). There is significant association between severe thrombocytopenia and severe vivax malaria ($P(\chi^2 > 59.546) = 0.0000$). Out of 138 plasmodium vivax malaria patients studied 56% had thrombocytopenia. Twelve (8%) patients had severe thrombocytopenia (<50,000 cells/cu mm) and 66(47%) patients had platelets between 50,000-1, 00,000 cells/cu mm. The association between thrombocytopenia and splenomegaly is significant ($P(\chi^2 > 8.492) = 0.0036$).

Significant correlation between hemoglobin level and platelets was seen. In severe malaria both platelet and hemoglobin are decreased ($p=.0191$). Majority of patients had normal leucocyte count in our study. Leucocytosis with total leucocyte count greater than 12000 cells/cu mm was seen in 4% of patients. All patients with leucocytosis had raised neutrophil count indicating superadded bacterial infection. Leukopenia with total leucocyte count below 4000 was seen in 5% of patients. 91% of 138 patients had leucocyte count within normal limits and similar results. Majority of patients had leucocyte count between 4000-12000 cells/cu mm. Patients (5% of them) had lymphopenia with leucocyte count below 4000 cells/cu mm. Patients (12% of them) with severe vivax malaria had multiple system involvement with CNS,

respiratory system and hepatobiliary system involvement together. Severe vivax malaria patient received ACT, whereas non-severe vivax malaria received chloroquine and primaquine. Renal failure in the form of AKI was noted in 8% of patients with severe vivax malaria. One (0.72%) patient with severe plasmodium vivax expired out of 138 patients studied. He had multi system dysfunction in form of deranged hepatic function, deranged hematological parameters in form of thrombocytopenia, acute renal failure and central nervous system involvement. Patients with Hb<7 gm% had longer stay in hospital and required blood transfusion and other measures to make them haemodynamically stable.

Discussion

Malaria is a major public health problem in India as well as West Bengal state, accounting for sizeable mortality, morbidity and economic loss. It is a parasitic infection with multi systemic manifestations. The present study was done to evaluate clinical and biochemical profile of severe plasmodium vivax malaria among patients seen in medical college and hospital, Kolkata where malaria incidence is high. According to WHO criteria for diagnosis of severe malaria [7], 25 (18%) out of 138 consecutive P. vivax malaria patients were identified to have severe malaria according to clinical and biochemical parameters. This data corresponds to that of studies conducted in Thailand, Indonesia, Papua New Guinea and India (27% of patients are with severe malaria [8].

In a study conducted by Farogh et al, maximum number of patients belonged to age group 21-30 years [9]. According to the study of Muddaiah M and Prakash maximum numbers of patients were in between age group 21-30 [10]. In a study conducted by Bashawri LAM et al the mean age group was 25.34 ± 14.34 years [11].

The working group is the age group which is predominately affected, because this is the group which is exposed to mosquito bites especially in fields and outdoor. The study follows the age pyramid of our country; the base of age pyramid is formed by young people and apex by older age group which constitute lesser percentage of population. In the present study, the maximum numbers of patients (32%) were in the group of 21-30 years, which was consistent with the above-mentioned studies.

Male preponderance in malaria prevalence has been observed by various studies [11, 12]. In a study by Bashawri *et al*, the ratio of male to female patients were 3.15:1 and according to Jadhav *et al*, the male to female ratio was 1.40:1 [11,12]. A plausible explanation for this is that males are more frequently exposed to the risk of acquiring malaria than females because of their outdoor life. Further, females in India are usually better clothed than males. In our present study, the total number of males also outnumbered the females, with

ratio of 2.06:1. In the study by Muddaiah M. *et al*, symptom analysis showed that all cases had fever (100%), while other features seen include nausea and vomiting in 37.36% of cases, headache in 33.6% of cases, jaundice in 15.78% cases, cough in 11.57% cases, abdominal pain in 5.78% cases and altered level of consciousness in 4.21% of cases [10]. Our present study also shows these similar symptoms which are depicted in Table-1

Altered sensorium and Breathlessness were seen in severe vivax malaria cases only. Thus fever, jaundice, vomiting, headache and pain abdomen were commonest presenting symptom of vivax malaria. Even though malaria is commonly associated with thrombocytopenia, rash and petechial haemorrhages in the skin or mucous membranes are not the common presentation features.

In India, about 70% of the infections reported are due to P. vivax; 25-30% due to P. Falciparum and 4-8% are due to mixed infections. P. malariae is responsible for less than 1% of infections in India [13].

In our Study Anemia was present in 32% of patients with severe vivax malaria. Among 25 patients with severe vivax malaria, 2 had haemoglobin level below 5g/dl. 3 patients with severe malaria based on other criteria had Hb level between 5-8 mg/dl.

14(56%) patients had splenomegaly which suggests an association with anemia. It is known that in heavily endemic malaria areas, it is almost inevitable that malaria infection will be associated with anaemia, although malaria may not be the only cause of it. Out of 138 plasmodium vivax malaria patients studied 12(8%) patients had severe thrombocytopenia (<50,000 cells/cu mm) in cases of severe vivax malaria.

In our study 43% of patients with thrombocytopenia had splenomegaly, indicating that splenic sequestration is not the only mechanism for thrombocytopenia and other causes like immune mediated lysis and dyspoietic process in marrow may be responsible. Majority of patients had normal leucocyte count in our study. Leucocytosis with total leucocyte count greater than

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12000 cells/cu mm was seen in 4% of patients. All patients with leucocytosis had raised neutrophil count indicating superadded bacterial infection. Patients suffering from jaundice are depicted in Table-1. Haemolysis alone is unlikely to cause conjugated hyperbilirubinaemia along with raised liver enzymes [14].

Hence, other factors such as hepatocellular damage by malaria parasite may be the cause for deranged liver parameters. Total serum protein and albumin: globulin ratio in this study was all within normal range signifying absence of chronic liver dysfunction. The acuteness of hepatic dysfunction was probably too short for manifestation of impaired synthesis of serum proteins by the liver, if any.

Death was seen in 1 patient of severe vivax malaria patients. Death was due to multi organ dysfunction. He had deranged hepatic, haematological and renal parameters. Death was not seen in any patient in the non-severe vivax group. All 25 patients classified under severe vivax malaria were treated with ACT (artemisinin based combination therapy) and rest of 113 patients were treated with chloroquine and primaquine.

Strength and limitation- This study focuses on the severe vivax malaria cases which despite being so prevalent and widely distributed remains over shadowed by falciparum malaria. Only *P. vivax* mono-infections were considered and even mixed infections were ruled out. Previously diagnosed cases of chronic kidney diseases, chronic liver disease, neuropsychiatric patients and patients with haematological abnormalities were excluded from the study so as to elicit the effect of *P. vivax* effects on various systems of human body. Patients greater than 60 years were excluded from the disease since elderly patients might have pre-existing haematological, kidney and liver problems which might add as confounding factors.

There are also limitations in our study. This is a hospital based prospective study. The sample size should be bigger and population-based studies should be done. The follow up period was only 4 weeks which need to be longer to include cases of relapse and resistant cases of *P. vivax*.

Conclusion

This study highlights the fact that *P. vivax* malaria though traditionally considered to be a benign entity can also have a severe and complicated course which is usually associated with *P. falciparum* malaria.

Thrombocytopenia and hepatic dysfunction are commonly seen and are early indicators for the severity of the disease (as evident from clinical evaluation). Life threatening complications such as ARDS, AKI, cerebral malaria and MODS do complicate benign tertian malaria as seen in our study.

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Abbreviations: ACT, Artemisinin based Combination Therapy, AKI, Acute kidney injury, MODS, Multiple organ dysfunction syndrome.

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