A Comparative Study of Clinical Profile and Severity of Vivax and Falciparum Malaria Cases In A Tertiary Care Hospital on Western Coast of India

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Abstracts: Objectives: To assess clinical profile of malaria cases and compare the severity of vivax and falciparum cases admitted to our hospital. Methods: This was an observational study. All patients diagnosed as malaria were included and exposed to all routine investigations. Data was analysed to assess severity of vivax cases and compare it with that of falciparum cases. Result: Vivax patients had similar degree of thrombocytopenia as that of falciparum. Risk of developing severe manifestations like breathlessness, convulsion and jaundice were also similar in the two groups. Almost all complications seen in falciparum were also seen in vivax positive cases. Conclusion: Vivax cases develop all complications thought to be limited to falciparum. Increasing reports of severe complications in vivax demand revision of treatment strategy of vivax to detect severe cases earlier and treat aggressively. [Mitali R NJIRM 2017; 8(3):105-110]

Key Words: Vivax malaria, severity, complications

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Introduction: Malaria is a disease of global importance. It imposes great socio-economic burden and with six other diseases (diarrhea, HIV/AIDS, tuberculosis, measles, hepatitis B, and pneumonia), it accounts for 85% of global infectious disease burden.

The World Health Organization (WHO) estimates 3.3 billion people at risk, 247 million malaria cases and one million estimated annual malarial mortality worldwide[1]. According to the latest estimates, 198 million cases of malaria were recorded globally in 2013 (uncertainty range 124–283 million) and the disease led to 5,84,000 deaths (uncertainty range 3,67,000 –7,55,000). Approximately 2.48 million cases are reported annually from South-east Asia. Out of these, 75% cases are contributed by India alone. As reported by WHO, malarial mortality rate in India is 15000 per year; however, a recent study by Million Death Collaborators suggested a much higher annual malarial mortality (overall 2,05,000 per year)[2]. In India, 51% malaria cases are caused by Plasmodium falciparum (Pf) while Plasmodium vivax (Pv) is responsible for the remaining 49% .[3]

Pv has been thought to be benign and not related to severe manifestations although it threatens approximately 2.8 billion people globally. Also because of its particular biological characteristics, it is more difficult to eradicate than Pf[4-7]. However, in recent past many case series[10,11], surveillance studies[12-15] and reviews [16-19] have linked Pv malaria with a number of severe manifestations similar to those found in Pf infection, but most of these studies have been done in pediatric population[21-30]; only few are from adult population.

In our hospital, since last few years, we have come across many cases of Pv mono-infection with severe manifestations. Hence, we conducted this study to assess the burden of severe malaria in Pv monoinfection and to compare the clinical manifestations and severity of Pv with Pf malaria cases admitted to our hospital.

Methods: This was an observational study which was carried out in the medicine department of a tertiary care hospital situated in western part of India. The study was started after getting approval from the institutional ethics committee.

Inclusion criteria:

1. Patients of age ≥18 years with confirmed diagnosis of malaria either on peripheral smear or the malaria rapid diagnostic test (MRDT) (using antibodies against Pf histidine-rich protein 2 and Pv lactate dehydrogenase - Nano sign) were included. (According to current WHO report, if there is no other diagnostic support, it is appropriate to use MRDTS. If microscopy is available both should be used to detect malaria.)[29]
2. Who gave written consent for study.

Exclusion criteria: Patients with history of chronic diseases like diabetes mellitus, tuberculosis, cirrhosis of liver, chronic kidney disease or connective tissue disease were excluded from the study.

All the participants were be subjected to the routine investigations like Complete blood count (coulter method), Peripheral smear for identification of malarial parasite (MP), MP Antigen, urine routine microscopy, renal function test, liver function test, serum electrolytes, Chest X ray PA view, random blood sugar and ECG. Other special investigations like USG abdomen, 2D echo, CT/MRI, ABG were done if required. Giemsa-stained peripheral blood smears and the malaria rapid diagnostic test (using antibodies against Pf histidine-rich protein 2 and Pv lactate dehydrogenase- Nano sign) were used for the diagnosis of malaria.

Clinical presentation of malaria was classified as severe on the basis of the WHO's 2010 severe falciparum malaria criteria [30]

Result: Out of 60 patients with positive malarial antigen, 32 (53.3%) patients had Pv infection and & 28(46.7%) patients were positive for Pf malaria. (Table 1)

Table:1 Distribution of Pv and Pf cases in the study population.

MP Antigen	No. of patients	Percent (%)
Pv	32	53.3
Pf	28	46.7
Total	60	100.0

Basic characteristics of study population : (Table 2) Mean ages of patients with Pv and Pf malaria were 36.78 ± 17.39 years & 37.43 ± 17.46 years respectively. Male:female ratio in Pv & Pf was 21:11 & 22:6 respectively. There was no significant difference between the two groups in terms of temperature, pulse and diastolic BP. However, at the time of presentation, mean systolic blood pressure (SBP) was significantly lower in Pf (83.29 ± 12.48 mm of Hg) than Pv (mean was 91.81± 16.56 mm of Hg); p=0.03. Mean SpO_2 was also significantly lower in Pf (88.86 ± 6.803 %) than Pv (92.78 ± 5.701 %); p=0.018.

Blood investigations (Table 3) revealed significantly lower mean Hb in Pf positive cases (9.42 ± 2.99 gm%) as compared to that in Pv (11.77 ± 2.33 gm %) with p = 0.00. Mean total count was 5607.81 ± 2401.55 cells/cumm & 8542.86 ± 7517.70 cells/cumm amongst Pv & Pf respectively with p=0.04; hence TLC was significantly higher in Pv cases. However, there was no statistically significant difference between the two groups in terms of mean platelet count, RBS, SGPT and mean total billirubin. Mean direct bilirubin was also not significantly different but mean indirect bilirubin was significantly higher in Pf cases (3.35 ± 3.5mg% in Pf & 1.79 ± 1.23 mg% in Pv; p=0.022. Mean SGOT was also significantly higher in Pf (Pf 255.21 ± 311.78 IU/L & Pv 121.56 ± 150.463 IU/L; p=0.035). Mean blood urea was significantly higher in Pf (143.29 ± 48.025 mg%) than in Pv (90.84 ± 65.47 mg%) ; p=0.001.

Table 2 : Basic characteristics of the study population.

Variables	MP Antigen	Mean ± Std. Deviation	p-value
AGE (years)	Pv	36.78 ± 17.392	0.886
	Pf	37.43 ±17.460	
Temp. (°F)	Pv	101.82 ± 1.255	0.161
	Pf	102.32 ± 1.442	
Pulse(rates/min)	Pv	111.00± 12.412	0.273
	Pf	114.43± 11.461	
SBP(mm of Hg)	Pv	91.81 ± 16.565	0.030
	Pf	83.29 ± 12.475	
DBP(mm of Hg)	Pv	63.31 ± 10.197	0.071
	Pf	58.00 ± 5.606	
SpO_2 (%)	Pv	92.78 ± 5.701	0.018
	Pf	88.86 ± 6.803	

The mean s. creatinine level was also significantly higher in Pf (4.47 ± 1.912 mg%) as compared to that in Pv (2.59 ± 1.618 mg%); p≤ 0.001.

Thus, we observed a statistically significant difference in the lab values of Hb, TLC, indirect bilirubin, SGOT, blood urea and s. creatinine with mean values being higher in Pf. However, there was no significant difference between the two groups in terms of the degree of thrombocytopenia, total and direct bilirubin, as well as blood sugar levels. Risk of developing clinical manifestations of chills, rigors, vomiting and headache were similar in the two groups (p value > 0.05). The risk of developing more severe manifestations like breathlessness, convulsion and jaundice in Pv infection was also same as that in Pf malaria (p value 0.134, 0.796, 0.232 respectively). However, the incidence of altered sensorium, bleeding and oliguria was significantly greater in the Pf positive patients (p value 0.005, 0.006 and 0.017 respectively). (Table 4)

Table 3: Variations in blood investigations amongst Pv & Pf malaria

	Pv /Pf	Mean ± Std. Deviation	P-value
Hemoglobin (gm%)	Pv	11.77 ± 2.334	0.001
	Pf	9.42 ± 2.998	
Total Counts (cells/cumm)	Pv	5607.81±2401.55	0.041
	Pf	8542.86±7517.70	
Platelet Count (lacs/cumm)	Pv	0.88 ± 0.569	0.502
	Pf	0.77 ± 0.685	
SGPT (IU/l)	Pv	211.75 ± 288.13	0.133
	Pf	321.19 ± 258.10	
SGOT (IU/l)	Pv	121.56 ± 150.46	0.035
	Pf	255.21 ± 311.77	
Billirubin (mg%)	Pv	4.40 ± 3.20	0.065
	Pf	7.91 ± 10.05	
Direct Billirubin (mg%)	Pv	2.75 ± 2.10	0.131
	Pf	4.63 ± 6.606	
Indirect Billirubin (mg%)	Pv	1.79 ± 1.228	0.022
	Pf	3.35 ± 3.497	
S.Urea (mg%)	Pv	90.84 ± 65.465	0.001
	Pf	143.29 ± 48.025	
S.Creat (mg%)	Pv	2.59 ± 1.618	<0.001
	Pf	4.47 ± 1.912	
RBS (mg/dl)	Pv	86.66 ± 39.25	0.725
	Pf	83.39 ± 31.08	

One patient in our study population expired who belonged to Pf group while no deaths were noted in the Pv group.

Table 4: Pf malaria: Relative risk of developing various symptoms among patients with Pf malaria as compared to that in Pv malaria

Symptom	Relative risk (95% CI)	p value
Chills	0.926 (0.396-2.167)	0.863
Rigors	1.524 (0.879-2.642)	0.128
Vomiting	1.308 (0.765-2.237)	0.330
Headache	1.186 (0.622-2.261)	0.592
Breathlessness	1.509 (0.880-2.587)	0.134
Altered sensorium	2.257 (1.226-4.155)	0.005
Convulsion	1.091 (0.573-2.077)	0.796
Bleeding	2.126 (1.334-3.389)	0.006
Jaundice	1.533 (0.710-3.314)	0.232
Oliguria	2.300 (1.029-5.142)	0.017

Discussion: Among cases of malaria, proportion of Pv and Pf varies in different parts of India with 51% cases caused by Pf and remaining 49% by Pv in most parts of the country. Malaria due to Pv has been thought to be benign and not related to severe manifestations although it threatens approximately 2.8 billion people globally. However, it is also known that because of its particular biological characteristics it will be more difficult to eradicate than Pf [4-9].

Over recent years many case series [10,11], surveillance studies[12-15] and reviews [16-19] have linked vivax malaria with a number of severe manifestations similar to those found in Pf infection, but most of these studies have been done in paediatric population, only few are from adult population. In our setting, since last few years, we came across many cases of Pv monoinfection with severe manifestations. So we conducted this prospective study to see the burden of severe vivax malaria and to compare it with falciparum malaria in adult population to provide greater insight regarding vivax malaria and its severe manifestations.

Till now, in many cases who presented with severe malaria, even after valid microscopic diagnosis of P. vivax monoinfection, Pf infection has been presumed to explain the severity of infection attributing absence of Pf in peripheral blood smears to its adherent properties. This view is now being challenged. Many studies have reported severe disease due to vivax that resembles that of falciparum. Cerebral malaria (including generalised seizure and status epilepticus), hepatic dysfunction with severe jaundice, acute lung injury, acute respiratory distress syndrome (ARDS), pulmonary oedema, shock, renal failure, splenic rupture, severe thrombocytopenia and haemorrhage, and severe anaemia.[31] have all been reported now in cases of vivax malaria.

In our study, there was no statistically significant difference in basic characteristics of the two groups (i.e. Pv and Pf infected patients) in terms of age, temperature, pulse and diastolic blood pressure (DBP) with p value >0.05. Similarly symptoms and signs at presentation in Pv malaria like chills, rigors, vomiting, headache were same as compared to Pf malaria. The risk of developing more severe manifestations like breathlessness, convulsion and jaundice in Pv infection was also same as that in Pf malaria. Thus, we observed that Pv cases were almost as severe as the Pf cases. We observed a significant difference only in their systolic blood pressure (SBP), TLC and spO_2 at room air at the time of presentation. In terms of severity, only altered sensorium and bleeding

manifestations requiring blood transfusion were more common in Pf malaria.

Similar results were found in a study done in Venezuela which reported 58.9% cases with Pv malaria out of which 25.6% patients required platelet transfusion.[32] Similarly in a systematic review and metaanalysis thrombocytopenia was reported as the most common presentation in monoinfection with Pv malaria. The case fatality was 0.3%.[33] Thus, there is ample evidence that thrombocytopenia is a common finding in both Pv and Pf cases, although transfusion is more often required in Pf cases. The mechanism of thrombocytopenia is not clear. Fajardo and Tallent demonstrated Pv within platelets by electron microscopy and suggested direct lytic effect of the parasite on the platelets.[34] They showed a role of antibodies in lysis of platelets and development of thrombocytopenia.[35,36]

Similar to our study the liver enzymes and bilirubin were reported to be raised in both Pf and Pv cases in a study conducted from 2009-2011 in Karachi, Pakistan (p- 0.690)[37] and a study from Mumbai. Another study from Bikaner done in adults in the year 2009 reported marked hepatic dysfunction in 23(57.5%) patients out of 40 cases of Pv mono-infection.[38] However, a study from Karachi conducted in Aga khan university between 1997-2001 reported a higher prevalence of jaundice, anemia and hemoglobinuria in Pf cases. Thus, some studies have shown more severe hepatic dysfunction in Pf cases while a few have also reported more severe liver dysfunction in Pv cases. The cause of this discrepancy in results is not clear but may be attributed to more virulent vivax strain in some areas or may be to some underlying liver dysfunction leading to more severe presentation with superinfection with Pv.

Although we found statistically more significant deranged renal function in Pf cases as compared to Pv, a Bikaner study reported 18(45%) of the forty Pv cases developed ARF.[38] The chances of developing renal failure in Pv malaria were reported to be almost similar to Pf malaria, in another study done in Karachi by Ali Bin Sarwar Zubairi et al.[37] Anstey et al reported that Pv can also cause acute renal failure (ARF), may be due to hypovolemia or due to sequestration.[39] Thus, ARF has been commonly seen and reported in Pv cases as is seen in our study although the severity is observed to be greater in Pf.

There are studies which reported pulmonary involvement as well in Pv mono-infection.[39] They attributed this to Pv infected erythrocytes in pulmonary microvasculature and greater inflammatory response to a given parasite burden. Small airway obstruction, gas exchange alteration, increased phagocytic activity and accumulation of pulmonary monocytes are the other suggested mechanisms for respiratory complications.

One patient expired in our study, who was Pf positive. In the study conducted in Mumbai by Charulata S limaye the mortality was significantly lower in Pv malaria than in Pf malaria cases[40]. A study of hospitalized malaria patients at the Aga Khan University showed mortality rates of 1.5% and 2.0% in P. vivax and P. falciparum respectively.[11] In another study done in Karachi the mortality rate was 2.1% for P. falciparum patients and 1.0% for P. vivax patients.[37] The study done in Dehradun by S P Singh et al in 2013 showed 10.0 % mortality in Pv comparable to Pf mortality which was 7(14.3%). Thus, various studies have shown that mortality is also similar in cases of Pf and Pv highlighting the need of treating Pv aggressively.

Conclusion: Although Pf still remains the more severe counterpart of Pv, Pv infected cases have been reported to develop all types of complications in adults that were previously thought to be limited to Pf cases only. Increasing reports of severe complications in Pv demand for revising the treatment strategy of Pv malaria to detect more severe cases earlier and treat them more aggressively to reduce morbidity and mortality related with Pv cases.

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