Original Article

Severity of *Plasmodium vivax* Malaria in Karachi: a cross-sectional study

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Abstract
Introduction: *Plasmodium vivax* malaria affects billions of people annually. This study aimed to note the presentations and complications and subsequently to identify the determinants of in-patient hospital care of *P. vivax* malaria patients presenting to a tertiary care hospital in Karachi, Pakistan. Severity of the shock was also assessed using a shock index.
Methodology: This study descriptive cross-sectional study was conducted at the Emergency Department of Aga Khan University Hospital, Karachi. All adult patients with a positive *P. vivax* peripheral film and/or immunochromatography admitted through the department were studied during 2009. Data was entered and analyzed using SPSS version 16. Keeping the length of stay at a cut-off of 48 hours after admission, the independent Student-t test was applied. Level of significance was taken at 0.05.
Results: A total of 97 patients were included in the study. Fever was the most common presentation. A significant number of patients had nonspecific complaints, but tachycardia, altered mental status, and adult respiratory distress syndrome were important findings. Mean shock index was 1 (SD 0.26). Common reasons for admission were thrombocytopenia and dehydration. Some patients were admitted for more than 48 hours. Complications included pneumonia and bleeding requiring platelet transfusion.
Conclusion: This study highlights that the debilitating impact of *P. vivax* malaria remains high. Although the effects of severe *vivax* malaria can be contained through aggressive resuscitation and specific therapy, sensitivity and awareness of this complicated course must be highlighted among caregivers.

Key words: malaria; *Plasmodium vivax*; Karachi; severity; shock index

Introduction

Plasmodium vivax (P. vivax) malaria is a public health problem that puts billions of the world's population at risk of infection as highlighted in the World Malaria Report 2010 [1]. Despite malaria control strategies, an estimated 100-300 million cases are reported each year [2, 3]. *P. vivax* has a greater ability to survive in non-conducive environments*;* however, it is still considered to run a relatively benign disease course as compared to *Plasmodium falciparum*. This impression has not only resulted in a lesser focus on control strategies, funding and research, but its economic burden on health-care systems has also been underestimated [4-6].

Outside Africa, more than 50% of malaria cases are caused by *P. vivax*. Most of the disease burden is born by countries in the Middle East, South Asia, Western Pacific and Latin America [3]. Pakistan has also contributed to this burden with drug resistant *P. falciparum* and *P. vivax* malaria [7]. In Pakistan, malaria has been a persistent problem despite the Malaria Eradication Program of the 1970s. A recent study from Pakistan revealed that anti-folate resistance mutations were detected in 93.5% of *P. vivax* isolates [8].

P. vivax malaria is commonly called "benign tertian malaria"; however, features of acute presentation are confounded by multiple relapses occurring as a result of the activation of dormant hypnozoites residing in the liver. The classical clinical presentation in a non-immune patient causes high-grade fever with headaches and prostration with a regular 48-hour periodicity. Most patients are treated as outpatients in endemic areas, with chloroquine being the cornerstone of treatment [7-9]. Recently, changes have been noted in the epidemiology, resistance patterns and clinical presentations of *P. vivax*. A variety of common gastrointestinal symptoms have been noted [3-4,10-11], in addition to severe anaemia, pulmonary complications, and renal failure reported from various parts of the world [12-14].

The rapid progression of a febrile illness into a systemic infection requires advanced care with the

need of aggressive resuscitation and in-hospital care. Frequent observations of such complicated *P. vivax* patients presenting to our Emergency Department (ED) led us to conduct this study to note the presentations and complications and subsequently to identify the determinants of in-patient hospital care of *P. vivax* malaria patients presenting to a tertiary care hospital in Karachi, Pakistan. Clinical severity of the disease was assessed using the Shock Index (SI) which reflects the hemodynamic response to the shock [15,16].

Methodology

This descriptive cross-sectional study was conducted in the ED of Aga Khan University Hospital, Karachi. Being one of the busier tertiary care facilities and a major referral centre of the city, our department has an annual patient turnover of 50,000 with a 38% admission rate.

All adult patients with a positive *P. vivax* peripheral film and/or immunochromatography (MP-ICT) admitted through the ED were enrolled. The medical records were extracted for all *P. vivax* International Classification of Diseases-9 coded patients from January 2009 to December 2009. Patients who were managed as outpatients were not included in the study.

A pre-tested data collection tool was designed with variables including the patients' demographic details as well as clinical presentation. Presenting complaints, co-morbidities, hemodynamic parameters at arrival, and physical examination findings were noted. Laboratory workup including haemoglobin (Hb), haematocrit (Hct), platelets (Plt) count, total leukocyte count (TLC), and serum creatinine (SCr) were checked for malarial parasites (MP) and MP ICT was also recorded. Further in-patient management, follow-up laboratory tests, inpatient complications, length of stay, and outcome of the patients were noted as well as specific reasons for admission. Clinical severity of the disease in terms of hemodynamic response was assessed according to the SI at the time of ED presentation, which is defined as the ratio of the heart rate to systolic blood pressure (SI = HR/SBP). SI in normal subjects is 0.50 and a higher ratio reflects severity of circulatory shock. We adapted a cut-off level of 0.70 in our data set to determine the hemodynamic response to the illness [15,16].

Data was extracted from the patients' files by the research team and double-checked for accuracy before analysis. Data was entered and analyzed using SPSS version 16 (IBM, Chicago, USA). Frequencies and percentages of categorical data were calculated. Mean and standard deviation along with median and inter-quartile range (IQR) were reported for skewed continuous variables. Multiple response analysis was used for calculations involving co-morbidities, presenting complaints, examination findings, reasons for admission in hospital, inpatient treatments, and subsequent platelet trends. Keeping the length of stay at a cut-off of 48 hours after admission, the independent student-t test was applied to assess the effect of determinants on length of inpatient hospital stay. Level of significance was taken at 95% CI with alpha of 0.05. The study was approved by the Ethical Review Committee of the university.

Results

Demographics, presenting symptoms and co-morbidities of the study participants are given in Table 1. A total of 97 patients were included in the study. Fever was the most common presentation involving 93 (97%) patients. Time duration of fever varied with a median span of five days (IQR three days) before presentation. A significant number of patients had nonspecific complaints along with fever including headache, poor oral intake, generalized weakness and myalgias, but abdominal complaints were observed in almost half of the patients. These symptoms included nausea, vomiting, abdominal pain, diarrhoea and abdominal distension. About 12% of patients had respiratory symptoms including shortness of breath and cough; however, one patient had adult respiratory distress syndrome (ARDS) at the time of presentation. Neurological symptoms including confusion, disorientation, and drowsiness were present in seven patients and one patient also had seizures as a presenting complaint. Decreased urinary output was the main complaint in two patients along with high-grade fever.

Mean temperature on arrival was $38 \pm 1°C$. Although mean systolic blood pressure (SBP) was normal (114 ± 21 mm of Hg), initial evaluation in the ED demonstrated that most of the patients were tachycardiac (mean pulse rate 110 ± 22 beats/min). Also, 28 (27%) patients had a SBP of less than 100 mmHg at the time of arrival, requiring aggressive fluid replacement. This hemodynamic compromise leading to shock is better reflected through the shock index (SI). The mean value of SI was 1 (SD = 0.26); Median SI was 0.9 (IQR 0.5). Minimal value calculated was 0.5 and the maximum was 1.6. Hepatomegaly was noted in two patients. Figure 1

Table 1. Demographics, presenting symptoms, co-morbidities of study participants

Characteristics	Frequency (Percentage)
Age Median (IQR) Years	41 (32)
Gender	
Male	78 (81)
Female	19 (19)
Presenting Symptoms[+]	
Fever with rigors	93 (97)
Gastrointestinal dysfunction	54 (67)
Non-specific symptoms	26 (32)
Respiratory symptoms	10 (12)
Neurological symptoms	7 (9)
Renal dysfunction	2 (2)
Cardiac dysfunction	1 (1)
Co-Morbidities[+]	
Diabetes mellitus	17 (45)
Hypertension	16 (42)
Ischemic heart disease	10 (26)
Renal disorder	7 (18)
Infectious disease	6 (16)
Others*	15 (39)

*Asthma, benign prostatic hyperplasia, chronic liver disease, vitamin B12 deficiency,
seizure disorder, dyslipidemia, factor X deficiency and osteroarthritis
+Multiple response analysis   IQR interquartile range

Table 2. Comparison of factors affecting participants' length of stay in hospital

Factors	Up to 48 hrs Mean (SD†)	More than 48 hrs Mean (SD)	p-value	95%CI	
				Upper bond	Lower bond
Age	40.5 (17.3)	46.3 (21.8)	0.21	-15.04	3.41
Days of fever	6.6 (4.1)	8.1 (2.2)	0.10	-.51	5.59
Systolic BP*	112.0 (20.4)	117.5 (22.0)	0.10	-.51	5.59
Diastolic BP	67.7 (13.0)	68.9 (12.4)	0.69	-6.80	4.53
Heart rate	111.3 (22.8)	106.2 (19.7)	0.30	-4.61	14.80
Temperature	38.2 (1.0)	38.2 (1.1)	0.99	-0.49	0.49
Oxygen saturation	97.8 (1.5)	97.2 (2.4)	0.22	-.38	1.60
Hemoglobin	12.6 (1.7)	13.3 (3.9)	0.22	-1.88	.43
Hematocrit	37.1 (5.1)	37.0 (6.0)	0.89	-2.23	2.56
Leukocytes	6.5 (3.0)	10.6 (14.6)	0.16	-10.09	1.81
Platelets	68.6 (52.1)	59.5 (39.0)	0.35	-10.14	28.36
Serum creatinine	1.1 (0.4)	1.7 (2.7)	0.26	-1.66	.47

† Standard Deviation *BP Blood Pressure

describes the common abnormal physical findings, with dehydration, abdominal tenderness, and jaundice the most frequently observed signs.

P. vivax smear was positive in 94 (98%) subjects. For the remaining three patients a mix-positive MP-ICT test along with high-grade fever was taken as a proxy indicator, in case the workup for other febrile illnesses was negative. Other laboratory workup showed mean Hb: 13 ± 3 mg/dl with Haematocrit : $37 \pm 5\%$, Plt count : $50 \text{ x}10^9/\text{L}$, TLC : $8 \pm 9 \text{ x}10^9/\text{L}$ and SCr : 1 ± 1 mg/dl. Important findings include 88 (89%) patients who had thrombocytopenia with a platelet count of less than $150 \text{ x}10^9/\text{L}$. Half of the patients had platelets less than or equal to $50 \text{ x } 10^9/\text{L}$. Acute kidney injury marked by decreased urine output and high BUN/ creatinine ratio was present in 45 (46.4%) patients, which improved after fluid resuscitation. Abnormal liver function tests (LFTs) were reported in 32 (42%) out of 77 patients, in whom it was tested. Prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) were noted in 15 (23%) and 12 (19%) patients respectively.

More than 56 patients (58%) were treated with chloroquine and 37 (38%) with artemether; another 17 (18%) received antibiotics at the time of presentation, which were discontinued after establishment of diagnosis. In one patient anti-malarial treatment was not documented. While only one patient required packed red blood cells transfusion, five patients received multiple platelet transfusions due to persistently low platelets and bleeding complications. The majority of the patients (67%) required initial intravenous fluid resuscitation, which was continued as in-patient in 43 (44%) patients due to dehydration and/or persistent vomiting.

Reasons for admission were mentioned for 84 patients, out of whom 42 (50%) had low platelets with or without bleeding complications; 14 (17%) presented with signs and symptoms of septic shock requiring continuous monitoring; 4 (5%) had electrolyte imbalance including hyponatremia, acute renal failure; 2 (2%) had altered mental status at the time of presentation; 2 (2%) had concomitant cardiac problems; and 1 (1%) had ARDS. The remaining 19 (23%) were admitted for other reasons including dehydration and vomiting/nausea with poor oral intake. We also divided the patients according to their length of stay in two groups (Table 2). However, the analysis failed to demonstrate any statistically significant association of the clinical or laboratory features such as age, blood pressure, Hb or Plt levels with the duration of hospital stay.

The majority (82; 85%) of the patients were admitted in the general ward; 13 (13%) were treated in the high dependency or special care units and 2 (2%) in the intensive care unit. The mean length of stay was 2 ± 1 days. The majority, (67; 70%) were managed within 48 hours of admission but 29 (30%) had to be admitted for more than 48 hours.

Thirty-eight (39%) patients had co-morbidities (Table 1); however, the majority (63%) of the patients had less than three chronic illnesses. Among the 38 patients with co-morbidities, the reasons for admission were similar to those of the rest of the patients including thrombocytopenia (n = 3), electrolyte imbalance (n = 3) and dehydration (n = 2), with the exception of cardiac problems in two patients. Only one patient required a platelet transfusion in this group and none required transfusion of packed RBCs. Twenty-six (68%) patients were admitted in the general ward, 10 (26%) in the special care ward, and 2 (0.5%) in intensive care unit. However, among this subgroup, the majority of patients (82%) had SI of more than 0.7. Seven cases reported complications during their stay in the hospital, including platelet drop, non ST-elevation myocardial infarction (NSTEMI), pneumonia and ARDS. There were no mortalities among this subgroup. The number of patients with co-morbidities was so small that no statistically significant outcome could be measured when compared with those who had no co-morbid conditions.

A total of 16 patients had complications during their in-hospital stay, such as pneumonia and bleeding requiring platelet transfusion. Relapse was noted in five patients (5.2%), while ARDS, drug induced urticaria and NSTEMI was reported in one each.

Discussion

In this paper we present a cross-sectional study describing the characteristics of *Vivax* malaria patients who were managed in a tertiary hospital. Despite a small number of subjects over a one-year period, we observed that all these patients had signs and/or symptoms and laboratory parameters warranting in-patient management.

With respect to presenting complaints, high-grade fever with generalized body aches and gastrointestinal complaints were the commonest presentation. The classic description of tertian fever

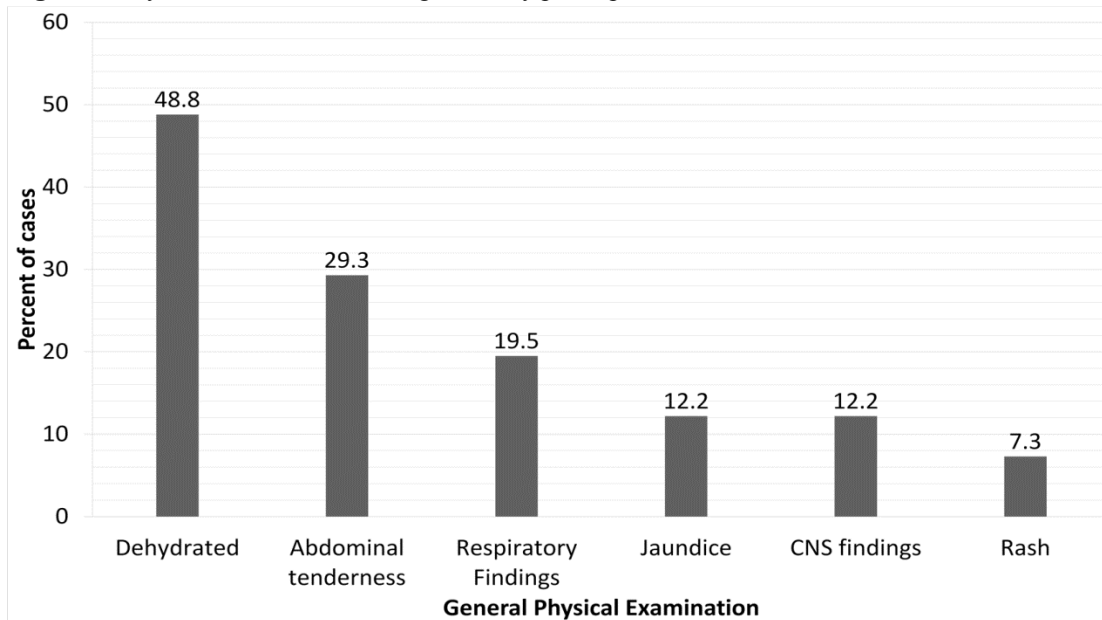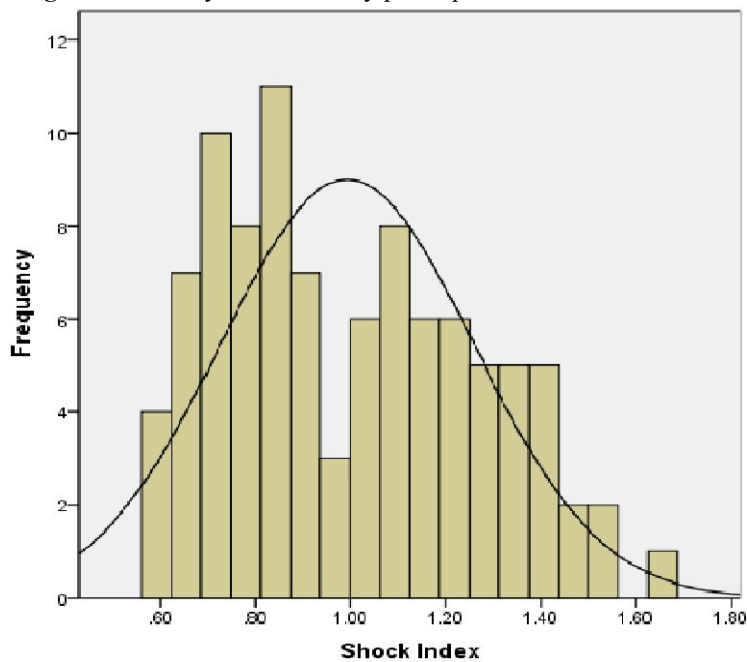**Figure 1.** Physical examination findings of study participants[+]

Figure 2. Severity index of study participants

with high, swinging temperature was found only in a minority of patients, while many patients presented with non-specific symptoms, abdominal pain, altered mental status, vomiting and dehydration which not only required laboratory work-up but also intravenous fluid resuscitation. Muddaiah and Prakash have reported that, among those malaria patients who were managed in-hospital, 47% had *vivax* malaria [9]. Also, nausea/vomiting, abdominal pain and headaches were observed commonly in those who were managed as in-patients [9,10]. Less frequently reported but important signs and symptoms that were pertinent to the central nervous system included drowsiness and seizures, and respiratory complications including ARDS and respiratory distress.

Organ dysfunction was noted in a considerable proportion of patients who presented with signs of systemic sepsis manifested by low blood pressure, depressed consciousness, and respiratory and renal dysfunction. Andrade and Kaur also reported severe *P. vivax* malaria manifesting as acute renal insufficiency and respiratory failure [17-18]. In our data set 9% of patients had CNS related symptoms including drowsiness and seizures. It is important to note that some researchers have identified cerebral malaria caused by *Plasmodium vivax*; however, no specific diagnostic tests so far can confirm this diagnosis in suspected patients [2,19,20].

P. vivax is known to evoke a profound systemic inflammatory response as compared to *Plasmodium falciparum*. Some cytokines and *vivax*-specific "malaria toxins" are believed to cause greater organ-specific inflammation, increased alveolar-capillary membrane permeability, capillary leakage, and leukocyte aggregation [17,21]. It is responsible for respiratory complications such as ARDS and acute kidney injury, as described in several case reports [14,17,21,22]. A large number of patients with hypotension, high shock index, high-grade fever, decreased urinary output, and some with respiratory complications reflect an intense systemic response similar to that of severe sepsis [13,17,18,21]. Higher SI (> 0.7) is related to deteriorating left ventricular stroke, as reported by Rady *et al*. [15,16].

Anaemia is a common clinical feature that is caused by increased fragility and destruction of infected and non-infected RBCs, [9,12,13,17] which was not found in our study subjects; the mean haemoglobin level was 13 ± 3 mg/dl. However, we found a significant number of patients at risk of bleeding complications due to low platelet counts.

Severe thrombocytopenia has been reported by other researchers [18,23,24]. Altered thrombostasis, thrombocytopenia and microvascular thrombosis contribute to bleeding complications and microvascular obstruction [13]. Thrombocytopenia at the time of admission was one of the major reasons for admission in 30% of cases as well as prolonged length of stay. Regardless of the platelet levels, only 5% of the patients developed major bleeding complications requiring multiple blood and platelet transfusions and most of the patients exhibited a rising platelet trend after initiation of antimalarial therapy. This finding is supported by other investigators in Pakistan. In 2010, Rasheed *et al*. reported such thrombocytopenia [25], and also found that despite low platelets, bleeding complications were rare and platelets responded well to antimalarial therapy.

Although more than a third of our patients had co-morbid conditions, the presenting complaints, clinical findings, reasons for admission, and complications were similar in both groups. Increased severity of SI was noted among those who had no co-morbidities and also needed in-patient resuscitation. The literature supports that the fever and anaemia of acute *vivax* malaria exacerbating hypoxia and/or hemodynamic compromise has the potential to convert a non-fatal co-morbidity into a fatal one. However, in our study, no fatal complications were observed. The numbers, however, were so small that no statistical results can be obtained.

Most of the patients were discharged within 48 hours of admission and the discharge was guided by improvement in symptoms coupled with hemodynamic stability in the majority of patients after confirmation of negative parasitemia and improving platelet count.

The main limitation of our study was its retrospective descriptive design. This study was neither designed nor powered to predict the risk factors associated with severe disease or poor prognosis. We included only those patients who were treated as in-patients in a single tertiary care centre to identify determinants of disease severity warranting in-patient care. Also, confirmatory tests such as PCR were not routinely performed on these patients.

This study highlights the fact that the debilitating impact of *P. vivax* malaria, although less than it was in former times, remains high. Although the effects of severe attacks of *P. vivax* can be contained through aggressive resuscitation, sensitivity toward and awareness of this complicated course varies among

caregivers. Additional studies are required to find the predictors of severe disease, cellular factors or host characteristics contributing to certain more frequently observed complications.

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