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Clinico-pathological studies of *Plasmodium falciparum* and *Plasmodium vivax* – malaria in India and Saudi Arabia

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Abstract

Malaria is one of the most devastating diseases of tropical countries with clinical manifestations such as anaemia, splenomegaly, thrombocytopenia, hepatomegaly and acute renal failures. In this study, cases of thrombocytopenia and haemoglobinemia were more prominent in subjects infected with *Plasmodium falciparum* (Welch, 1897) than those with *Plasmodium vivax* (Grassi et Feletti, 1890). However, anaemia, jaundice, convulsions and acute renal failure were significantly high (3–4 times) in subjects infected with *P. falciparum* than those infected with *P. vivax*. The incidence of splenomegaly and neurological sequelae were 2 and 6 times higher in *P. falciparum* infections compared to the infections of *P. vivax.* Both in *P. vivax* and *P. falciparum* malaria, the cases of splenomegaly, jaundice and neurological sequelae were almost double in children (<10 years) compared to older patients. The liver enzymes were generally in normal range in cases of low and mild infections. However, the AST, ALT, ALP activities and serum bilirubin, creatinine, and the urea content were increased in *P. falciparum* and *P. vivax* malaria patients having high parasitaemia, confirming liver dysfunction and renal failures in few cases of severe malaria both in India and Saudi Arabia.

Keywords

Pathology, liver enzymes, splenomegaly, malaria, India, Saudi Arabia

Introduction

Malaria is one of the most widespread infectious diseases of tropical and sub-tropical countries which continue to claim around 655,000 lives throughout the WHO African region (WHO, 2011). There are 99 countries and territories with ongoing malaria transmission. Globally, an estimated 3.3 billion people are at risk of malaria, with maximum cases recorded from sub-Saharan Africa. It mainly affects children, pregnant women and non-immune adults who frequently die as victims of cerebral manifestations and anaemia (Quintero *et al*. 2011). In the African region, approximately 90% of deaths among children under the age of five occur due to malaria. Children with impaired consciousness and respiratory distress are at the highest risk of death associated with malaria (Marsh *et al*. 1995). Neurological involvement in *P. falciparum* malaria is common and nearly a quarter of children who survive cerebral malaria, develop neurological sequelae (Idro *et al*. 2007). *P. vivax* infection is responsible for a significant proportion of malaria cases worldwide and is increasingly reported as a cause of severe disease (Lanca *et al*. 2012). However in the past few years, *P. vivax* infection has been increasingly recognized as a cause of severe malaria in young children even causing death (Sharma and Khanduri 2009, Singh *et al*. 2011, Limaye *et al*. 2012). Despite having lower densities than *P. falciparum*, *P. vivax* causes similar absolute reduction in red blood cell mass because it results in proportionately greater removal of uninfected red blood cells (Douglas *et al*. 2012*)*. Recent findings indicate that *P. vivax* is also responsible for a dramatic toll in many endemic areas other than Africa. Cerebral malaria, acute kidney injury, liver dysfunction, severe respiratory distress, abnormal bleeding, severe anaemia and multiple organ failure were the recently reported symptoms of *P. vivax* – malaria (Prakash *et al*. 2003, Picot and Bienvenu 2009, Sonkar *et al*. 2011). In view of above facts, the present study was aimed at assessing the clinico-pathological symptoms of malaria in India and Saudi Arabia.

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Materials and Methods

Blood samples were collected from patients admitted to the hospitals and clinics of Aligarh, India and Jazan, Saudi Arabia during 2012–2013. The blood samples thus collected were preserved in deep freezer at –80C until analyzed for liver and kidney function markers. Thick and thin blood smears were prepared on glass slides by pricking the finger of the patients having fever and headache. These slides were stained with Giemsa and Leishman stains and the probabilities of *P. falciparum* and *P. vivax* were microscopically confirmed at 100x (Nikon E-600). Rapid diagnostic test kits were also used during outdoor collections.

Patients having any pre-existing disease and symptoms resembling with malaria were excluded from this study. Clinical symptoms such as high fever, thrombocytopenia, anaemia, splenomegaly, jaundice and neurological sequelae were recorded in both *P. falciparum* and *P. vivax* malaria cases. Main emphasis was given on liver and kidney functions of the patients. Liver enzymes such as aspartate aminotransferase (AST) alanine aminotransferase (ALT) and alkaline phosphatase (ALP), and urea and creatinine levels of the patients were estimated as per standard techniques. The ALT and AST enzymes were estimated as per the method described by Wilkinson *et al*. (1972) whereas the ALP was estimated as described earlier by Burtis and Asood (1999). The kidney function markers such as creatinine and urea were measured according to the procedure detailed by Thomas (1998) and Kalpan (1965), respectively. Complications in children suffering both from *P. falciparum* and *P. vivax* were given special attention as there are increasing reports of malignancy among children infected with *P. vivax* in many countries. To determine the above hemato-biochemical parameters, samples were analysed by aforesaid techniques and the findings are presented in the form of tables and figures.

Statistical Analysis:

The Chi-square test was applied to assess various clinical parameters of *P. falciparum* and *P.vivax* malaria. The level of significance was set at $p<0.05$. The software SPSS (version 16.0, SPSS Inc., Chicago, IL, USA) was used. Results were expressed as mean ± standard deviation (SD).

Results

Results of the present study are summarized in Tables 1–3. Except for thrombocytopenia and haemoglobinaemia, other parameters showed significant differences ($P<0.05$). Malaria paroxysm was more irregular in *P. falciparum* infection compared to *P. vivax* which did not show regular periodicity until the illness had continued for a week or more. Thrombocytopenia was observed in 64% *P. falciparum* and 45% *P. vivax* patients. Haemoglobinaemia was more prominent in *P. falciparum* (33%) than in *P. vivax* (24%). In healthy individuals, no anaemia was observed in mild infections although 36% of *P. falciparum* and 12% of *P. vivax* patients having high parasitaemia developed anaemia. Splenomegaly was recorded in 57% *P. falciparum* and 31% *P. vivax* patients, mostly in children, while jaundice was observed in 13 and 3% cases of these infections. Convulsions and neurological sequelae were noticed only in 9% and 2%, and 18% and 3% cases of *P. falciparum* and *P. vivax*, respectively, whereas acute renal failure was observed in 12% and 3% *P. falciparum* and *P. vivax* malaria, respectively (Table 1). Both in *P. falciparum* and *P. vivax* infections, splenomegaly, jaundice and neurological sequelae were almost twice among children under the age of ten years compared to older groups (Fig. 1).

Liver impairment is common in malaria and its dysfunction enhances sickness. Hepatic function was assessed by measurement of bilirubin, aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP). Normal values of AST, ALT and ALP were 0–45, 3–60, 30–71 IU/L while value for serum bilirubin was 3–20 micromoles/L. Serum bilirubin ranged from 32.2–49.35 µmoles/L in severe infections of *P. falciparum* and *P. vivax* in patients of India and Saudi Arabia without much difference ($P>0.05$) in these species. Liver enzymes were elevated in *P. falciparum* malaria patients who had high parasitaemia (more >10 parasite/field). AST, ALT and ALP showed raised values of 65.36 ± 18.07, 82.91 ± 6.50, 87.10

Table I. Thrombocytopenia, anaemia, splenomegaly, jaundice, convulsions, neurological sequelae and renal failures in *P. falciparum* and *P.vivax* malaria

Parameters / Infections	*Plasmodium falciparum* (n = 91)		*Plasmodium vivax* (n = 106)		p-value
	Number	Percentage	Number	Percentage	
Thrombocytopenia	58	64%	48	45%	0.069
Haemoglobin (<7g/dl)	30	33%	25	24%	0.233
Anaemia	33	36%	13	12%	0.001
Splenomegaly	52	57%	33	31%	0.006
Jaundice	12	13%	3	3%	0.012
Convulsion	8	9%	2	2%	0.035
Neurological Sequelae	16	18%	3	3%	0.001
Acute Renal Failure	11	12%	3	3%	0.020

Table II. Liver enzymes, serum bilirubin, creatinine and urea at different levels of parasitaemia in *falciparum* malaria patients of India and Saudi Arabia

Countries	**India (n = 64)**			**Saudi Arabia (n = 27)**		
Parameters/Parasitaemia	Low (n=21)	Medium (n = 29)	High (n = 14)	Low (n = 6)	Medium (n = 11)	High (n = 10)
AST(IU/L) (0–45 IU/L)	17.92 ± 3.919	36.88 ± 6.416	65.36 ± 18.07	14.28 ± 2.96	43.13 ± 4.1	59.51 ± 5.19
ALT(IU/L) (3–60 IU/L)	15.76 ± 3.127	33.26 ± 5.29	82.91 ± 6.5	15.28 ± 2.73	41.71 ± 6.36	79.86 ± 10.74
ALP(IU/L) (30–71 IU/L)	53.27 ± 6.158	73.80 ± 3.78	87.10 ± 3.23	49.45 ± 2.36	72.42 ± 5.796	81.13 ± 1.95
Serumbilirubin (3.0–20.0 µmoles/L)	7.10 ± 2.93	15.28 ± 2.90	40.73 ± 6.85	8.23 ± 3.7	15.61 ± 2.97	39.68 ± 7.22
Creatinine (72.0–126 µmoles/L)	74.45 ± 4.733	92.41 ± 9.09	146.11 ± 5.93	72.31 ± 5.89	92.8 ± 8.63	149.09 ± 5.54
Urea (3.0–6.0 mmoles/L)	3.12 ± 0.765	4.54 ± 0.623	8.07 ± 1.05	3.30 ± 0.89	40.27 ± 0.56	10.53 ± 1.489

Table III. Liver enzymes, serum bilirubin, creatinine and urea at different levels of parasitaemia in *vivax* malaria patients of India and Saudi Arabia

Countries	**India (n = 90)**			**Saudi Arabia (n = 16)**		
Parameters/ Parasitaemia	Low (n=48)	Medium (n=30)	High (n=12)	Low (n=7)	Medium (n=5)	High (n=4)
AST(IU/L) (0–45 IU/L)	14.79 ± 3.071	31.27 ± 5.39	60.66 ± 7.43	13.11 ± 19.6	46.1 ± 3.39	64.47 ± 3.91
ALT(IU/L) (3–60 IU/L)	13.61 ± 4.29	31.06 ± 5.01	82.55 ± 7.23	13.61 ± 3.44	42.86 ± 2.53	79.45 ± 10.86
ALP(IU/L) (35–71 IU/L)	44.63 ± 4.59	58.65 ± 3.93	83.21 ± 6.06	40.47 ± 6.50	63.72 ± 4.86	87.17 ± 5.54
Serumbilirubin (3.0–20.0 µmoles/L)	7.18 ± 2.17	15.68 ± 3.414	49.35 ± 5.63	9.614 ± 1.94	17.36 ± 1.61	32.20 ± 3.20
Creatinine (72–126 µmoles/L)	70.62 ± 2.73	79.19 ± 2.729	130.13 ± 14.44	70.45 ± 3.53	85.53 ± 4.14	126.01 ± 10.04
Urea (3.0–6.0 mmoles/L)	4.45 ± 0.546	6.01 ± 0.609	8.29 ± 1.206	3.88 ± 0.67	7.38 ± 1.41	11.1 ± 1.20

± 3.23 IU/L in Indian and 59.51 ± 5.19, 79.86 ± 10.74, 81.13 ± 1.95 IU/L in Saudi malaria patients infected with *P. falciparum* (Fig. 2), while values recorded for these respective enzymes were 60.66 ± 7.43, 82.55 ± 7.23, 83.21 ± 6.06 and 64.47 ± 3.91, 79.45 ± 10.86, 87.17 ± 5.54 IU/L in Indian and Saudi strains of *P. vivax* (Fig. 3). Patients with low and mild infections of both *P. falciparum* and *P. vivax* showed values almost within normal range. Increased levels of liver enzymes clearly indicated liver damage in severe malaria cases having high parasitaemia.

Impairment of renal functions in malaria patients was assessed by measurement of serum concentrations of creatinine and urea. Elevated mean creatinine values were recorded in Indian (146.11 micromoles/L) and Saudi patients (146.11 micromoles/L) suffering from *P. falciparum* malaria with high

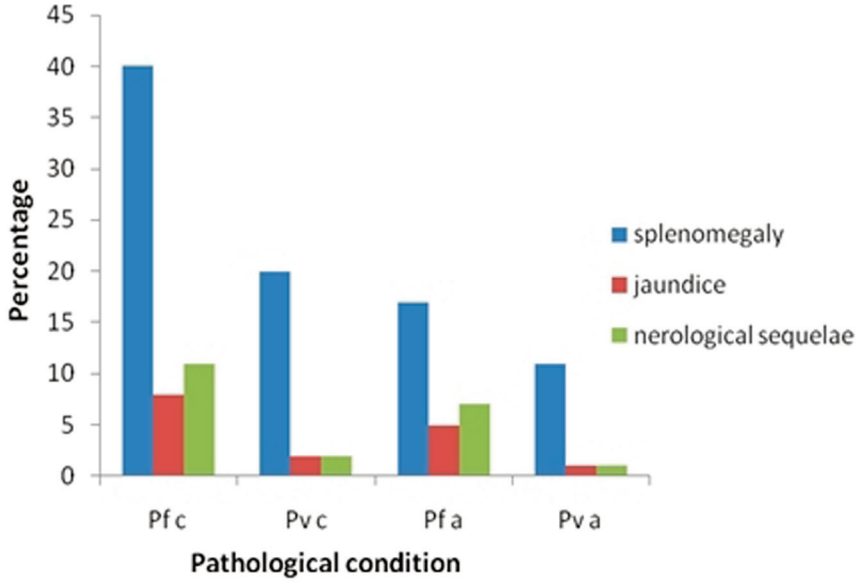

Fig. 1. Splenomegaly, jaundice and neurological sequelae in children (c) under ten years of age and older patients (a)

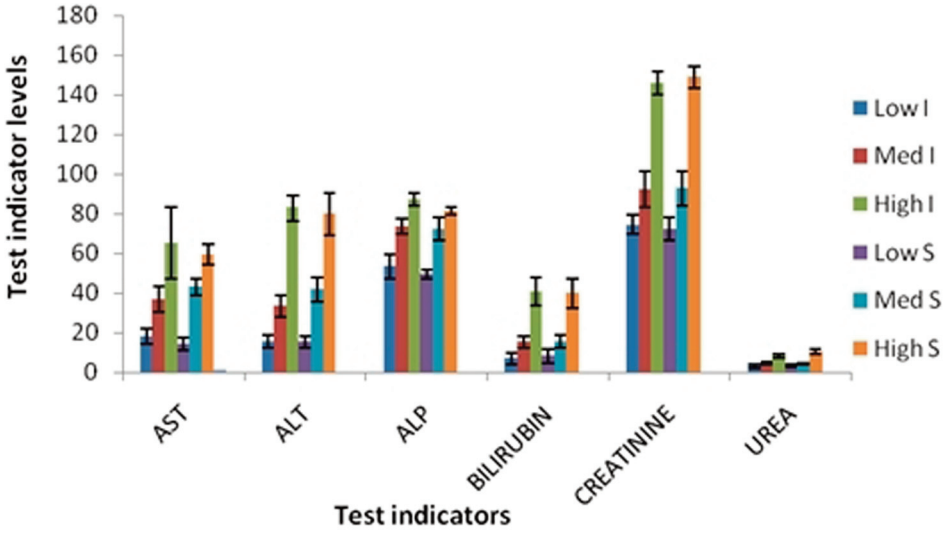

Fig. 2. Liver enzymes, serum bilirubin, creatinine and urea at different levels of parasitaemia in *falciparum* malaria patients of India (I) and Saudi Arabia (S)

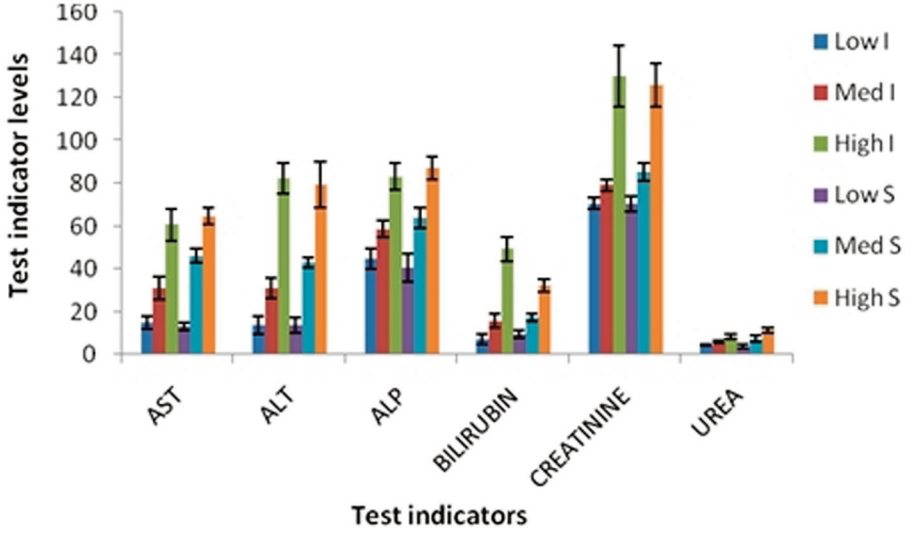

Fig. 3. Liver enzymes, serum bilirubin, creatinine and urea at different levels of parasitaemia in *vivax* malaria patients of India (I) and Saudi Arabia (S)

parasitaemia against the normal range of 72–126 micromoles/L. However, a slight increase in the mean creatinine value (126.02–130.13 micromoles/L) was recorded in severe *P. vivax* infections (Figs 1, 2). As far as serum urea is concerned, slightly higher values (8.07–11.1 micromoles/L) were recorded in *P. falciparum* and *P. vivax* malaria patients of both the countries having high parasitaemia (Figs 2, 3).

Discussion

Malaria affects almost all blood components and is a true haematological infectious disease. Anaemia and thrombocytopenia are the most frequent malaria associated haematological complications and have received much attention due to their associated mortality (Wickramasinghe and Abdalla 2000, Rodriguez *et al*. 2006). Thrombocytopenia is defined by platelet counts under 150,000/UL and is very frequent among malaria patients but there is no report of mortality excepting in cases of severe thrombocytopaenia. In our study, thrombocytopenia was detected in 64% *P. falciparum* and 45% *P. vivax* cases, while it was 50% in *P. falciparum* and 65% in *P. vivax* malaria from other parts of India (Jadhav *et al*. 2004). Slightly higher rates of thrombocytopenia (68–83%) were recorded from Uttarakhand and Mumbai India (Srivastava *et al*. 2011, Limaye *et al.* 2012). 53–56% thrombocytopaenia which is from

Saudi Arabia and Qatar (Bashawari *et al*. 2001, Joseph *et al*. 2011) is very close to the values observed in our studies (Bashawari *et al*. 2001, Joseph *et al*. 2011). Contrary to this, low incidence of thrombocytopenia (24.6%) was recorded in malaria patients from Bikaner (Kochar *et al*. 2010). The variations in values might be due to drug resistance and endemicity, as drug resistant parasites prolong their stay in their hosts and do more damages resulting in thrombocytopenia (Tjitra *et al*. 2008). These might be the reasons of the worldwide inconsistent prevalence of thrombocytopenia. Recent data from India have shown an increase in thrombocytopenia (43%) in cases of severe infection of *P. vivax* (Kochar *et al*. 2010). This is in agreement with our findings in which we recorded thrombocytopenia in 45% *P. vivax* malaria patients. In fact, these elevated figures show an increasing trend of thrombocytopenia.

Anaemia has frequently been associated with both *P. falciparum* and *P. vivax* malaria. The two common causes of anaemia are increased haemolysis and decreased rates of erythrocyte production from bone marrow. World Health Organization criterion for severe malaria is haemoglobin <5g/dL in children and <7gm/dl in adults. Following this criterion we observed anaemia in 36% and 12% patients of *P. falciparum* and *P. vivax*, respectively. In contrast, anaemia was recorded in 60% *P. falciparum* malaria patients in eastern region of Saudi Arabia which is a comparatively much higher figure (Bashawri *et al*. 2001). High rate of anaemia in *P. vivax* infection (19%) was also reported in Eastern Indonesia (Tjitra *et al*. 2008). Anaemia observed in 12.62% (*P. falciparum*) and 2.96% (*P. vivax*) patients in Mumbai (Limaye *et al.* 2012), is a low count if compared with our findings. This variation might be due to degree of parasitaemia and level of immunity against *P. falciparum* and *P. vivax* in individuals in different types of malaria in endemic and non-endemic regions of different countries.

The spleen in malaria plays a crucial role in the immune response against the parasites and controls parasitaemia due to phagocytosis of parasitized RBCs (Engwerda *et al*. 2005). The spleen enlarges more in *P. falciparum* than in *P. vivax*. We observed splenomegaly in 57% and 31% patients of *P. falciparum* and *P. vivax* malaria cases, respectively. Splenomegaly was two times greater in children under ten years of age infected with *P. falciparum* and *P.vivax* malaria. Much higher rate of splenomegaly was recorded in *P. falciparum* malaria (71%) from Bikaner (Kochar *et al.* 2006). In *P. falciparum* infection, splenomegaly reported from Jazan and Asir region of Saudi Arabia was 39 and 45% (Malik *et al*. 1998, Banzal *et al.* 1999), less than what we reported from India and Saudi Arabia. In contrast to this very low rate of splenomegaly ranging from 6.5 to 13% was reported from malaria patients of Saudi Arabia, Columbia and Thailand (Bashawri *et al.* 2001, Echeveri *et al.* 2003, Tangpukdee *et al*. 2006). These variations might be due differences in the age of patients included in the study as spleen enlargement is more common in children.

We observed 40 and 48% cases of bilirubinaemia in *P. falciparum* and *P. vivax* infections among Indian patients which were little less in Saudi patients (39% and 32%). 46% bilirubinaemia was recorded in *P. falciparum* patients from Karnataka, India (Joseph *et al*. 2011) which is very close to our findings. However, a relatively low rate of bilirubinaemia (22 and 5%) was observed in *P. falciparum* and *P. vivax* patients from Mumbai, India (Limaye *et al.* 2012). As far as jaundice is concerned, 13% patients infected with *P. falciparum* in this study were diagnosed for jaundice. Other workers from India and Saudi Arabia reported jaundice in 17–47% *P. falciparum* patients (Chawla *et al*. 1989, Banzal *et al*. 1999, Mazumder *et al.* 2000, Harris *et al*. 2001, Ahsan *et al*. 2008). In case of *P. vivax* malaria we observed jaundice only in 3% patients while other workers reported it in 14 and 15% patients from Columbia and India (Echeverri *et al*. 2003, Kochar *et al*. 2006). The variations in values might be due to the reasons that in our study area, the level of drug resistance is not as high that found in Columbia or Bikaner, India. It appears that jaundice is caused by combined effects of haemolysis, hyper bilirubinaemia and raised liver enzymes, and these parameters generally increase in severe malaria cases having high parasitaemia.

Neurological syndrome is the most lethal clinical complication of severe *P. falciparum* malaria. It may manifest as impaired consciousness, convulsions or coma. During this study, we observed convulsions in 9% *P. falciparum* and 2% *P. vivax* patients but none in coma. Coma was observed in 5% children suffering from severe malaria in Orissa (Tripathy *et al*. 2007). In other studies, 11–12% patients were reported to have convulsions and other neurological deficits after surviving cerebral malaria (Brewster *et al.* 1990, Thanachartwet *et al*. 2013). Still more cases (28%) presented persistent neurological sequelae just after and a few months following cerebral malaria with associated symptoms of bucco-facial dyspraxia, diplegia and frontal syndrome, dystonia, epilepsy, and behavior and attention disorders (Ngoungou *et al*. 2007). We observed convulsions in few patients only which might be due to the reason that majority of the patients had low- mild parasitaemia and low level of drug resistance.

Acute renal failure (ARF) is suspected in patients having serum creatinine >3.0 mg/dL. It has been reported in severe *P. falciparum* and *P.vivax* malaria cases mostly in Southeast Asia and Indian subcontinent where intensity of malaria transmission is usually low with occasional microfoci of intense transmission (Mehta *et al*. 2001). ARF is probably caused by mechanical obstruction by infected adherent erythrocytes, immune mediated glomerular pathology and alterations in the renal microcirculation, etc. We observed 12% *P. falciparum* patients with ARF, while earlier studies from India and Thailand reported ARF in 19 and 21% patients (Tripathy *et al*. 2007, Vannaphan *et al*. 2010). In *P. vivax* we observed only 3% cases of ARF from Aligarh and Saudi Arabia. Almost similar findings were reported from Pakistan and India where ARF was recorded in 2.5, 3.55 and 5.9% cases (Naqvi *et al*. 2003, Maheshwari *et al*. 2004, Tripathy *et al*. 2007). Higher ARFs (12.5% and 20.4%) in *P. vivax* infection had also been reported

by other workers (Mehta e*t al.* 2001, Prakash *et al.* 2003). Increased level of creatinine in the range of 126.01–149.09 μmoles/L was recorded in present study in patients having high parasitaemia. Slightly raised values of urea (8–11 micromoles/L) were also recorded in patients with severe malaria from India and Saudi Arabia (Figs 1, 2). We did not observe higher rate of ARFs in infections with *P. falciparum* and *P. vivax* from India and Saudi Arabia, as cases of severe malaria were less in number. Generally acute renal failures occur in non-immune individuals having high parasitaemia. But what is remarkable in this study is renal failure in *P. vivax* which was generally considered as a benign infection during the past.

We observed mean AST, ALT and ALP values to be 65.36 ± 18.07, 82.91 ± 6.50, 87.10 ± 3.23 IU/L in *P. falciparum* and 60.66 ± 7.43, 82.55 ± 7.23 and 83.21 ± 6.06 IU/L in *P. vivax* with high parasitaemia from India, while 59.51 ± 5.19, 79.86 ± 10.74 and 81.13 ± 1.95 IU/L in *P. falciparum* and 64.47 ± 3.91, 79.45 ± 10.86 and 87.17 ± 5.54 IU/L in severe *P. vivax* malaria patients from Saudi Arabia. This data clearly indicates that the maximum increase in AST, ALT and ALP was recorded in severe malaria patients of both the countries. Slightly lower values for these enzymes (33.76, 39.74 and 91.36) were recorded in mild *P. falciparum* malaria cases in Nigeria (Onyesom and Onyemakonor 2011, Uzupegbu and Emeka 2011). Higher levels of AST, ALT and ALP (75, 162 and 265 IU/L) were also recorded in *P. vivax* patients from Delhi, India (Anikar *et al*. 2010). There was a significant difference in the activities of liver enzymes in severe malaria infection as compared to low and mild infections. Results clearly indicate that both *P. falciparum* and *P. vivax* can induce changes in liver enzymes, especially when parasitaemia is high. It seems that the parasites during their hepatic phase destroy membrane of parasitized cells leading to leakage of the liver enzymes into blood circulation. AST, ALT and ALP are the marker enzymes of liver toxicity. Since liver is the major site of drug metabolism, increased level of these enzymes in blood might be due to the effect of antimalarials administered to treat malaria patients which damaged the liver and leakage of enzyme occurred.

From these results, it may be concluded that higher rate of hepatic dysfunctions and acute renal failures occurred in severe *P. falciparum* infections as compared to *P. vivax* cases. Similarly splenomegaly, jaundice and neurological sequelae were more common in severe *P. falciparum* malaria especially among children under ten years age. Some patients with severe *P. vivax* malaria showed symptoms similar to *P. falciparum* malaria exhibiting hepatic dysfunction and renal impairments which is a matter of concern as it was considered as a benign species. It is, therefore, suggested that *P. vivax* patients must also be treated radically in order to avoid complication especially among children.

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