### **Original Research Article**

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# A study of correlation between hepatic and renal dysfunction in malarial patients in Rajasthan, India

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#### **ABSTRACT**

**Background:** Our purpose of this study is to evaluate the correlation between hepatic and renal dysfunction due to falciparum malaria and vivax malaria in this region.

**Methods:** This study had conducted on patients of malaria admitted in wards in the department of pediatrics, SMS Medical College, Jaipur, Rajasthan during the resurgence of various outbreaks of malaria in the year January 2015 to December 2015. The diagnosis of malaria has confirmed by examination of thick and thin smear/optimal tests.

**Results:** The mean age of patients with hepato and /or renal dysfunction in malaria was 5-10 years and M:F ratio observed is 2:1. Association between serum bilirubin level and development of renal failure was significant, as 8 (100%) out of 8 patients with serum bilirubin >10 mg/dl had renal failure. Incidence of renal failure in malaria patients with hepatic dysfunction was found to be 22.2% (20 out of 90). Oliguric renal failure was present in 13 (43.33%) of patient with malarial renal dysfunction who had renal failure and 17 (56.67%) had non-oliguric renal failure. Association between hepatic and renal dysfunction was significant as 9 (40.9%) out of 22 patients with serum bilirubin > 3 mg/dl had renal failure in *P. falciparum* and 5 (71.43%) out of 7 patients in mixed (P.V. and P.F.) patients. This association was not significant in *P. vivax* as 6 (10.52%) out of 57 patient with serum bilirubin >3 mg/dl had renal failure.

**Conclusions:** In this hospital based observational study we observed that ARF was more common in subjects who have jaundice and incidence increased with higher level of bilirubin in malaria Early diagnosis of ARF and intervention in subjects who have hepatic dysfunction in malaria can save many lives.

Keywords: Hepatorenal dysfunction, Malaria

#### INTRODUCTION

Malaria is endemic in more than 100 countries, affecting 300-500 million people and causing 1.0-2.5 million deaths annually. It is endemic in tropics and subtropics, affecting 40% of world's population living in this areas. <sup>1-3</sup>

Jaundice is one of the common manifestations of severe malaria. Incidence varies from 10-45% in different reports and more common in adults than in children. Over a decade ago cerebral malaria was the predominant

manifestation of severe malaria, whereas today the combination of hepatic dysfunction and renal failure is more common. 10 Presence of jaundice in malaria indicates more severe illness with higher risk of complications. Mortality rate was also higher in this group of patients

Acute renal failure is one of the important manifestations of severe falciparum malaria, although it can also occur with vivax malaria. WHO has defined ARF in malaria as serum creatinine > 3 mg/dl with urine output <0.5

ml\kg\hr., inspite of rehydration in patients, having asexual forms of plasmodium falciparum in their peripheral blood film. Acute renal failure in malaria is usually oliguric or anuric but urine output may be normal or increased.

Multiple etiological factors contribute to the development of ARF in malaria like volume depletion (51%), intravascular hemolysis (39%), heavy parasitaemia (36%), cholestatic jaundice (33%), hypotension (30%), sepsis (9.6%) and DIC (7.4%).

Cholestatic jaundice (both conjugated and unconjugated bilirubin) and bile acid as well have been shown to be involved in the pathogenesis of acute renal failure in malaria. Endotoxin released in jaundice increases the vascular response to catechol amines, increases plasma renin activity further increasing renal ischemia and compromising renal function. Hyper uricosuria due to jaundice could further compromise renal function in states of low urine flow and acidic urine.

#### **METHODS**

This study was conducted on pediatric patients of malaria admitted in the department of pediatrics, SMS Medical College, Jaipur, Rajasthan during January 2015 to December 2015. The diagnosis of malaria has confirmed by examination of thick and thin smear/optimal test. Only those cases, which showing the asexual forms of plasmodium in the blood by smear examination or have positive optimal test for plasmodium and derangements in either the liver or renal function tests or both at the time of presentation were included in the study. All Cases were subjected to detailed history, physical examination and laboratory investigations. Informed consent was taken from the parents of all patients

#### Selection criteria

Patients positive for malaria parasite with malarial hepatorenal dysfunction at presentation were included in the study. Malarial hepatic and renal dysfunction is defined as patients having derangements in either the liver or renal function tests or both at the time of presentation as per WHO 2010.

#### Exclusion criteria

Patients having co-Infection with other organisms like enteric fever, brucellosis, leptospirosis, hepatitis A, hepatitis B, hepatitis C, hepatitis E and dengue which can also cause hepatorenal dysfunction were excluded diagnosis of malaria.

- Peripheral blood film thick and thin blood smear examination
- Optimal test (rapid diagnosis test).

#### **RESULTS**

The mean age of patients with hepato and/or renal dysfunction in malaria was 5-10 years as children of these groups is more mobile. There was preponderance towards males as M:F ratio observed 2:1. The spectrum of symptoms included fever in (100%), followed by jaundice in 90%, hypotension in 43%, altered sensorium in 40% patients, bleeding manifestations in 31%, renal failure in 30%, and severe anemia in 17% and pulmonary edema in 14% patients.

Table 1: Relation of level of S. Bilirubin with renal dysfunction (n = 90).

level of S. Bilirubin	No. of cases	Renal dysfunction
3-10	82	12 (15%)
>10	8	8 (100%)
Total	90	20 (22%)

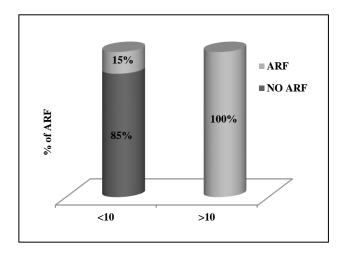


Figure 1: level of S. Bilirubin.

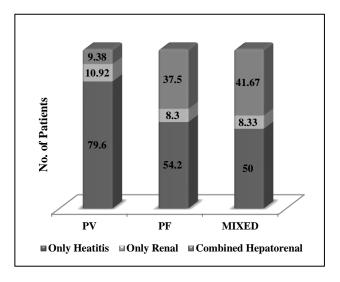


Figure 2: Correlation between hepatic and renal dysfunction (n = 100).

Serum bilirubin was more than 10 mg% in 8% of patients with malarial hepatic and/or renal dysfunction and predominantly conjugated hyper bilirubinemia was present in majority of patients suggesting a component of direct liver injury and malarial hepatitis. Markedly increased serum bilirubin AST, ALT, Alkaline phosphatase and prothrombin time in patients of malarial hepatorenal dysfunction suggest that besides hemolysis some other mechanism like cholestasis and hepatocellular injury may also play a role in causation. Association between serum bilirubin level and development of renal failure was significant as 8 (100%) out of 8 patients with serum bilirubin >10 mg/dl had renal failure. Observed mortality was only in this group.

Incidence of renal failure in malaria patients with hepatic dysfunction was found to be 22.2% (20 out of 90).

Acute renal failure probably developed as a part of multi organ dysfunction and volume depletion, severe jaundice, nephrotoxic effect of bile pigments, hypotension, endotoxin, intra-vascular hemolysis and hemoglobinuria also contributed to deterioration in renal function. Oliguric renal failure which was found to carry poor prognosis was present in 13 (43.33%) of patient with malarial renal dysfunction who had renal failure and 17 (56.67%) had non-oliguric renal failure which carried a good prognosis.

Table 2: (	Correlation	between	hepatic and	renal	dysfunction	(n = 100).

Malarial species	Only hepatic dysfunction	Only renal dysfunction	Combined hepatic and rena dysfunction	
P. vivax(P.V.)	51	7	6 (9.38%)	p-0.0004 odd ratio-0.162
P. falciparum (P.F)	13	2	9 (37.5%)	p-0.022 odd ratio-3.545
Mixed (P.V./P.F.)	6	1	5 (41.67%)	p-0.03 odd ratio-3.724
Total	70	10	20	

Majority of patients who presented with hepatorenal dysfunction were symptomatic for up to 10 days. Mortality was significant in patients of combined hepatic and renal dysfunction all mortality were belonging to this group. Multi-organ failure was the major cause of death in 80% followed by septicemia with pulmonary edema/ARDS in 20% of the patients. Association between hepatic and renal dysfunction was significant as 9 (40.9%) out of 22 patients with serum bilirubin > 3 mg/dl had renal failure in *P. falciparum* and 5 (71.43%) out of 7 patients in mixed (P.V. and P.F.) patients. This association was not significant in *P. falciparum* as 6 (10.52%) out of 57 patient with serum bilirubin >3 mg/dl had renal failure.

Table 3: Serum creatinine in patients of malaria with hepatic and/or renal dysfunction.

Malarial species	S. creatinine (≤3 mg/dl)	S. creatinine (>3 mg/dl)
P. vivax(P.V) n-64	51 (80%)	13 (20%)
P. falciparum (P.F) n-24	13 (54%)	11 (46%)
Mixed (P.V./P.F.) n-12	6 (50%)	6 (50%)
Total	70	30

Increased prevalence of malarial hepatorenal dysfunction in this region can be due to increase in partially immune population due to decreased prevalence of malaria over the last 5 years of draught. Genetic changes due to assimilation of characteristics of plasmodium from different region of the country leading to antigenic variation from movement of people to this region could have also contributed. Aggressive management of malarial patients with hepatorenal dysfunction with antimalarial, meticulous fluid intake output balance and early dialysis as indicated can bring a significant improvement in outcome of these patients and deranged liver and renal function tests to normal within 1-2 weeks of institution of therapy. Medical care providers at the periphery should be well versed with complication of malaria and early recognition and referral of these patients who developed hepatorenal dysfunction to higher centers can increase the outcome drastically.

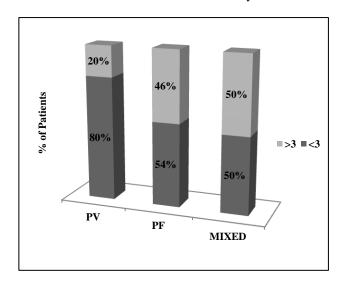


Figure 3: Level of S. creatinine.

#### **DISCUSSION**

Although hepato-renal dysfunction has invariably been reported in *P. falciparum* malaria but its association with *P. falciparum* malaria is also being noticed. Annual report of Government of India reported that 38.6% of all cases from different parts of the country were due to plasmodium falciparum.<sup>10</sup>

Although our study do not reflect the true prevalence of P. falciparum and P. falciparum malaria in the community as most of our patients were from Jaipur tehsil and others were serious and complicated cases referred from primary health centers situated in rural areas with semi developed medical facilities. 64% of the total cases were of P. falciparum, 24% cases were due to P. falciparum, and 12% were due to mixed infection with P. falciparum and P. falciparum. Two parasite species can develop in the same vector species and infection can be transferred with a single bite. In such cases clinical picture gets mixed up and fever might occur daily. In India, about 70% of the infections are reported to be due to P. falciparum, 25-30% due to P. falciparum and 4-8% due to mixed infection.<sup>10</sup>

Majority of the patients (52%) were between 5-10 years of age followed by 26% in 10-15 years age and 22% of 0-5 year age group. Out of the 100 patients, 65 patients were males and 35 were females. Most studies have reported a slight male preponderance. Prevalence of *P. falciparum*, P. falciparum and mixed infection was quite different in males and females. Out of 65 males 45 (69.2%) were positive for *P. falciparum*, 12 (18.5%) for *P. falciparum*, and 8 (12.3%) had both PV and PF. In females, *P. falciparum* was detected in19 (54.3%), P. falciparum in 12 (34.3%) and mixed in 4 (11.4%).

Jaundice was present in 90%, cerebral malaria in 40%, renal failure in 30%, multi organ dysfunction in 23% and S. anemia was present in 17%. Thus, prevalence of cerebral malaria, S. anemia, jaundice, renal failure and multi-organ dysfunction has significantly increased in last two decades. This could be attributed to change in the environment due to various causes as discussed earlier. Possibility of changes in the antigenic and pathogenic characteristics of the parasite cannot be ruled out.

76 out of 100 patients of malarial hepatic and/or renal dysfunction having moderate anemia with hemoglobin levels between 5 to 10 gm/dl and only 17 had S. anemia having hemoglobin below 5 gm/dl.

According to WHO, jaundice is one of the cardinal manifestations of the severity of malaria and is commonly seen in adult patients than children.

In this study on 100 patients of malaria with hepatic and/or renal dysfunction the level of total S. bilirubin was in range of 0.3-22.3 mg%, S. bilirubin >3 mg% was observed in 90% cases out of them 8% has S. bilirubin of

>10 mg%. Maximum value of S. bilirubin observed was 22.3 mg%.

In patients having serum bilirubin > 10 mg%, the hepatocellular injury should be an important causative factor in the pathogenesis of hyperbilirubinemia, as compared to patients having serum bilirubin < 10 mg%, in which the hemolysis, disseminated intravascular coagulation are the important factors. Incidence of complications was higher in patients with increased S. bilirubin level. It has also been reported that hyperparasitemia is associated with higher serum bilirubin level along with increased incidence of complications like anemia, hemoglobinuria leading to black water fever, algid malaria and acute renal failure.

In this study we observed that many patients of malaria with jaundice had significant higher level of AST and ALT. Patients of malaria with jaundice had linear increase in level of AST and ALT with increased level of S. bilirubin. Lowest AST level on starting study in patients of malaria with jaundice was 21 IU/L while highest level was 532 IU/L. ALT level range between 22-488 IU/L

Patients of malarial hepatic and/ or renal dysfunction had increased S. alkaline phosphatase with their increased S. bilirubin level. The range of S. alkaline phosphatase in patients of malaria with jaundice was 60-280 IU/L. Out of all patients 80% had>110 IU/L.

Prothrombin time in patients of malaria with jaundice was ranging from 14 seconds to 23 seconds. Hills et al observed moderately prolonged prothrombin time in patients of malaria with jaundice. <sup>11</sup> These observations are in accordance of this study.

Renal failure is defined by WHO as serum creatinine concentration > 3 mg/dl and urine output < 0.5 ml/kg/hr.<sup>4</sup> In spite of rehydration. ARF in malaria is usually oliguric or anuric but urine output may be normal or increased.

Acute renal failure was present in 30% of the cases of malaria who were admitted in the hospital with hepato or renal dysfunction. Overall prevalence of renal failure in the community is likely to be much less since hospital records do not reflect the true prevalence of malaria.

11 (36.7%) of the cases having renal failure were due to *P. falciparum*, 13 (43.3%) were due to *P. falciparum* and 6 (20%) cases had mixed infection with *P. falciparum* and P. falciparum. Table further reveals that out of all 24 (100%) cases of *P. Falciparum* 11 (46%) and out of 12 (100%) of mixed PV and PF 6 (50%) had renal dysfunction in comparison to 13 (20%) out of 64 in *P. falciparum*. These findings were statistically significant (p - 0.018).

Some urinary abnormalities were present in all patients having renal failure. Microscopic hematuria was present in 17 (56.6%) pts. of which 8 pts. were of *P. falciparum*, 6 pts. of *P. falciparum* and 3 were of mixed (P.V./P.F). Proteinuria in the range of (>0.5 g/m²/24 hr.) was present in 16 (53.3%) patients of which 6 were of P. falciparum, 4 of mixed infection and 6 of *P. falciparum*. Granular casts were present in the urine of 19 (63.3%) pts. of which 10 were of *P. falciparum* and 8 pt of *P. falciparum* and 1 mixed infection.

92 (95.8%) out of 95 survived patients recovered within 10 days of malarial hepatorena dysfunction whereas only 3 (3.2%) had symptoms for more than 10 days after hospitalization and 5 were expired during treatment. Out of 100 patients who presented with hepatic and/or renal dysfunction 5 patients died, all who died had S. bilirubin >10 mg%. All expired pts. had both hepatic and renal dysfunction. So mortality was more (62.5%) 5/8 in patients with combined hepatic and renal dysfunction having S. bilirubin level >10 mg.

The overall mortality in our study of patients with malarial hepatic and/or renal dysfunction was 5%. Cause of death was found to be multifactorial. However prognosis was grave when multiple organs were involved and pulmonary edema develops. In present study multiorgan involvement and pulmonary edema was found to be the commonest cause of death.

In hepatic and renal dysfunction in patients of malaria is usually associated with poor prognosis, severe anemia, hypotension, bleeding manifestations electrolyte in balance and increased mortality. Most common cause of mortality is multi organ dysfunction.

20 out of 100 had combined hepatic and renal dysfunction and 70 had hepatic and 10 had renal dysfunction alone. P. falciparum is commonly associated with multi organ failure out of 24 patient 9 (37.5%) had combined hepatic and renal failure, P. falciparum is not commonly associated with multi organ failure, it presents with isolated hepatic or renal dysfunction out of 64 patient 58 (90.62%) had either hepatic or renal dysfunction and only 6 patient (9.38%) had combined hepatic and renal dysfunction and in mixed infection 5 (41.67%) patient had combined hepatic and renal dysfunction remaining had isolated hepatic or renal dysfunction. These findings were statistically significant as odd ratio increased 3.545 in PF comparison to PV 0.1626. As it was discussed the most common cause of mortality is multi organ failure and because of this mortality is more in P. falciparum patient as compared to P. falciparum patient.

Incidence of renal dysfunction was higher in patients with increased S. bilirubin level. As all 8% cases had S. bilirubin>10 mg% also had renal dysfunction whereas only12 (15%) out of 82 cases had renal dysfunction with S. bilirubin level 3-10.

It can be prevented by prompt diagnosis of malaria in patients of pyrexia by intensive active and passive surveillance followed by adequate treatment with antimalarial and by early hemodialysis if indicated.

#### **CONCLUSION**

In spite of high prevalence of hepatorenal dysfunction in malaria it is not reported early due to lack of awareness among healthcare providers as lack of suspicion of malaria and shortage of rapid and sensitive diagnostic facilities. The specific reason for presenting our observation is to develop awareness regarding the early complications of malaria and to prevent these prompt actions can be taken.

In this hospital based observational study we observed that ARF was more common in subjects who have jaundice and incidence increased with higher level of bilirubin in malaria. Mortality and morbidity is more in subjects who had both hepatic and renal dysfunction.

Early diagnosis of ARF and intervention in subjects who have hepatic dysfunction in malaria can save many lives. In the light of our study, further studies are recommended with large sample size to see the association of hepatic and renal dysfunction in malaria.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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