

HEPATIC DYSFUNCTION IN FALCIPARUM MALARIASubhash Chandra¹, Sanjay Dhawale², Arvind Chouhan³**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: BACKGROUND AND OBJECTIVE: Malaria, a disease with protean manifestations is endemic in India with an estimated 70-100 million cases each year. Of these 45-50% are plasmodium falciparum. The present study is aimed at to study clinical features, complications, response to treatment and outcome in a tertiary care hospital. **METHODOLOGY:** This hospital based prospective study was done on 100 confirmed cases of falciparum malaria (either by peripheral smear or rapid diagnostic test) admitted in Department of Medicine, G.R. Medical College, Gwalior (M.P) from July 2013 to November 2014. A case sheet proforma was prepared and data (demographic profile, clinical feature, investigation, treatment, and complication) from all indoor patients was collected and analyzed. **RESULT:** Out of 100 patients, 65(65%) were males and 35 (35%) were females. Most of the patients were between the age group 21-40 years. The numbers of admissions due to malaria increased from July onward with maximum number of cases were found in the month of August. Fever was the most common symptom followed by headache, nausea and vomiting. Anemia was present in 50(50%) patients followed by hepatomegaly (32%) and splenomegaly (30%). Jaundice was seen in 47% cases in this study while significant jaundice was seen in 19% case out of which 4% cases was predominantly unconjugated jaundice and 15% cases was predominantly conjugated jaundice. In this study 9% cases found to have malarial hepatopathy. Prothombin time is usually normal and significant prolongation seen in 15% cases. Severe hypoalbuminemia (<2 gm%) was seen in 5% cases out of which 1% case was presented with very high level of bilirubin. Incidence of renal dysfunction was 18% out of which 14% patients associated with significant rise in serum bilirubin. In patients of significant jaundice duration of hospital stay was prolonged. Mortality was seen in 2% cases, 1% presented with significant hepatocellular jaundice and another 1% presented with significant cholestatic jaundice. These 2% cases had also associated with renal dysfunction. **CONCLUSION:** Liver is commonly involved in falciparum malaria and ranges from mild elevation in serum bilirubin and liver enzymes to elevation above significant level. Jaundice is a serious complication in falciparum malaria. Prognosis of these patients is poor.

KEYWORDS: Falciparum malaria, Malarial hepatopathy, Prothrombin time.

INTRODUCTION: Malaria is a febrile illness caused by protozoa of the genus plasmodium transmitted by the bite of infected female Anopheles mosquito and clinically manifested by three stages namely cold stage, hot stage and sweating stage.¹

The 5 species of the genus are P. Vivax, P. falciparum, P. ovale, and P. Malariae and P. knowlesi. There are about 100 malarious countries in the world with more than 2400 million people at risk, 300-500 million case/year and 1.5-3 million deaths/year.¹

Majority of deaths occur due to severe malaria, having one or more complications in a patient of Falciparum infection.²

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Liver involvement in malaria is common in patients of severe malaria and may manifest as jaundice, hepatomegaly and elevated liver enzymes like aspartate and alanine transaminases. Hyperbilirubinemia has been linked with increased malaria related mortality.³

It is often seen in association with other complications such as acute renal failure or cerebral malaria. Alanine aminotransferase is found largely in the liver. Hence, it serves as a marker of liver damage while Aspartate aminotransferase is found in a diversity of tissues including liver, muscle, heart, kidney, and brain. It is increased when any of these tissues is injured. Therefore it is not highly specific indicator of liver damage.⁴ The increased serum alkaline phosphatase activity among the patients indicates that the liver stage of falciparum malaria infection is accompanied by a perturbation of the host hepatocytes drainage pathways and damage to hepatocytes membrane leading to leakage of this enzyme out of the liver cells.⁵

MATERIAL & METHODS:

Study Area: This study was conducted in Department of Medicine, G.R. Medical College, Gwalior (M.P.), a tertiary care hospital in central India. Being a teaching hospital & tertiary referral centre, case input was primarily from this region and also from bordering district and state.

Study Design: This was a hospital based prospective study and was done on confirmed 100 cases of Falciparum malaria admitted in hospital during the period July 2013 to Nov. 2014. All patients were informed about the study & informed consent was obtained. Approval of Institutional ethical committee was taken. A case sheet proforma was prepared & Data (demographic profile, detailed history with physical examination and investigation) from all indoor patients was filled and analyzed. Falciparum Malaria was diagnosed as per guidelines of WHO. Patients were enrolled in the study with the following inclusion and exclusion criteria.

Inclusion Criteria:

- 100 cases tested positive for Falciparum Malaria (Either by MPPS/FM or Rapid diagnostic test) admitted in Medicine ward during above period were included in the study.
- Only first 100 patients were collected after excluding as per criteria including the study.

Exclusion Criteria:

- Falciparum negative other Malaria cases.
- Patients having evidence of liver disease prior to admission.
- Patients with H/o chronic alcoholism.
- Patients with H/o repeated blood transfusion.
- Patients taking hepatotoxic drugs.

The clinical and biochemical data of all patients were gathered and analyzed. In all cases a detailed history was taken with presenting complaints to exclude prior hepatic disease (Their related past history, medical & surgical history, Family history, H/o blood transfusion, H/o Alcohol, H/o drugs and addiction and any herbal used. Their detailed general and systemic examination was done.

The patients were followed from admission till discharge or death whichever was earlier.

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INVESTIGATIONS:

- LFT's - Serum bilirubin Total and direct.
- SGOT, SGPT, Serum ALP, Serum Albumin and prothombin time.
- Other test are being done as per hospital protocol and included.
- CBC.
- MPPS / FM or RDTs.
- Serum creatinine & Blood urea.
- USG abdomen.

RESULTS AND OBSERVATIONS: Total number of patients included in the study was 100 patients of all age groups and both genders were included in the study. They were divided into three groups.

- Group A:** S. bilirubin level < 1.20 mg% (53 cases)
Group B: S. bilirubin level 1.21-3.0 mg% (28 cases)
Group C: S. bilirubin level > 3.0 mg% (19 cases)

In a total 100 patients 65% males and 35% females. Male to female ratio 1.86: 1. Age of patients ranged between 14 years to 80 years (Mean 34.84±17.97). Most affected Age group was 21-40 years (42%). Main patient load was seen between July to November (Rainy season) (98%). Most common presenting symptom was fever (100%) followed by headache(60%) and nausea/vomiting (32%) while most common presenting sign was pallor (50%) followed by hepatomegaly and splenomegaly (32% and 30% respectively).

S. bilirubin (mg%)	No. of patients (n=100)	%	Group
< 1.20	53	53	A
1.21 to 3.0	28	28	B
> 3.0	19	19	C

Table No. 1: S. bilirubin

Types of jaundice	No. of patients (n=100)	%	Group B (n=28)	Group C (n=19)
Predominantly unconjugated (Direct < 15% of total)	12	12	8	4
Predominantly conjugated (Direct > 15% of total)	35	35	20	15

Table No. 1.1: In a total 47patients with raised bilirubin (47%) (n=100)

Hyperbilirubinemia seen in 47% patients (S. bilirubin > 1.20) while serum bilirubin above 2 mg% was seen in 35% cases. Serum bilirubin ranged from 0.45 to 18.96 mg%(mean 2.19+/-2.62).

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Serum bilirubin > 3 mg%	No. of patients	Percentage
Predominantly unconjugated (Direct < 15% of total)	04	04
Predominantly conjugated (Direct > 15% of total)	15	15

**Table No. 2: Significant biochemical jaundice
(i.e. S. bilirubin > 3 mg%) (Group C)**

Out of 19 cases with significant hyperbilirubinemia, 15% cases have conjugated type jaundice and 4% cases have unconjugated type of jaundice.

SGOT (IU/L)	No. of patients (n=100)	Percentage	Group A (n=53)	Group B (n=28)	Group C (n=19)
< 40 (normal)	21	21	14	6	01
40-120 (upto 3 times)	66	66	34	21	11
> 120 (>3 times)	13	13	05	01	07

Table No. 3: SGOT (AST)

$$X^2 = 14.28, \quad DF = 4, \quad p = 0.006$$

SGOT is not specific to liver diseases as it is also secreted by heart, skeletal muscles, kidneys, brain, and RBCs. It is therefore also increased in number of other diseases. Out of 13% showing significant rise in SGOT, only 7% patients have significant jaundice. Range(mean)= 19-358 IU/L(mean70+/-54.31).

SGPT (IU/L)	No. of patients (n=100)	Percentage	Group A (n=53)	Group B (n=28)	Group C (n=19)
< 40 (normal)	46	46	31	12	3
40-120 (Upto 3 times)	47	47	21	16	10
> 120 (>3 times)	07	07	01	00	06

Table No. 4: SGPT (AST)

$$X^2 = 27.32, \quad DF = 4, \quad p = 0.00001$$

It is more specific indicator of liver inflammation. In our study out of 7 patients of significant rise in SGPT, 6 patients also showed significant rise in bilirubin. Range(mean)= 8-220 IU/L(mean 54.8+/-42.5).

SAP(IU/L)	No. of patients (n=100)	Percentage	Group A (n=53)	Group B (n=28)	Group C (n=19)
22-127 (normal)	82	82	48	23	11
28-440 (upto 3 times)	12	12	05	05	02
> 440 (>3 times)	06	06	00	00	06

Table No. 5: Serum alkaline phosphatase (SAP)

$$X^2 = 28.53, \quad DF = 4, \quad p = 0.00001$$

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Out of 6% patients showing significant rise in SAP, all 6% patients also had significant rise in bilirubin. Range (mean)= 27-1520 IU/L(mean 128+/-179.0).

Prothrombin time Prolongation (sec)	No. of patients (n=100)	Percentage	Group A (n=53)	Group B (n=28)	Group C (n=19)
< 3 (non-significant)	85	85	52	22	11
>3 - <5(mod. Prolonged)	13	13	01	6	6
> 5(significant)	02	02	00	00	02

Table No. 6: Prothrombin time (PT) prolongation

$X^2 = 22.99$, DF = 4, p = 0.0001

Only 2% cases have significant prolongation of prothrombin time. Range(mean)= 1-6 sec (mean 2.55+/-0.84).

S. albumin (gm%)	No. of patients (n=100)	Percentage	Group A (n=53)	Group B (n=28)	Group C (n=19)
< 2	5	5	03	01	01
> 2 - < 3.5	50	50	23	18	09
3.5 - 5.2 (Normal)	45	45	27	09	09

Table No. 7: Serum albumin (gm%)

$X^2 = 3.26$, DF = 4, p = 0.61

Severe hypoalbuminemia was seen in 5% patients (< 2 gm%) of which 1 patient presented with very high level of serum bilirubin. Range (mean)=1.0-5.10 gm%(mean 3.21+/-0.68).

18% cases showed rise in serum creatinine level but only 2% cases have significant rise in serum creatinine (> 3.0 mg%). Range (mean)=0.15-3.84 mg%(mean 1.04+/-0.66.)

Duration of hospital stay significantly prolonged in group C (serum bilirubin >3mg%) patients. Range (mean)=1-14 days(mean 5.71+/-2.98).

DISCUSSION: We studied "LIVER FUNCTION TESTS" in 100 patients of falciparum malaria admitted in Department of Medicine, G.R. Medical College & J.A. Group of Hospitals, Gwalior (M.P.) between the period from July 2013 to November 2014.

The data was analyzed using software the SPSS version 17 (or Epi-info version 7). The comparison of difference in mean and proportion was compared by chi-square test. Results were expressed as mean and standard deviation. P-value of <0.05 was taken as significant and >0.05 was taken as non-significant for all statistical analysis.

In this study, the incidence of falciparum malaria was higher in males (65% vs. 35% in females) with male to female ratio 1.86:1 while in study done by Saha et al (2013)⁶ it was 57.4% to 42.59% and male to female ratio was 1.34:1 and in study done by Preetam et al (2012)⁷ 75% male affected with male to female ratio 3:1.

In our study the peak incidence of falciparum malaria was seen between the age group 21-40 years while study done by Mohan et al (2014)⁸ and Preetam et al (2012)⁷ it was also between age group 20-40 yrs.

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Highest incidence of falciparum malaria in this region was noted in rainy season from July to November with maximum incidence being found in month of August (35%) while in study done by Preetam et al (2012)⁷ in Nagpur area found maximum admission in between August to December with the highest incidence in the month of September (32%).

Fever \pm chills (100%) was the most common presenting symptom followed by headache (60%), nausea and vomiting (32%) in this study while most common clinical sign was pallor (50%) followed by hepatomegaly (32%), splenomegaly (30%) and icterus (19%) while in study done by Mohan et al (2014)⁸ fever was present in 94% of patients followed by Nausea & vomiting 21% and CNS manifestation 10%. Splenomegaly was seen in 53% in their study.

Incidence of jaundice in falciparum malaria is increasing. It was seen 47% in this study while significant jaundice was seen in 19% cases out of which 4% cases of was of predominantly unconjugated jaundice and 15% cases was of predominantly conjugated jaundice.

There was significant hepatic involvement in cases of falciparum malaria as proved by several studies in the past, this study showed 9% of cases having malarial hepatopathy.

In another study done by Saha et al (2013)⁶ incidence of hyperbilirubinemia was 60.9% and in study done by Preetam et al (2012)⁷ it was 35%. Significance jaundice ($>3\text{mg}\%$) in a study done by Hassan et al (2009)⁹ was seen in 43% cases and in study done by Lokesh KC (2012)¹⁰ it was 26%. Out of which all cases had predominant conjugated jaundice. In study done by Lokesh KC (2012)¹⁰, 10% cases showed evidence of malarial hepatopathy.

In present study range (mean) of PT prolongation was 1-6 sec. (2.55 ± 0.84). PT was prolonged (>3 sec.) in 15% cases out of which 2% cases had significant (>5 sec.) PT prolongation. And both cases were associated with a very high level of serum bilirubin. P value was significant. A study done by Mohan et al (2014)⁸ found PT prolongation in 21% cases while another study by Singh R et al (2010)¹¹ did not found PT prolongation in most of the cases except a few cases of very high level of bilirubin with severe malaria.

Another study done by Hassan A et al (2008)¹² PT did not prolong significantly in cases of falciparum malaria.

Prothrombin time is usually normal, even in patients with marked elevation of enzymes. Since severe coagulopathy is almost never seen in isolation with severe malaria, its presence should alert the physicians to look for an underlying infection with a hepatotropic virus or disseminated intravascular coagulation associated with sepsis.

In present study range (mean) of serum albumin was 1-5.10 gm% (3.21 ± 0.68). Incidence of hypoalbuminemia ($<3.5\text{gm}\%$) was 55% and that of severe hypoalbuminemia ($<2\text{gm}\%$) was seen in 5% cases out of which only 1% cases was presented with very high level of bilirubin. Other 4% cases were in normal range of serum bilirubin. Other non-significant cases of hypoalbuminemia (50%) may be because of poor nutrition status of patients rather than decreased hepatic functionality. P value was not significant. Studies are needed to establish the relation of hypoalbuminemia and severity of hepatic dysfunction in falciparum malaria.

In present study range (mean) of serum creatinine was seen 0.15-3.84mg % ($1.04+ 0.66$) incidence of rise serum creatinine ($>1.40\text{mg}\%$) was seen in 18% of cases out of which 13% had concurrent rise in serum bilirubin.

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2% cases was reported with significant rise in serum creatinine (>3mg %). Similar studies done by Preetam et al (2012)⁷ found incidence of rise of serum creatinine 32.5%, Singh R et al (2010)¹¹ reported 39.02% with mean (1.8+0.8), P value was significant.

Studied done by Hassan A (2008)¹² found incidence of rise in serum creatinine in 22% cases and Murthy GL et al (1998)¹³ found in 60% cases. So results are comparable with other studies.

In total 18% cases of raised serum creatinine, 14% (77.8%) were of group C patients i.e. patients with significant rise in bilirubin level. It shows that in severe falciparum malaria. There was multiorgan dysfunction seen specially a combination of hepatic + renal dysfunction. Some patients also needed hemodialysis for their management.

In present study range (mean) of hospital stay was seen 1-14 days (5.71+2.98). In this study hospital stay of group C patients (serum bilirubin >3mg %) had prolonged with increased morbidity. P value was significant.

A study done by Hassan A. et al (2008)¹² also found increase in duration of hospital stay of patients with LFT derangements.

In present study mortality was seen in 2% of cases, 1% presented with significant hepatocellular jaundice and another 1% presented with significant cholestatic jaundice. These 2% cases were also associated with significant increase in serum creatinine level (>3mg %).

A study done by Preetam et al (2012)⁷ in their study mortality was reported 6.25%. Another study done by Lokesh K.C. (2012)¹⁰ mortality reported in 4% of cases. Similar studies done by Kochar D. K. et al (2006)¹⁴ and Murthy G. L. et al (1998)¹³ also concluded that if a patient of falciparum malaria developed multi-organ dysfunction, the outcome is usually poorer.

CONCLUSIONS:

- In this study, we observed that liver is commonly involved in falciparum malaria and liver function tests abnormalities range from mild elevation in serum bilirubin and liver enzymes to elevation above significant level.
- It is also noted that hepatic dysfunction with jaundice is a serious complication in falciparum malaria and it indicates severe illness.
- Prognosis of these patients is poor with higher incidence of other complications (i.e. renal and cerebral), longer duration of hospital stay, increased morbidity and mortality in comparison to those patient who had normal liver functions.

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