International Journal of Advances in Medicine
Mehta DP et al. Int J Adv Med. 2021 Sep;8(9):1330-1334
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20213184

Original Research Article

A cross-sectional observational study assessing the liver function in malarial patients

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Received: 10 July 2021
Accepted: 03 August 2021

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ABSTRACT

Background: Malaria is a major cause of morbidity in the tropics, being a disease of global importance that results in 300-500 million cases annually. Liver involvement manifests as jaundice, hyperbilirubinemia, hepatomegaly and elevated enzymes (transaminases and alkaline phosphatase). Our objective in this study was to evaluate the role of liver function as an indicator of malaria in endemic regions and as a marker of disease severity.
Methods: This was an observational cross-sectional study conducted in central laboratory, department of pathology, central laboratory, department of biochemistry, and out-patient department, department of medicine, medical college Baroda and SSG hospital over a period of ten months, from February, 2019 to November, 2019 and included 137 microscopy proven malaria positive cases. The parasite density on peripheral smear was graded as scanty, moderate and heavy. After procuring the records of serum bilirubin, SGPT and SGOT, statistical analysis of the data was performed.
Results: All the 3 parameters show maximum derangement in severe parasitemia with mean values of 3.57, 81.44, and 92.9. While comparing vivax and falciparum malaria, all the LFTs studied show greater derangement in *Plasmodium Falciparum* when compared to *Plasmodium vivax*, with greatest difference seen in bilirubin levels (27.78% cases with hyperbilirubinemia in *Plasmodium vivax* versus 71.43% cases of *Plasmodium falciparum* showing hyperbilirubinemia).
Conclusions: We conclude that altered liver function in form of hyperbilirubinemia and increased liver enzymes in a patient with acute febrile illness increase the probability of malaria, hence directing the clinician along the correct path of further work-up and accurate treatment.

Keywords: Malaria, Aspartate aminotransferases, Alanine aminotransferases, Bilirubin

INTRODUCTION

Approximately 2.48 million malarial cases are reported annually from South Asia, of which 75% cases are contributed by India alone.[1] Infection is caused by a parasite of genus Plasmodium, which is transmitted to human beings by infected female anopheles' mosquito. Clinical features include fever, chills, sweating, headache, vomiting-diarrhoea, abdominal pain and distension, cough, splenomegaly and hepatomegaly.[2,3] Liver involvement manifests as jaundice, hyperbilirubinemia, hepatomegaly and elevated enzymes (transaminases and alkaline phosphatase).[4] Changes in physicochemical parameters of malaria infected blood may vary with level of malaria endemicity, demographic factors, level of malaria immunity and nutritional status.[5,6] In most endemic areas, conventional method of microscopic slide examination of peripheral blood remains the most widely used test as well as the gold standard for detecting malaria parasitaemia.

Liver is involved in malaria at two stages: during the pre-erythrocytic cycle and the erythrocytic phase. The first step is linked to the binding of merozoite circumsporozoite protein CSP-A and TRAP protein to hepatocytes via the heparan sulphate glycosylaminoglycans (GAG) and

promotes minimal liver damage.[7] In the erythrocytic phase, jaundice is directly caused by the infection (malarial hepatitis, intravascular hemolysis of parasitized RBC, septicemic hepatitis), or by indirect causes (microangiopathic hemolysis associated with disseminated intravascular coagulation, G6PD-related hemolysis, antimalarial drug induced-hemolysis) or completely unrelated (coexisting acute viral hepatitis or underlying chronic hepatitis).[7] Intravascular hemolysis of parasitized and non-parasitized RBC causes an increase of unconjugated bilirubin with mild to moderate jaundice while conjugated hyperbilirubinemia indicates hepatocyte dysfunction.[8] Reduction in portal venous flow as a consequence of micro-occlusion of portal venous branches by parasitized erythrocytes, intrahepatic cholestasis due to reticuloendothelial blockage and hepatic microvilli dysfunction, suppression of bilirubin excretion due to effect of parasitemia or endotoxemia or metabolic acidosis, apoptosis and oxidative stress are all mechanisms involved in hepatic damage.[9] 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. There are inflammatory as well as direct plasmodial effects in the damage to hepatocytes. As serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase (ALP) is synthesized in the liver, hence it is possible that initial inflammation of the liver may increase their production due to infection of plasmodium in the liver. Also, symptoms of malaria associated with vomiting could have caused increased hemoconcentration and led to initial increase in SGOT, SGPT and ALP due to breakdown of the liver cells after infection.[10]

The incidence of jaundice and liver dysfunction in *Plasmodium falciparum* malaria varies from 5.3% to 62% and from 2.5% to 21%, respectively, in different reports, while malarial hepatitis is rare in *Plasmodium vivax* infection.[11-14] Case-fatality rate in malaria-related hepatic failure is elevated to 40% when high parasite density is associated with jaundice and liver dysfunction.[15,16] The objective of our study was to evaluate changes in biochemical parameters in malaria patients and to correlate them with parasite density calculated using the gold standard (thick smear microscopy). We also evaluated the role of liver function as an indicator of malaria in endemic regions and as a marker of disease severity. Hence, liver function tests could help in prompt provisional diagnosis in conjunction with clinical status of the patient. Also, their correlation to parasite density would prevent disease progression and complications by facilitating physicians in clinical correlation for better treatment regime.

METHODS

This was an observational cross-sectional study conducted in central laboratory, department of pathology, central laboratory, department of biochemistry, and out-patient department, department of medicine, medical college Baroda and SSG hospital over a period of ten months, from February, 2019 to November, 2019 and included 137 microscopy proven malaria positive cases. Exclusion criteria consisted of patients with coexistent dengue infection proven by IgG, IgM, NS1 positivity and those patients in whom only gametocytes were detected. We processed the fresh EDTA samples of cases to be included in the study by preparing one thick and one thin smear of each case with Giemsa stain. Peripheral smear positivity for malarial parasite was taken as a gold standard for the diagnosis of malaria. At least 100 fields were examined before reporting the smear as negative. Effort was made to identify the plasmodium species morphology on thin smear and detection and the crude quantitative estimation of parasitemia was done on thick smear. The parasite density was graded by the plus system of WHO and then as scanty, moderate and heavy for our study purpose.[17] The records of serum Bilirubin, SGPT and SGOT for the respective cases were procured from the department of biochemistry.

Sample size (n=137) of this study was calculated with the help of previously published papers keeping the p value at less than 0.05 and power of study at 80%. All the data was analyzed using appropriate statistical tests. A p value of less than 0.05 was considered significant assuming normal distribution of dependent variables and randomization of independent variables. Qualitative data was expressed in percentage and quantitative data was expressed as mean±standard deviation. Data was entered with the help of Microsoft word and Excel and analyzed by MedCalc software version 12.5.0.

RESULTS

All the 137 cases studied were evaluated microscopically for the reporting of malarial parasites in the peripheral smear. However, only 136 cases were considered for statistical analysis and the single mixed infection case was excluded.

Tables 1 to 3 compare the frequency and percentage of derangement of liver function with increasing severity of parasitemia in *Plasmodium vivax*, *Plasmodium falciparum* and overall. The cut off values for considering the liver function parameters as deranged are taken as follows: serum bilirubin >2 mg/dl, SGPT and SGOT both >40 U/L. Among the 108 *Plasmodium vivax* cases studied, all the three liver function parameters show increased frequency of derangement with increase in parasite load with SGPT and SGOT showing maximum frequency of derangement in severe category, 71.88% (n=23) and 84.38% (n=27) respectively. However, serum bilirubin shows increased involvement in moderate parasitemia in this study (30.77%, n=20). Among the 28 cases of *Plasmodium falciparum* studied, also, maximum frequency of derangement is seen in severe parasitemia in all the liver function parameters except SGPT, which shows more derangement in moderate parasitemia with all the cases involved (100%, n=8). This might be due to overall a

smaller number of cases of moderate parasitemia in *Plasmodium falciparum*. In all the cases of malaria studied, all the three parameters show increased frequency of derangement with increase in parasite load, with most frequent derangement seen in severe parasitemia. Bilirubin - 50% (n=25), SGPT- 80% (n=40) SGOT-86% (n=43).

Table 5 records the lowest and highest values of liver functions observed in this study. Table 6 study the mean values (±SD) of all the liver functions at various parasitemia levels in malaria. Talking about the liver function parameters, i.e., bilirubin, SGPT and SGOT, all show significant increase in mean values i.e., more derangement with increase in parasitemia (p values being 0.0006, 0.0026 and 0.0052 respectively). All the three parameters show maximum derangement in severe parasitemia with mean values of 3.57, 81.44, and 92.9. While comparing vivax and falciparum malaria, all the LFTs studied show greater derangement in *Plasmodium falciparum* when compared to *Plasmodium vivax*, with

greatest difference seen in bilirubin levels (27.78% cases with hyperbilirubinemia in *Plasmodium vivax* versus 71.43% cases of *Plasmodium falciparum* showing hyperbilirubinemia).

Table 1: Comparison of frequencies of altered liver functions at different parasitemia levels in *Plasmodium vivax*.

Parameters	Frequency			Percentage (%)		
	Mild (11)	Moderate (65)	Severe (32)	Mild (%)	Moderate (%)	Severe (%)
Bilirubin	1	20	9	9.09	30.77	28.13
SGPT	5	35	23	45.45	53.85	71.88
SGOT	6	43	27	54.55	66.15	84.38

Table 2: Comparison of frequencies of altered liver functions at different parasitemia levels in *Plasmodium falciparum*.

Parameters	Frequency			Percentage (%)		
	Mild (2)	Moderate (8)	Severe (18)	Mild (%)	Moderate (%)	Severe (%)
Bilirubin	0	4	16	0	50	88.89
SGPT	1	8	17	50	100	94.44
SGOT	1	7	16	50	87.5	88.89

Table 3: Comparison of frequencies of altered liver function at different parasitemia levels (overall).

Parameters	Frequency			Percentage (%)		
	Mild (13)	Moderate (73)	Severe (50)	Mild (%)	Moderate (%)	Severe (%)
Bilirubin	1	24	25	7.69	32.88	50
SGPT	6	43	40	46.15	58.90	80
SGOT	7	50	43	53.85	68.49	86

Table 4: Compares frequencies of derangement of liver functions between *Plasmodium vivax* and *Plasmodium falciparum*.

Parameters	Frequency			Percentage (%)		
	Vivax (108)	Falciparum (28)	Total (136)	Vivax (%)	Falciparum (%)	Total (%)
Bilirubin	30	20	50	27.78	71.43	36.76
SGPT	63	26	89	58.33	92.86	65.44
SGOT	76	24	100	70.37	85.71	73.53

Table 5: Range of liver function tests in *Plasmodium vivax* and *Plasmodium falciparum*.

Parameters	*P. vivax*	*P. falciparum*
Bilirubin (mg/dl)	0.6-10	0.6-23.1
SGPT (U/L)	12-170	29-258
SGOT (U/L)	16-220	32-224

Table 6: Mean values of liver function at various parasitemia levels.

Parameters (Mean±SD)	Mild	Moderate	Severe	P value
Bilirubin (mg/dl)	1.3±0.89	1.78±0.96	3.57±4.24	0.0006
SGPT (U/L)	43.23±22.28	58.33±35.12	81.44±55.33	0.0026
SGOT (U/L)	53.46±43.10	63.56±35.39	92.9±54.84	0.0052

Test applied is ANOVA.

Table 7 compares the mean values (±SD) of all the liver functions in *Plasmodium vivax* and *Plasmodium falciparum*. In the liver function parameters, all the three parameters were significantly raised in *Plasmodium falciparum* as compared to *Plasmodium vivax* with the p values of all three being <0.0001.

Table 7: Mean values of liver function in *Plasmodium vivax* and *Plasmodium falciparum*.

Parameters (Mean±SD)	*P. vivax*	*P. falciparum*	P value
Bilirubin (mg/dl)	1.81±1.24	4.63±5.19	<0.0001
SGPT (U/L)	55.91±31.68	101.92±64.7	<0.0001
SGOT (U/L)	64.92±37.48	106±61.83	<0.0001

Test applied is Student's unpaired t test.

DISCUSSION

Three liver function parameters, i.e., total bilirubin, SGPT and SGOT were taken and evaluated in this study for their frequency/ percentage of involvement and their mean values in *Plasmodium vivax*, *Plasmodium falciparum* and overall as well as their frequency of derangement and mean values in various parasitaemia levels.

The alteration in liver function varied widely among various studies. The present study showed 36.76% cases with hyperbilirubinemia which falls within the range of the above group of patients from various studies, minimum observed frequency being 27.88% by Khuraiya et al and maximum being 46.5% by Arevalo-Herrera et al.[18,19] Khuraiya et al, Godse et al and Arevalo-Herrera et al showed lower frequencies of involvement in SGOT and SGPT which ranged between 19.23% in Godse et al and 45.5% in Arevalo-Herrera et al.[18-20] However, in present study, the involvement of SGPT and SGOT was much higher compared to what other studies observed, as well as much higher than the frequency of involvement of bilirubin, indicating liver damage in increased proportion. This might be due to the population type presenting in the set-up, and greater cases with complicated delayed stage infection.

Al-Salahy et al demonstrated significant increase in mean activity enzyme values of SGOT, SGPT and ALP as well as serum bilirubin.[21] The mean value of bilirubin (4.1±0.41) was within the mean±SD range observed in present study. The mean value of bilirubin in Khuraiya et al 2.84 (±3.88) was very close to that observed in present study, 2.39 (±2.80).[18] The SGPT and SGOT means encountered in our study, 65.43 (±44.37) and 73.74 (±46.45) respectively, are within the range observed among the above studies, i.e. minimum values being 37.92 (±2.04) in SGPT by Al-Salahy et al and 25.52 (±4.02) in SGOT by Godse et al and maximum values observed by Khuraiya et al being 164.56 and 165.69 respectively.[18,20,21] Khuraiya et al obtained nearly similar mean values for both SGPT and SGOT.[18] However, in most studies like the ones by Arevalo- Herrera et al, Al-Salahy et al as well as the present study, mean derangement was observed more in SGOT compared to SGPT.[19,21] This was exactly opposite to the observation of Godse et al where the mean SGPT was more deranged compared to SGOT.[20]

When the liver function profile among the *Plasmodium vivax* and *Plasmodium falciparum* cases of various studies were compared, it was observed that in most studies, mean value of bilirubin was more deranged in *Plasmodium vivax* compared to *Plasmodium falciparum*, as observed by Sundar et al and Arevalo-Herrera et al.[19,22] Sundar et al however observed higher frequency of hyperbilirubinemia in *Plasmodium falciparum* (31%) compared to *Plasmodium vivax* which is also true in present study (72% vs 28%).[22] Arevalo-Herrera et al stated that there is mild to moderate derangement in serum bilirubin mainly in patients with *Plasmodium vivax* (p<0.01).[19] However, the present study observed a different result here where the mean bilirubin values were significantly higher in *Plasmodium falciparum* compared to *Plasmodium vivax*. This may again be owing to the severity of parasitemia and complications in our study subjects, with 64.29% cases of *Plasmodium falciparum* falling in severe parasitemia range. This indicated that hyperbilirubinemia in our study subjects was not just due to hemolysis but also due to hepatocellular damage. Arevalo-Herrera et al also stated that in severe malaria, hepatic dysfunction and alteration of liver enzymes was more frequent and so more derangement is observed in SGOT and SGPT in *Plasmodium falciparum* cases compared to *Plasmodium vivax*.[19] The observations of present study and Arevalo-Herrera et al. were similar with respect to comparison of mean values of SGOT and SGPT in *Plasmodium vivax* and *Plasmodium falciparum*, where the mean SGOT as well as SGPT was observed to be much higher in *Plasmodium falciparum* compared to *Plasmodium vivax* in all the cases.[19] The mean SGPT and SGOT observed in the present study i.e. ~101 and ~106 respectively, were within the range observed for SGPT and SGOT by Arevalo Herrera et al i.e. 19-141 and 32-154 respectively.[19]

In terms of liver function at various parasitaemia levels, present study was compared to the study by Al-Salahy et al where in, both the studies encountered similar trends in association with parasitemia.[21] The serum bilirubin levels, SGPT and SGOT, all three showed significant increase with increase in parasitaemia levels. Al-Salahy et al found that the level of parasitaemia correlates positively with mean liver enzyme activities as well as serum bilirubin levels, specifically moderate and high parasitaemia showing higher values of liver enzyme activities as compared to low and mild parasitemia.[21] Arevalo-Herrera et al also found positive correlation between Total serum bilirubin levels and parasitaemia (rs=0.155, p<0.001).[19] This was similar to the trend observed in the present study in which the serum bilirubin levels and liver enzyme activities showed significant increase with increase in parasite density with a p<0.05. Overall, many parameters

were much more deranged in our study as compared to other studies. This might be attributed to the population type presenting in our hospital (i.e., low socioeconomic states), pre-existing higher baseline levels in those parameters, higher level of parasitaemia's and greater complications in our study group as compared to others.

CONCLUSION

Hence, we conclude that altered liver function in form of hyperbilirubinemia and increased liver enzymes in a patient with acute febrile illness increase the probability of malaria, hence directing the clinician along the correct path of further work-up and accurate treatment.

ACKNOWLEDGEMENTS

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Mehta DP, Shah PC, Daveshwar M. A cross-sectional observational study assessing the liver function in malarial patients. Int J Adv Med 2021;8:1330-4.