

# AST/ALT Ratio In Acute, Uncomplicated Falciparum Malaria Infection: Comparison In Relation To The AST/ALT Ratios In Diseases Of The Liver

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## Abstract

**Introduction:** Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were assayed in 110 adult patients (age range 18-40 years) presenting with acute, uncomplicated falciparum malaria infection and a control group of 80 age and sex-matched adults.

**Methods:** Patient selection was done by simple random sampling of adult males and females presenting at the Bauchi State Specialist Hospital with a history of fever and malaise not lasting more than seven days and who were subsequently confirmed to be malaria-positive by microscopic examination of Giemsa-stained thin blood slides.

**Results:** The mean serum AST and ALT activities were found to increase significantly relative to the AST and ALT values in the control group. Serum AST activity was  $38.29 \pm 1.37$  IU in the falciparum malaria patients and  $30.19 \pm 1.37$  IU in the healthy controls,  $p < 0.05$ . Similarly serum ALT activity was  $31.06 \pm 0.58$  IU in falciparum malaria patients and  $24.96 \pm 0.92$  IU in the control group,  $p < 0.05$ . The mean AST/ALT ratio in acute falciparum malaria infection was found to be  $1.22 \pm 0.14$ . This ratio differs significantly from the AST/ALT ratios reported for patients with Non-alcoholic steatohepatitis, chronic hepatitis C, alcoholic liver disease, hepatitis B and cirrhosis,  $p < 0.05$ .

**Conclusion:** An AST/ALT ratio greater than 1 during acute falciparum infection contradicts earlier reports that the ratio is highly specific to cirrhosis alone or has application as marker of liver disease only. Therefore the application of the AST/ALT ratio as a non-invasive means of assessing liver disease must be done with caution in the tropics where *P. falciparum* malaria infection is among the leading causes of hospital attendance.

## INTRODUCTION

The transaminases are two closely related enzymes of clinical significance <sup>1</sup>, particularly in the assessment of liver function. Among the duo, aspartate aminotransferase (AST) is known to exist in two electrophoretically distinct forms; a cationic isoenzyme associated with the mitochondria <sup>2</sup> and the anionic form associated with the cytoplasm <sup>3</sup>. Tissue levels of AST are highest in the heart and liver <sup>4</sup>. Significant amounts are also found in skeletal muscle and kidney, with lower levels in pancreas, spleen and lung. Low levels of AST are also found in erythrocytes <sup>5</sup>. Alanine aminotransferase (ALT) is present in varying concentrations in the liver, heart, skeletal muscle, kidney, pancreas, spleen, lung and red blood cells <sup>6</sup>. Both enzymes increase in many disorders related to liver damage; hence they have been proven to be sensitive indicators of liver-cell injury <sup>7</sup>. In particular, patients with viral hepatitis present with marked increases in the serum activities of both ALT and AST

frequently before clinical symptoms of the disease become apparent <sup>8,9</sup>. ALT is more elevated than AST in various necro-inflammatory conditions of the liver, reflecting its greater efficiency as a liver disease marker <sup>10</sup>. Other conditions associated with increased serum ALT are infectious mononucleosis and intra-hepatic cholestasis. Serum AST levels are found to increase in myocardial infarction, muscle disease and hemolytic anemia <sup>11</sup>. Other reported causes of elevated serum aminotransferase activities include alcohol abuse <sup>12,13</sup>, medication <sup>7</sup>, autoimmune hepatitis <sup>14,15</sup>, hepatic steatosis and non-alcoholic steatohepatitis, hemochromatosis <sup>18</sup>, Wilson's disease and alpha1-antitrypsin deficiency <sup>7</sup>. However, it is not only diseases affecting the liver that are associated with elevated serum aminotransferases. Non-hepatic causes of raised serum aminotransferases include occult celiac sprue <sup>7</sup>, muscular dystrophy <sup>19,20</sup>, acute appendicitis <sup>21</sup>, obesity <sup>22</sup> and circulating aminotransferase-immunoglobulin complexes

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(macro-enzymes) <sup>23</sup>. Because of their usefulness as serum markers of liver diseases, the AST/ALT ratio has been postulated to be good indicators of hepatic diseases in adults <sup>24,25</sup>. In particular, the AST/ALT ratio has been used to distinguish cirrhotic from non-cirrhotic patients <sup>26</sup> and patients with non-alcoholic steatohepatitis from those with alcoholic liver disease <sup>17</sup>. In this study we assayed for the serum activities of both AST and ALT in adult presenting with acute *P. falciparum* malaria infection and compared the AST/ALT ratio obtained with the AST/ALT ratios reported for other diseases. The aim was to assess if the predictive and differential diagnostic value of this ratio is unique only to the diseases of the liver.

## SUBJECTS AND METHODS

**Study Locale:** The southern and northern limits of Bauchi State where the study was conducted are demarcated by latitudes 9°30' North and 10°30' North respectively. Its Western and Eastern limits are bounded by longitudes 8°45' East and 11°0' East respectively. Two thirds of the land area is in the south of latitude 11°15'. Mean daily temperature in August, the month in which the study was conducted is 29.2° C and a humidity range of 68 %. August is the month of year where the incidence of falciparum malaria endemicity is at its highest peak because the highest average rainfall occurs in that month.

**Patients and Study Design:** Patient selection and pre-qualification was done by simple random sampling of individuals presenting at the Bauchi Specialist Hospital Outpatient Department with a history of fever and malaise within a period of 1-8 days, and who were confirmed to be infected with the falciparum malaria parasite by microscopic examination of Giemsa stained thin blood slides. Based on the following selection criteria, only 111 patients were found to be qualified for participation in the study. The age of patients is within the range of 18 – 40 years.

**Patient Selection Criteria:** Patients whose case history showed a concomitant presentation with the following conditions: Anemia, liver cirrhosis, hepatitis and other liver diseases, alcoholism and kidney disorders and those with a body-mass index > 25 were excluded from this study. Similarly patients on self-medication with any antimalarial drug prior to presentation were also excluded from the study.

**Controls:** For comparative purposes, a control group of 48 healthy adults (age interval, 18 – 40 years) were also enrolled in the study.

**Serum:** Venous blood (5 ml) was obtained from each of the patients by venepuncture of the antecubital vein using a sterile needle and syringe between the hours of 9 – 11.00 am local time. The blood samples were then transferred into clean, sterile centrifuge tubes and allowed to clot. Each clotted sample was centrifuged at 3000g for 10 minutes to obtain the sera. Enzyme assay was carried out within 24 hours of collection.

**Enzyme assays:** Serum AST and ALT activities were assayed according to the method described in Stoeve and Makarova <sup>27</sup>. All the reagents used in the work were of analaR grade.

**Data analysis:** Data was analyzed using the Openstat4 statistical software (Version 6, mod 3). The difference between the mean serum AST and ALT activities in healthy controls and infected adult falciparum malaria patients was analyzed using the Student's t-test for correlated samples. The difference between AST/ALT ratios in acute falciparum malaria infection and other diseases were analyzed using the Student's t-test for independent samples. p values < 0.05 were considered significant.

**Ethics:** This work was conducted in accordance with the following ethical declarations: World Medical Association's Declaration of Helsinki <sup>28</sup>, APA Ethical Principles in the Conduct of Research with Human Participants <sup>29</sup>, World Medical Association's Declaration of Lisbon on the Rights of the Patient <sup>30</sup> and CIOMS / WHO International Guidelines for the Conduct of Research Involving Human Subjects <sup>31</sup>.

## RESULTS

**Figure 1**

Table 1: AST and ALT activities in adult malaria patients and control (IU).

Enzymes	Mean ± SD	
	Patients	Control
ALT 0.92 <sup>a</sup>	31.06 ± 0.56 <sup>a</sup>	24.96 ±
AST 1.37 <sup>b</sup>	38.29 ± 1.37 <sup>b</sup>	30.19 ±
AST/ALT Ratio	1.23	1.21
% increase in serum ALT activity relative to controls = 20.43		
% increase in serum AST activity relative to controls = 26.83		

Values with the same superscript on a row differ significantly at p < 0.05

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**Figure 2**

Table 2: Relative AST/ALT Ratios in acute malaria infection and some selected diseases.

Diseases REFERENCE	AST/ALT Ratio
Acute <i>falciparum</i> malaria infection	1.22 <sup>a</sup>
Alcoholic liver disease 17	2.60 <sup>b</sup>
Non-alcoholic steatohepatitis 17	0.90 <sup>c</sup>
Chronic hepatitis C infection 26	0.99 <sup>d</sup>
Hepatitis B 32	0.80 <sup>e</sup>
Cirrhosis 33	0.93 <sup>f</sup>
<i>P. Vivax</i> infection 34	0.90 <sup>g</sup>

<sup>a-b, a-c, a-d, a-e, a-f, a-g</sup> (Differences significant at p = 0.003)

The normal healthy reference values for both aspartate and alanine aminotransferases in the selected study locale are as follows: 30.19 ± 1.37 IU (AST) and 24.96 ± 0.92 IU (ALT), table 1. ALT and AST values in acute *falciparum* malaria infection were found to be as follows: 31.06 ± 0.58 IU and 38.29 ± 1.37 IU respectively as shown in table 1. Relative to the healthy reference values, the activities of both ALT and AST were found to be significantly higher in acute *falciparum* malaria patients, p < 0.05. These values represent 20.43 % and 26.83 % increases in the serum activities of ALT and AST respectively. Table 2 shows the AST/ALT ratios in acute *falciparum* malaria patients and other disease conditions. The AST/ALT ratio of 1.22 in malaria patients is significantly higher than the AST/ALT ratio in all the other diseases except alcoholic liver disease, P < 0.05, which has the highest AST/ALT ratio.

### DISCUSSION

The normal, healthy values for serum AST and ALT as reported by Pratt and Kaplan<sup>7</sup>, and later supported by Prati et al.,<sup>35</sup> are in the range of less than 30-40 U per liter. These values are above the normal range obtained in our study as shown in table 1. The differences in the normal, healthy ranges are not unexpected. This is because the normal, healthy ranges differ from one laboratory to another.<sup>7</sup> The possible reasons for such variations include environmental, nutritional status and anthropometric indices<sup>36</sup>. Acute *P falciparum* malaria infection is the leading cause of death and disability, particularly in tropical Africa. The pathogenesis of this parasitic infection involves the liver stage where infective sporozoites invade and multiply in the hepatocytes and an erythrocytic stage where merozoites cause the destruction of infected red blood cells prior to their differentiation into male and female gametocytes<sup>37,38</sup>. Since

both the liver and erythrocytes are rich sources of AST and ALT, the activities of the invading *P falciparum* parasites in these organs/tissues can lead to damage to the membranes of these organs/tissues and the consequent release of AST and ALT, resulting in the observed increase in the serum activities of these enzymes. The lower AST/ALT ratio observed in *P. vivax* infection is a reflection of the differences in the degree of pathogenesis between *vivax* and *falciparum* malaria infection. It is also suggestive that parasite activities in *P. vivax* infection is associated with a lesser degree of hepatocytes and red cell damage and a confirmation that *falciparum* malaria is the most lethal of all the human malaria parasites. In relation to alcoholic liver disease, the AST/ALT ratio in *falciparum* malaria infection is significantly lower.

This is not an unexpected finding since alcohol consumption has a more damaging effect on centriportal liver cells which are rich in AST. In addition, this high AST/ALT ratio in alcoholic liver disease is a reflection of the low serum activity of ALT in patients with this disease<sup>12</sup>. The comparatively low AST/ALT ratios in the other disease can be explained by the differences in the etiologies of these conditions relative to that of *falciparum* malaria infection. Considering earlier reports which indicates that an AST/ALT ratio > or = 1 is unique and indicative of cirrhosis<sup>25,26</sup>, the finding of an AST/ALT ratio > 1 in acute *P. falciparum* malaria infection is a justification that changes in AST/ALT ratios in disease should be interpreted with caution, particularly in malaria-endemic areas. This is more so since there is no unanimity in the predictive value of AST/ALT ratio in cirrhosis<sup>39,40</sup>. Furthermore, the interpretation of an AST/ALT ratio in a tropical setting where *falciparum* infection is endemic could be indicative of malaria infection not cirrhosis.

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