

# ALTERATION OF LIVER FUNCTION AMONG PATIENTS WITH HEPATITIS AND CIRRHOTIC DISORDERS

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## ABSTRACT:

**Background:** Interpretation of abnormalities in liver function tests is a common problem faced by clinicians, especially in hepatitis and hepatic cirrhosis. Serum ALP, AST, ALT, direct bilirubin, indirect bilirubin, albumin, globulin level, and AST/ALT ratio are significantly altered in liver diseases. This study aimed to investigate the alteration of the liver function tests (LFT) in patients with liver disorders.

**Methods:** This study included 85 patients diagnosed with hepatitis and 78 with cirrhosis of liver. Liver function tests were analyzed by using standard methods. Data analysis was performed using SPSS ver. 11.5 (SPSS Inc., Chicago, IL, USA).

**Results:** Patients with cirrhosis had higher age, serum indirect bilirubin, and globulin than those with hepatitis whereas patients with cirrhosis had lower serum ALP, ALT, direct bilirubin, and albumin. Patients with AST/ALT ratio greater than 1.5 tend to be diagnosed as having cirrhosis, 30.3 times more than hepatitis. Patients with albumin level  $\leq 3.5$  g/dl were 12.0 times more likely to diagnosed as having than hepatitis. Patients with age higher than 45 years old tended to diagnosed as having cirrhosis 7.1 times more than those with hepatitis.

**Conclusions:** The most significant marker for differentiation between hepatitis and cirrhosis condition was AST/ALT ratio which was more than 1.5, serum albumin level  $\leq 3.5$  g/dl and age of patients more than 45 years old, respectively. It will be worthwhile for clinicians to have such data as a guide to appropriate and effective treatment.

**Keywords:** Liver function test, Hepatitis, Cirrhotic disorders

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## INTRODUCTION

Liver disease like hepatitis can be caused by various factors like viral infections, alcohol, and drugs. Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infection can lead to a wide spectrum of liver disease including fulminant hepatic failure which will develop to chronic hepatitis, cirrhosis, and finally hepatocellular carcinoma (HCC) in the end [1]. Alcohol related liver cirrhosis is a major cause in Europe and Latin America. In Asia, more than half of the liver cirrhosis burden is attributable to hepatitis B and hepatitis C. Hepatitis B accounted for 44% and 42% of disability adjusted life years (DALYs) from liver cirrhosis estimated for East

Asia and Central Asia, respectively. In sub-Saharan Africa, 34%, 18% and 17% of liver cirrhosis was attributable to hepatitis B, alcohol intake and hepatitis C, respectively [2]. Up to 85% of HCV infected patients develop a chronic infection, with 10–20% progressing to cirrhosis [3]. About 7% of cirrhosis patients develop HCC [4].

The most common “liver function tests (LFTs)” generally include alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase, serum bilirubin, prothrombin time, serum albumin, and total protein. Each test reflects different functions of the liver like capacity to excrete anions is measured by bilirubin, hepatocellular integrity using transaminases, formation and subsequent free secretion of bile by bilirubin and ALP, and protein synthesis using

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albumin and total proteins [5].

Within a few weeks of appearance of viral markers, ALT and AST levels begin to rise and jaundice may appear [6]. In acute hepatitis, serum ALT levels rise and high levels of HBsAg and HBV DNA are detectable whereas patients with chronic hepatitis may develop markedly elevated serum ALT. ALT and AST are often elevated in these patients but may not correlate well with severity of liver disease. Bilirubin, prothrombin time, and albumin often become abnormal with progressive disease of liver [7]. Alcohol can cause alcoholic hepatitis, which result in a prolonged prothrombin time and elevated liver enzymes, including AST, ALT, ALP and bilirubin in alcoholic patients. An AST-to-ALT ratio greater than 2 is common in patients with alcoholic hepatitis [8]. Drug can also cause acute hepatitis which is often due to the formation of reactive metabolites in the liver such as Anti-Tubercular Drugs, Non Steroidal Anti-Inflammatory Drugs (NSAID's), Anti-Retroviral Drugs, Anti-Hyperlipidemic Drugs, Anaesthetic Agents, Anti-Rheumatic Drugs and so on [9]. This formation of metabolites may lead to toxic hepatitis after huge overdoses (e.g. paracetamol), or to idiosyncratic toxic hepatitis after therapeutic doses [10]. Drug-induced autoimmune hepatitis (DIAIH) has been reported to be caused by several drugs [11].

Hepatitis in long term can lead to liver cirrhosis which is characterized by tissue fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. Chronic HCV infection and long term alcohol consumption represent the most common causes of cirrhosis. Other common causes of cirrhosis include hepatitis B, hepatitis D, primary biliary cirrhosis and autoimmune hepatitis [12]. Interpretation of abnormalities in liver function tests is a common problem faced by clinicians especially hepatitis and cirrhosis disorder. This study aims to determine alteration of the LFT among patients with hepatitis and cirrhosis disorders. In addition, efficiency of each liver enzyme to prognosis of liver disorder was also investigated.

## MATERIALS AND METHODS

The methods were carried out in accordance with the approved guidelines. Data collection protocol of this study was approved by The Phop Phra Hospital and The Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects of Walailak University (EC

number 57/075). Data were collected from the Medical Technology Laboratory Unit, Phop Phra Hospital, Tak province during January 2012 to September 2014. Laboratory records of LFT and demographic data among people suspected with liver diseases as medical doctor recommended were reviewed and this was only a study on the biochemical data so informed consent was not obtained. One hundred and ninety-eight patients with full data recorded were included in this analysis. This included 85 patients diagnosed as hepatitis and 78 cirrhosis cases. The biochemical analysis was carried out by Analyticon Biotechnologies (AG, Germany). The Analyzer provided data on alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), serum bilirubin, serum albumin, serum bilirubin, and total protein. AST/ALT ratio was also calculated for analysis. The Chemistry Analyzer have an internal quality control (IQC) two times daily (first time in the morning before running sample and second time in the afternoon) and also external quality control (EQC) three times per year with Department of Medical Sciences.

Diagnosis of liver diseases was based on medical doctor evaluation. Data analysis was performed using SPSS ver. 11.5 (SPSS Inc., Chicago, IL, USA). Normally distributed continuous data were compared using The Kolmogorov-Smirnov Test, while comparison between 2 groups with continuous data was done using an Unpaired T test, data that was not have normal distribution were compared by a Mann-Whitney U test. Categorical data were compared using Chi-Squared Test.

## RESULTS

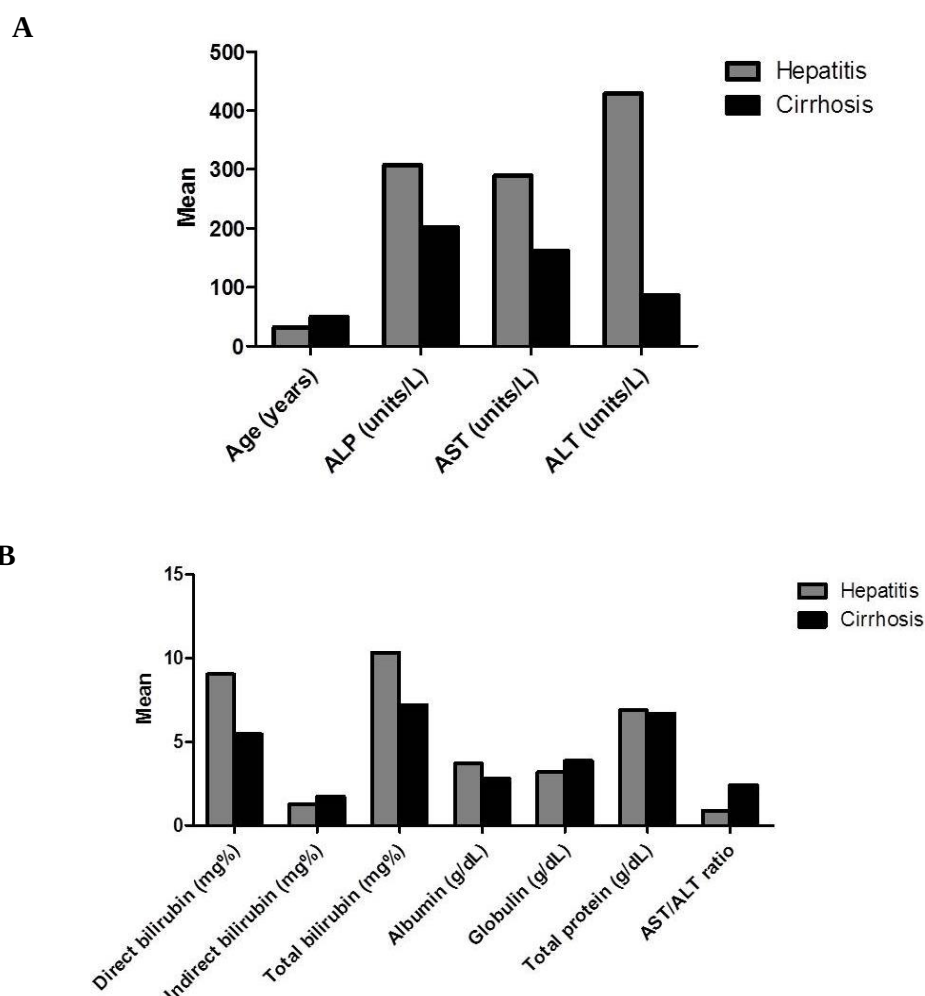
One hundred and sixty-three patients were included in this study. The mean age was 40.25 years (range 10-79) and 56.4% were males. Eighty five ( $n = 85$ ) of the subjects had hepatitis while the remaining were cirrhosis. There were significant differences between age of patients among the two groups ( $P$  value  $< 0.001$ ) but no significant differences between gender (Table 1).

The median values of LFT parameters of hepatitis and cirrhosis group were compared using Mann-Whitney U Test due to non-parametric distribution of data. The average ALT value in patients with cirrhosis was significantly lower than hepatitis (85.9 u/L vs 429.1 u/L;  $P < 0.001$ ) (Figure 1A). Again, the average value of direct bilirubin

**Table 1** General characteristic of patients

| Demographic                   | Hepatitis<br>n=85       | Cirrhosis<br>n=78       | <i>P</i> value |
|-------------------------------|-------------------------|-------------------------|----------------|
| Age, mean±SD                  | 31.86±18.75             | 49.38±11.95             | <0.001*        |
| Gender, male (%) / female (%) | 50 (58.8%) / 35 (41.2%) | 42 (53.8%) / 36 (46.2%) | 0.522**        |

\*Comparison of 2 groups using the independent sample t-test, \*\* Comparison of 2 groups using the Chi-squared test

**Figure 1** Mean of liver function test values in study population

(9.0 mg% vs 5.5 mg%);  $P = 0.03$ ) and albumin (3.7 g/dl vs 2.8 g/dl);  $P < 0.001$ ) were significantly higher in patients with hepatitis than those with cirrhosis ( $P$  value  $< 0.05$ ); whereas the average globulin (3.2 g/dl) were significantly lower than those with cirrhosis group. The average AST/ALT ratio in cirrhosis group was significantly higher than patients with hepatitis (2.4 vs 0.9;  $P$  value  $< 0.001$ ) (Figure 1B). There was no significant association between status of liver diseases and level of ALP, AST, indirect bilirubin, total bilirubin and total protein ( $P$  value  $> 0.05$ ) (Table 2).

To determine predictive values of LFT parameters to diagnose liver diseases, each different

variables and effect on LFT parameter was compared using sensitivity and specificity table. Age of patients had good sensitivity (80%) but lacked specificity (64%) to diagnose liver diseases. In contrast, albumin  $\leq 3.5$  g/dl lacked sensitivity (71%) but had good specificity (83%) for diagnosis of liver diseases. This parameter had better odds ratios. Patients with albumin  $\leq 3.5$  g/dl were up to 12 (OR) times more likely to diagnosed as cirrhosis than those with normal albumin level ( $P$  value  $< 0.001$ , OR = 12, 95%CI = 5.6-25.6) (Table 3). The best predictor of liver disease, was AST/ALT ratio, and had good sensitivity (89%) but lower specificity (78%). Patients with AST/ALT ratio  $> 1.5$  were up

**Table 2** Liver function test values in study population

| Parameters<br>(N=163)    | Hepatitis<br>(mean±SD) | Cirrhosis<br>(mean±SD) | P value |
|--------------------------|------------------------|------------------------|---------|
| ALP (u/l)                | 307.91±304.41          | 200.86±117.08          | 0.084   |
| AST (u/l)                | 289.45±427.50          | 161.60±122.25          | 0.623   |
| ALT (u/l)                | 429.09±565.54          | 85.87±108.21           | <0.001* |
| AST/ ALT ratio           | 0.88±0.84              | 2.43±1.23              | <0.001* |
| Direct bilirubin (mg%)   | 9.03±8.87              | 5.46±6.96              | 0.030*  |
| Indirect bilirubin (mg%) | 1.29±1.62              | 1.73±2.66              | 0.101   |
| Total bilirubin (mg%)    | 10.32±9.43             | 7.19±7.44              | 0.088   |
| Albumin (g/dl)           | 3.71±0.71              | 2.81±0.65              | <0.001* |
| Globulin (g/dl)          | 3.18±0.87              | 3.87±0.85              | <0.001* |
| Total protein (g/dl)     | 6.89±1.06              | 6.68±1.01              | 0.235   |

\*P-value by Mann-Whitney U Test

**Table 3** Sensitivity, specificity, predictive value and odds ratio of the liver function test parameters in diagnosis of liver diseases

| Parameters                        | Sensitivity*<br>(95% CI) | Specificity*<br>(95% CI) | PPV*<br>(95% CI) | NPV*<br>(95% CI) | P value  | OR (95%CI)       |
|-----------------------------------|--------------------------|--------------------------|------------------|------------------|----------|------------------|
| Age (≤45 vs >45 years)            | 80 (70-88)               | 64 (52-75)               | 71 (61-80)       | 75 (63-84)       | <0.001** | 7.1 (3.5-14.5)   |
| Gender                            | 59 (48-69)               | 46 (35-58)               | 54 (44-65)       | 51 (39-63)       | 0.532    | 1.2 (0.7-2.3)    |
| ALP (>250 vs ≤250 u/l)            | 38 (27-49)               | 77 (66-86)               | 66 (49-77)       | 53 (43-63)       | 0.061    | 2.0 (1.0-4.0)    |
| AST (>160 vs ≤160 u/l)            | 39 (28-50)               | 59 (47-70)               | 51 (38-63)       | 47 (37-57)       | 0.873    | 0.9 (0.5-1.7)    |
| ALT (>120 vs ≤120 u/l)            | 58 (46-63)               | 79 (69-88)               | 75 (63-85)       | 63 (53-73)       | <0.001** | 5.3 (2.6-10.6)   |
| AST/ ALT ratio (>1.5 vs ≤1.5)     | 89 (81-95)               | 78 (67-87)               | 82 (72-89)       | 87 (77-94)       | <0.001** | 30.3 (12.6-72.7) |
| Direct bilirubin (>5 vs ≤5 mg%)   | 58(46-68)                | 69 (58-79)               | 67 (55-78)       | 60 (49-70)       | 0.001**  | 3.1 (1.6-5.8)    |
| Indirect bilirubin (>1 vs ≤1 mg%) | 38(27-49)                | 45 (34-57)               | 43 (31-55)       | 40 (29-51)       | 0.029**  | 0.5 (0.3-0.9)    |
| Total bilirubin (>5 vs ≤5 mg%)    | 58 (46-68)               | 60 (49-71)               | 61 (50-72)       | 57 (45-67)       | 0.028**  | 2.1 (1.1-3.9)    |
| Albumin (>3.5 vs ≤3.5 g/dl)       | 71 (60-80)               | 83 (73-91)               | 82 (71-90)       | 72 (62-81)       | <0.001** | 12.0 (5.6-25.6)  |
| Globulin (>3.5 vs ≤3.5 g/dl)      | 72 (61-81)               | 71 (59-80)               | 73 (62-82)       | 70 (58-79)       | <0.001** | 6.1 (3.1-12.0)   |
| Total protein (>7 vs ≤7 g/dl)     | 52 (41-63)               | 60 (49-71)               | 59 (47-70)       | 53 (42-64)       | 0.157    | 1.6 (0.9-3.0)    |

\*PPV, positive predictive value; NPV, negative predictive value; \*Percent; OR, odds ratio.

\*\*P value by Fisher's Exact Test

**Table 4** The association between diagnosis of liver diseases and liver function test is independent of age and gender

| Analysis type | Variables                         | Hepatitis/Cirrhosis |         |
|---------------|-----------------------------------|---------------------|---------|
|               |                                   | B*                  | P value |
| Univariate    | ALP (>250 vs ≤250 u/l)            | -2.056              | 0.031   |
|               | AST (>160 vs ≤160 u/l)            | 2.395               | 0.021   |
|               | ALT (>160 vs ≤160 u/l)            | -1.947              | 0.047   |
|               | AST/ALT ratio (>1.5 vs <1.5)      | -2.309              | 0.015   |
|               | Direct bilirubin (>5 vs ≤5 mg%)   | -25.727             | 0.998   |
|               | Indirect bilirubin (>1 vs ≤1 mg%) | 0.518               | 0.459   |
|               | Total bilirubin (>5 vs ≤5 mg%)    | 22.271              | 0.998   |
|               | Albumin (>3.5 vs ≤3.5 g/dl)       | 3.633               | 0.003   |
|               | Globulin (>3.5 vs ≤3.5 g/dl)      | 1.683               | 0.033   |
|               | Total protein (>7 vs ≤7 g/dl)     | -0.114              | 0.916   |

\*unstandardized variables.

to 30 (OR) times more likely to diagnosed with cirrhosis than those with AST/ALT ratio <1.5 (*P* value < 0.001, OR = 30, 95%CI = 12.6-72.7). Moreover, adjusting for age and gender parameter did not confound the association between LFT parameters and liver diseases. Our results show ALP (>250 vs ≤250 u/l), AST (>160 vs ≤160 u/l), ALT (>160 vs

≤160 u/l), AST/ALT ratio (>1.5 vs <1.5), Albumin (>3.5 vs ≤3.5 g/dl) and Globulin (>3.5 vs ≤3.5 g/dl) were statistical significant (*P* value<0.05) (Table 4).

## DISCUSSION AND CONCLUSION

Liver disease are the most common causes of pathological elevation of ALP levels, although ALP

may originate from other tissue, such as the placenta, kidneys or intestines, or from leukocytes [13]. This study showed rising level of ALP in patients with hepatitis but was not significantly higher than those with cirrhosis. Hepatic ALP is present on the surface of bile duct epithelia. In some condition or diseases such as cholestasis or accumulating bile salts, it enhances the synthesis and release of ALP from the cell surface [14]. An increase in serum ALP levels is frequently associated with a variety of diseases including malignant biliary obstruction, primary biliary cirrhosis, primary sclerosing cholangitis, hepatic lymphoma and sarcoidosis [15]. Almost any disorder affecting the liver may cause moderate increase in serum ALP. This rising ALP is attributed to increased liver enzyme in serum [16] and the results were contrast with another study that had demonstrate decrease serum ALP in chronic liver disorders [17]. However, the degree and rate of ALP alteration may provide minor and nonspecific clues to diagnosis of liver diseases, but the presence of symptoms and the patient's history as well as liver ultrasound may reveal the presence of bile duct dilation, demonstrate signs of liver cirrhosis [18].

The previous study explained that injury to the liver, whether acute or chronic, eventually results in an increase in serum concentrations of both AST and ALT [18]. Our study showed higher level of serum AST and ALT in patients with hepatitis than those with cirrhosis. Both aminotransferases are highly concentrated in the liver. AST is located and found in the heart, skeletal muscle, kidneys, brain and red blood cells, and ALT has low concentrations in skeletal muscle and kidney [19]. In the liver, ALT is localized solely in the cellular cytoplasm, whereas AST is both in cytosolic (20% of total activity) and mitochondrial (80% of total activity) [20]. Our study, the serum AST and ALT level was more than 40 units per liter in almost all cases of liver disease. The elevation of AST in patients with hepatitis might be due to the reduction in the clearance of AST and mitochondrial injury [21]. Patients with acute hepatitis reach the highest aminotransferase levels whereas patients with chronic hepatitis and cirrhotic patients may have aminotransferase levels within the reference range which correlate with result of a previous study [18].

In patients with acute and chronic liver diseases of various origin, the AST/ALT ratio provides useful clinical information, and this is readily

available, easy to interpret, and inexpensive [22]. The present study revealed that AST/ALT ratio provided useful information in diagnosis of hepatitis/cirrhosis disorder. AST/ALT ratio was frequently less than 1.5 in patient with hepatitis and frequently more than 1.5 in patients with cirrhosis as compared to ratio more than 1.0 in 58% cases of a previous study [17]. Our study found AST/ALT ratio of less than 1.5 in 89.4% cases of hepatitis patients and AST/ALT ratio of more than 1.5 in 78.2% cases of cirrhotic patients. A previous study found AST/ALT ratio of more than 1 in 70% cases of cirrhosis [23]. The AST/ALT ratio has also been shown to correlate with histologic stage and liver diseases including chronic HBV and chronic HBC infection [24, 25]. In addition, our study showed that AST/ALT ratio has a best prognosis indicator to differentiate between patients with hepatitis and cirrhosis.

Direct bilirubin was significantly lower in cirrhotic patients than hepatitis patients. In healthy people, direct bilirubin is virtually absent from serum mainly because of the rapid process of bile secretion. The increased of direct bilirubin and concomitant, markedly elevated aminotransferase levels may suggest acute viral hepatitis or toxic or ischemic liver injury whereas in cirrhosis, direct bilirubin was high but aminotransferases may normal or only slightly elevated [18]. Indirect bilirubin was obtained from subtract direct bilirubin from total bilirubin. Our study, indirect bilirubin was higher in cirrhotic patients. This may be due to augmented bilirubin production or decreased hepatic uptake or conjugation or both [18].

Our study showed that albumin level in cirrhotic patients has statistically significantly lower than those of hepatitis patients. This may due to serum albumin is useful test for monitoring liver synthetic activity which tends to decrease in end-stage liver disease [26], albumin level decrease may be suspected when cirrhosis occurs. On the contrary, patients with acute, massive hepatocellular necrosis (acute toxic or viral hepatitis) may have normal albuminemia [18].

Our data, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy for all LFT parameters were determined. Among those parameters, AST/ALT ratio (ratio>1.5) had the best sensitivity, positive predictive value and negative predictive value (89% sensitivity, 82% positive predictive value, and 87% negative predictive value while the specificity was

quite good at 78%. The two most reliable LFT parameters for predicting cirrhosis among liver disorders were AST/ALT ratio and serum albumin level. Patients with AST/ALT ratio more than 1.5 were 30.3 times more likely to diagnosis as cirrhosis than those with ratio less than 1.5. AST/ALT ratio more than 1.5 and serum albumin level less than 3.5 g/dl had 71% and 83% of sensitivity and specificity respectively to predict cirrhotic condition. Patients with albumin level less than 3.5 g/dl were 12.0 times more likely to diagnose as cirrhosis than those with normal albumin level. However, our data show age of patient (>45 years) had good sensitivity (80%) but lacked specificity (64%) to screening of cirrhosis compared to AST/ALT ratio.

To conclude, alterations of LFT in liver disorders were observed. Patients with cirrhosis tend to have higher age, high serum indirect bilirubin, globulin, AST/ALT ratio than those with hepatitis. Patients with cirrhosis tend to have lower serum ALP, ALT, direct bilirubin, and albumin. Moreover, the most significant marker to differentiate between hepatitis and cirrhosis were AST/ALT ratio and serum albumin levels. Limitations of this study include low sample size, which could potentially affect the interpretation of the results. It will be worthwhile to have such study in large group of patients where such correlation could be established.

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## CONFLICT OF INTERESTS

The authors have declared that no competing interest exists.

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