The Significance of Transaminases and Deritis Ratio for Predicting Alcoholic Liver Disease: A Hospital Based Comparative Study in Western Nepal

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Abstract

Background
In Nepal, alcoholic liver disease (ALD) is a major public health problem. In testing for biochemical abnormalities in ALD, Deritis ratio (AST/ALT) is more sensitive than other conventional parameters, at any stage of the disease. The aim of our study was to assess closely the significance of transaminases and deritis ratio and their predictive implications among the patients of alcoholic liver disease in Pokhara valley.

Materials and Methods
It was a hospital based retrospective study carried out from the data maintained in the Department of Biochemistry of the Manipal Teaching Hospital, Pokhara, Nepal between 1st January 2009 and 31st July 2010. The variables collected were age, gender, total protein, albumin, AST, ALT and AST/ALT ratio. Descriptive statistics and testing of hypothesis were used for the analysis. Data was analyzed using EPI INFO and SPSS 16 software.

Results
Of the four hundred forty-five patients, there was a slight preponderance of males (55.5%) towards ALD as compared to females (44.5%), projecting the percentage of ALD to around 28.8. Males were 2.3 times more at risk of developing alcoholic liver disease than females (Odds Ratio=2.3, p=0.0001). Patients over 40 years of age had 3.2 times greater propensity of developing alcoholic liver disease (Odds Ratio=3.2, p=0.0001). In ALD patients, mean value of AST (131.5 ± SD94.46 IU/L) was markedly increased in comparison to ALT (85.12 ± SD58.24 IU/L) leading to significantly higher AST/ALT ratio (1.59 ± SD0.58). In cases, mean value of Deritis ratio was 1.59 with CI (1.49, 1.69) which was significantly increased as compared to the ratio in controls which was 1.04 with CI (1.02, 1.06) (p=0.001). 96.9% of patients with alcoholic liver disease had an AST/ALT ratio of >1.0 with CI (93.9%,99.9%). The mean value of each variable in cases was significantly elevated as compared to controls (p=0.001).

Conclusion
Ethanol consumption leads to a spectrum of liver diseases, the importance of which is magnified by its widespread use. Laboratory tests play an important role in this endeavor. Equally important is the fact that once complications of alcoholism are identified, it is imperative to be able to accurately determine their magnitude. Therefore, the estimation of deritis ratio is useful for the rational understanding of the extent of damage in alcoholic liver disease.

Key Words
Transaminase, Deritis ratio, Alcohol Liver Disease, Nepal
Background
The major risk factors for developing alcoholic liver disease are the quantity and duration of alcohol consumed by an individual and the other possible factors are the type of alcohol, drinking patterns, gender, ethnicity and genetic factors. Alcohol is a major cause of liver cirrhosis in western world and USA. The function of liver is not compromised even when 75% of the liver is damaged as it has the capacity to rejuvenate. The spectrum of alcohol-related liver injury varies from alcoholic fatty liver (steatosis) to alcoholic cirrhosis. Most alcoholics with liver disease imbibe at least 80gm of alcohol daily for years. Fatty liver develops in about 90% of individuals who drink more than 60g/day of alcohol. Although this condition is reversible with abstinence after about 4–6 weeks. At least 80% of heavy drinkers develop steatosis, 10%–35% develop alcoholic hepatitis and approximately 10% will develop cirrhosis. A daily alcohol intake of 60g/day in men and 20g/day in women is associated with an increased relative risk of developing cirrhosis and it is most severe form of alcoholic liver injury.

A prospective study conducted by Shrestha NM in 1992 comprising of 6534 Italian subjects showed that the risk threshold for developing ALD was 30g ethanol/day and the risk increase was dose dependent. Women are more likely to develop alcoholic cirrhosis for any given level of alcohol and are twice as sensitive to alcohol mediated hepatotoxicity due to lower activity of the alcohol metabolising enzyme (alcohol dehydrogenase) than men. The most common cause of chronic liver disease (cirrhosis) is alcohol in Nepal. Cirrhosis is a permanent irreversible form of liver damage. The fibrosis or scarring of the liver seen in cirrhosis leads to obstruction of the hepatic blood flow. In Nepal, easy availability, cultural acceptability and high social tolerance accentuates the danger of alcohol abuse. Production, sale, and consumption of alcohol is ever increasing. Production, sale, and consumption of alcohol is ever increasing. Drinking patterns, gender, ethnicity and genetic factors are the type of alcohol, drinking patterns, gender, ethnicity and genetic factors. Alcohol in Nepal is alcohol in Nepal. Alcohol was found to be the most widely abused substance (94.15%) among the medical students of Kathmandu in year 2010. Alcohol-induced liver diseases are serious conditions because the one year survival is 60%–70% and the five year survival is 35%–50%. The most sensitive tests for detecting liver cell injury due to alcohol are the aminotransferases and deritis ratio (AST/ALT) at any stage of alcoholic liver disease.

These intracellular enzymes are released into the circulation during hepatocyte damage or injury. The objective of our study is concerned primarily to evaluate the significance of transaminases and deritis ratio and their predictive implications among the patients of alcoholic liver disease in Pokhara valley.

Materials and Methods
It was a hospital based retrospective study carried out using the data maintained in the Department of Biochemistry of the Manipal Teaching Hospital, Pokhara, Nepal between 1st January 2009 and 31st July 2010. The variables collected were age, gender, total protein, albumin, AST, ALT and AST/ALT ratio. Approval for the study was obtained from the institutional research ethical committee. Total proteins were determined by Biuret method. The albumin was measured by BCG method. The total and direct bilirubin was estimated by Jendrassik/Grof method. The transaminases (AST and ALT) were estimated by liqiu uv test. All these laboratory parameters were analysed using Human reagent kits and with the help of semi autoanalyser (Human, Germany).

Analysis was done using descriptive statistics and testing of hypothesis. The data was analyzed using Excel 2003, R 2.8.0 Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and the EPI Info 3.5.1 Windows Version. The Chi-square test was used to examine the association between different variables. Z-test was used to compare the significance difference between two variables. A p-value of < 0.05 (two-tailed) was used to establish statistical significance.

Inclusion criteria: Patients with brief history of alcoholism with chief complaints related to hepatomegaly, jaundice or ascites.

Exclusion criteria: Patients with history of antibiotic intake for the past three months, malnutrition, who have undergone major surgeries related to gall stones, liver biopsies, those diagnosed with diabetes, sepsis, renal disorders, essential hypertension, on multivitamins and lipid lowering drugs were excluded from the study.

Controls: Healthy males and females with normal liver profile.

Results
Of the four hundred forty-five patients, there was a slight preponderance of males (55.5%) towards ALD as compared to females (44.5%), projecting the percentage of ALD to around 28.8.

Table 1: Relationship between alcoholic liver disease and variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Alcoholic Liver Disease</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>89</td>
<td>158</td>
</tr>
<tr>
<td>Female</td>
<td>39</td>
<td>159</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-40</td>
<td>29</td>
<td>152</td>
</tr>
<tr>
<td>41-100</td>
<td>99</td>
<td>165</td>
</tr>
</tbody>
</table>

** Statistically significant (p value<0.05)

Table 1 shows males were 2.3 times more commonly affected than women (Odds Ratio=2.3, p=0.0001) with increased frequency among people ages >40years (3.2 times) (Odds Ratio=3.2, p=0.0001) in alcoholic liver disease patients.
Table 2: Comparison of biochemical parameters in cases (alcoholic liver disease) and controls (N)

<table>
<thead>
<tr>
<th>Variables</th>
<th>ALD (128)</th>
<th>Controls (317)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.58 ± 14.93</td>
<td>42.65 ± 20.80</td>
<td>0.001*</td>
</tr>
<tr>
<td>Total proteins</td>
<td>6.72 ± 0.85</td>
<td>6.96 ± 0.69</td>
<td>0.002*</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.56 ± 0.53</td>
<td>3.81 ± 0.44</td>
<td>0.001*</td>
</tr>
<tr>
<td>AST</td>
<td>131.5 ± 94.46</td>
<td>27.07 ± 12.21</td>
<td>0.001*</td>
</tr>
<tr>
<td>ALT</td>
<td>85.12 ± 58.24</td>
<td>26.6 ± 10.67</td>
<td>0.001*</td>
</tr>
<tr>
<td>Ratio AST/ALT</td>
<td>1.59 ± 0.58</td>
<td>1.04 ± 0.20</td>
<td>0.001*</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>2.69 ± 1.46</td>
<td>0.85 ± 0.14</td>
<td>0.001*</td>
</tr>
<tr>
<td>Ratio Total bilirubin</td>
<td>1.44 ± 0.97</td>
<td>0.23 ± 0.08</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

* p<0.05 statistically significant

Table 2 depicts that mean value of each variable in cases was significantly elevated as compared to controls (p=0.001). The lowering of serum total proteins and albumin in patients of ALD indicates impaired liver function (p=0.002). The ALT level is a more specific indicator of hepatic injury than AST. However, in alcoholic patients, ALT level is usually elevated to a lesser degree than AST level. In cases, mean value of AST (131.5 ± SD94.46 IU/L) was markedly increased in comparison to ALT (85.12 ± SD58.24 IU/L) leading to significantly higher AST/ALT ratio (1.59 ± SD0.58). Mean value of Deritis ratio in cases was 1.59 with CI (1.49, 1.69) which was significantly higher as compared to controls 1.04 with CI (1.02, 1.06) (p=0.001). 96.9% of patients with alcoholic liver disease had an AST:ALT ratio of > 1.0 with CI (93.9%,99.9%). In healthy adults, virtually all of the measured serum bilirubin is unconjugated. In contrast, in patients with alcoholic liver disease, serum bilirubin levels are frequently elevated, with widely variable degrees of conjugation. The mean values of total and direct bilirubin were raised in cases and showed statistical significance as compared to controls.

Table 3 displays that there was quantitatively small gender differences in the relationship between each variable but they were not statistically significant.

**Discussion**

Alcoholic liver disease (ALD) encompasses a spectrum of injury, ranging from simple steatosis to chronic hepatitis with fibrosis or cirrhosis. The changes in histological pattern include steatosis (fatty change), lobular inflammation, periportal fibrosis, Mallory bodies, nuclear vacuolation, bile ductal proliferation, perivenular and perisinusoidal fibrosis. The present study revealed that males were 2.3 times more commonly affected than women with alcoholic liver disease with increased frequency among people aged greater than 40 years. These rates reflect the fact that men typically drink more than women do. The mortality due to alcoholic cirrhosis reached a peak among patients aged 45–54 years in a study done by Mann RE et al. Early laboratory diagnosis (Deritis ratio) of alcohol abuse has been emphasized in current study, as intervention might be more effective and less costly. An increase in serum concentrations of aminotransferases are potential sensitive indicators of liver cell injury and are helpful in recognising hepatocellular disease such as hepatitis, alcoholic liver disease (ALD) and cirrhosis. The major causes of elevation of liver transaminases include viral hepatitis, alcohol abuse and cirrhosis. No single laboratory parameter is 100% specific or sensitive for ALD. Biochemical tests reveal modest rise of serum transaminases in alcoholic patients. The elevation of aspartate amino transferase has specificity of 82% and for alanine amino transferase 86% for alcohol use >50 g/day among all forms of hepatic injury. In our study, mean levels of AST and ALT were 131.5 ± SD 94.46 IU/L and 85.12 ± SD 58.24 IU/L indicating a greater rise of AST as compared to ALT. The calculated AST/ALT ratio was 1.59 ± SD 0.58 which supports the diagnosis of a case of alcoholic liver disease. A study done by Majhi et al showed mean levels of AST and ALT to be 124.80 ± SD 86.24 IU/L and 54.21 ± SD 39.72 IU/L respectively, in patients of alcoholic liver disease in Nepal. In a landmark study by Cohen and Kaplan, AST/ALT ratio was >1 in 92% and >2 in 70% of ALD patients. The increased ratio reflects the low serum activity of alanine aminotransferase in patients with alcoholic liver disease. This decrease was due to an alcohol-related deficiency of pyridoxal 5-phosphate. It could also be due to the damage of mitochondria, cell necrosis, and increase in cell membrane permeability leading to an increase in serum aspartate transaminase (AST) especially in patients with high alcohol intake. The current study revealed that serum total protein and albumin was moderately reduced in patients with alcoholic liver disease. The increased AST/ALT ratio and reversal of albumin/globulin ratio facilitates the diagnosis of alcoholic liver disease. The levels of total and direct bilirubin were moderately increased in ALD patients indicating liver cell injury. Findings of a 1992 study by Magarian et al showed frequent elevation in serum bilirubin levels with widely variable degrees of conjugation in patients with alcoholic liver disease.
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21. The present study revealed that there were quantitatively small gender differences in the relationship between each variable, but they were not statistically significant, which concurred with the findings of Scott et al.22. A reasonable degree of diagnostic and prognostic accuracy can be achieved from a combination of readily available biochemical tests and liver biopsy. 90% of patients with histologically confirmed liver disorders and deritis ratio of at least 2:1 had alcoholic liver disease23. Carbohydrate deficient transferrin has a higher sensitivity (93.4%) and specificity (71.9%) than any of the conventional liver tests (AST:ALT ratio, γGT)24. The major drawback is that it is not widely available for clinical use. A deritis ratio of ≥ 2 is highly suggestive of alcoholic hepatitis and cirrhosis25. Deritis ratio appears to be a useful index and has potential value for distinguishing nonalcoholic from alcoholic liver disease26. Therefore, in routine practice, the magnitude and rate of change of aminotransferase alteration provides initial insight into a differential diagnosis.

Conclusion
Alcohol consumption leads to a spectrum of liver diseases, the importance of which is magnified by its widespread use. Among therapeutic interventions, abstinence is the cornerstone of management for patients of alcoholic liver disease. The reversibility of alcoholic damage at an early stage implies that the treatment of alcohol liver disease appears to be able to accurately determine their magnitude. Therefore, the estimation of deritis ratio is useful for rational understanding of the extent of damage in alcoholic liver disease.

What this study adds
Timely detection of alcohol liver disease patients with cost effective laboratory assay exploits the significance of Deritis ratio.

Conflict of Interests
The authors do not have any conflict of interest arising from the study.

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