Research Article

Evaluation of De Ritis ratio in liver-associated diseases

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Abstract

Background: Liver diseases are one of the common disorders encountered in clinical practice. Investigations in liver-associated diseases are used to detect type of hepatic abnormality, to measure its severity, to define its structural effect on the liver, to find out etiology of disorder, to assess prognosis, and to evaluate therapy. One should aim at a diagnosis with simple and possibly noninvasive means, avoiding extensive examinations. De Ritis ratio (the ratio of serum aspartate aminotransferase to serum alanine aminotransferase) has been proposed a valuable diagnostic marker to screen liver disorder.

Objective: To assess the significance of De Ritis ratio as a diagnostic marker in population of hepatic disorder.

Materials and Method: This is a retrospective study performed on records of 102 patients with liver diseases who were treated at the out-patient clinic or admitted to Nobel Medical College, Biratnagar, Nepal, between June 15, 2015 and July 15, 2015. De Ritis ratio of all the patients were calculated from documented biochemical tests of AST and ALT. De Ritis ratio and demographic profile of all the patients were analyzed by independent *t* -test and one-way ANOVA using software SPSS 20 version.

Results: De Ritis ratio was significantly decreased ($p < 0.05$) in viral hepatitis (0.8006 ± 0.14811) than the control group (1.0934 ± 0.13508) and markedly increased ($p = 0.000$) in alcoholic liver disorder. Similarly, It is significantly increased ($p < 0.05$) in nonalcoholic fatty liver disorder (1.2204 ± 0.17954), whereas insignificantly increased ($p = 0.408$) in cholestasis (1.1378 ± 0.18045).

Conclusion: De Ritis ratio can be used as a prognostic marker of liver disorder and can be considered as a noninvasive, cost–effective means of screening liver diseases.

KEY WORDS: De Ritis ratio, alcoholic liver disorder, viral hepatitis, nonalcoholic, fatty liver disorder, cholestasis

Introduction

The liver is the largest organ in the body weighing about 1,400–1,600 g in males and 1,200–1,400 g in females performing multifold functions such as metabolism of carbohydrates, proteins and lipids; synthesis and excretion of bile; synthesis of several plasma proteins such as albumin, fibrinogen, and prothrombin; storage of vitamins (A, D, and B_{12}) and iron; and detoxification of xenobiotic. Hepatic injury is therefore associated with distortion of all these functions.[1,2]

Liver diseases are classified into two categories—hepatocellular and cholestatic. In hepatocellular diseases, features of liver injury, inflammation, and necrosis predominate while in cholestatic diseases, features of inhibition of bile flow predominate.[2] Evaluation of patients with liver disease should be directed at establishing the etiologic diagnosis, estimating the disease severity (grading) and establishing the disease stage. Several biochemical tests are useful in the evaluation

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and management of patients with hepatic diseases. In view of multiplicity and complexity of the liver functions, a battery of liver function tests (LFTs) are employed for accurate diagnosis, which include the aminotransferases, alkaline phosphatase, bilirubin, albumin, and prothrombin time.[2]

Assessment of liver cell injury is done by the estimation of serum aspartate transaminase or AST (formerly glutamic oxaloacetic transaminase or SGOT) and serum alanine transaminase or ALT (formerly glutamic pyruvic transaminase or SGPT). AST is found in the liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lungs, leukocytes, and erythrocytes while ALT is found primarily in the liver. These enzymes are normally released into plasma at a constant rate due to programmed cell death of hepatocytes but its permeability is increased when there is damage to liver cell membrane.[2] Thus, ALT is more specific to hepatic necrosis in comparison to AST. ALT is present only in liver cytoplasm while AST is found in both hepatocyte cytoplasm (cAST) and mitochondria (mAST) with approximately 80% of total AST activity in human liver contributed by mAST.[3]

The hepatic proportion of AST/ALT is 2.5:1. But half-life ($t_{1/2}$) of AST and ALT is 18 and 36 h, respectively; thus, AST is removed from blood twice as faster compared to ALT resulting nearly equal levels of AST and ALT in serum in healthy person. Furthermore, in healthy person, circulating AST in blood consists mainly of cAST.[3] Any type of liver cell injury causes increased permeability of AST and ALT and can cause modest increase in the level of these enzymes. Levels upto 300 U/L are nonspecific, whereas levels >1000 U/L occur in disorders associated with extensive hepatocellular injury such as viral hepatitis, ischemic liver injury, and toxin- or drug-induced liver injury.[2] These conditions are characterized by extensive loss of hepatic parenchyma.[4] In alcoholic liver disorder (ALD), the level of AST is rarely >300 U/L and ALT is slightly increased or normal. These enzymes are not greatly elevated in cholestatic diseases except during the acute phase of biliary obstruction.[2]

The ratio of serum activities of AST and ALT was described by Fernando De Ritis in 1957 and since then it is known as De Ritis ratio. De Ritis described AST/ALT as useful indicator of hepatitis and his work was confirmed and further investigated by Wroblewski.[3] This ratio was originally used to distinguish aminotransferase elevations of the inflammation type (De Ritis ratio <0.7) from the necrosis type (De Ritis ratio >0.7).[5] Although there is considerable overlapping of values within a given diagnosis, several studies have shown that this ratio is useful in differential diagnosis and classification of hepatic disorders. The ratio is particularly useful to differentiate intrahepatic >1.5 and extrahepatic <1.4 lesions. This ratio is most useful when standard AST and ALT assays are used as recommended by the International Federation of Clinical Chemistry (IFCC), which is 1.15 normally.[6] For normal individual, De Ritis ratio vary from 0.7 to 1.4. In most of the acute hepatocellular diseases such as acute viral hepatitis and infectious mononucleosis, the De Ritis ratio is ≤1.[7] Chronic disorders such as alcoholic liver disease, postnecrotic cirrhosis, and chronic active hepatitis have De Ritis ratio greater than 1.[6] De Ritis ratio >2 is suggestive while >3 is highly suggestive of ALD.[2] A ratio >4 may suggest Wilson disease.[7]

There are many modalities available for imaging the liver, for example, USG, CT, and MRI. Liver biopsy is the most accurate means of assessing severity and stage of liver damage.[2] For accurate diagnosis of liver disorder, these techniques are more sensitive and specific.[1] But these are expensive and also liver biopsy is an invasive procedure with various complications.[8] De Ritis ratio is a noninvasive, cost–effective test to diagnose and differentiate liver disorder without causing any complications to the patient. But there are contradictory reports on the usefulness of De Ritis ratio in differentiating various types of liver diseases.

The aim of this study is to estimate De Ritis ratio in patients with viral hepatitis, ALD, nonalcoholic fatty liver disorder (NAFLD), and cholestasis.

Materials and Methods

This is a retrospective study. This study was performed on records of 102 patients with liver diseases who were treated at the out-patient clinic or admitted to Nobel Medical College, Biratnagar, Nepal, between June 15, 2015 and July 15, 2015. Data were collected from patient medical records and the computerized departmental database. Out of 102 patients, 20 were diagnosed with viral hepatitis, 20 with ALD, 20 with NAFLD, and 10 with cholestasis. Thirty-two patients were considered as control whose lab tests and imaging modalities were normal. Subjects with HIV, muscle disorder, renal disorder, drug abuse, or drug affecting the liver disease were excluded from the study. Demographic profile of all the patients were also recorded and analyzed.

Statistical Analysis

De Ritis ratio of all the patients was calculated. Values and means of AST, ALT, and De Ritis ratio for control, ALD, viral hepatitis, NAFLD, and cholestasis were calculated separately and analyzed using SPSS for windows version 20. Comparison of means of variables among different groups was performed with ANOVA. Comparison of means of De Ritis ratio between control and individual cases was performed with independent *t* test. The *p* value <0.05 was considered statistically significant.

Results

Out of 102 subjects, 39 were male and 63 were female of the age group 3–85 years. In control group 23 were females with mean age 33 and 9 were males with mean age 62. In ALD group, 12 were females with mean age 37 and 8 were males with mean age 43. In viral hepatitis group, 12 were females with mean age 26 and 8 were males with mean age 43. In NAFLD group, 10 were females with mean age 37 and 10

Table 1: Male and female patients

		Disorder				
		Control	ALD	Viral hepatitis	NAFLD	Cholestasis
		Count	Count	Count	Count	Count
Sex	Female	23	12	12	10	6
	Male	9	8	8	10	4

Table 2: Age and sex distribution in case and control

		Disorder														
		Control			ALD			Viral hepatitis			NAFLD			Cholestasis		
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
Age	F	33	14	70	37	19	72	26	4	48	37	10	70	28	18	44
Sex	M	62	39	84	43	19	56	43	15	78	52	3	85	29	10	60

Table 3: Mean serum levels of AST, ALT, De Ritis ratio in cases and control

Disorder	AST (Mean ± Std. Dev.)	ALT (Mean ± Std. Dev.)	De Ritis ratio (Mean ± Std. Dev.)
Control	28.9688 ± 7.12327	27.3125 ± 9.09249	1.0934 ± .13508
ALD	158.3000 ± 71.28084	78.8500 ± 39.71381	2.1253 ± .84766
Viral hepatitis	74.6500 ± 49.14883	94.4000 ± 59.87214	.8006 ± .14811
NAFLD	105.0500 ± 174.87243	96.1500 ± 174.55998	1.2204 ± .17954
Cholestasis	34.4000 ± 12.13992	31.2000 ± 13.02817	1.1378 ± .18045
P value	0.000	0.011	0.000

were males with mean age 52. In cholestatic group, 6 were females with mean age 28 and 4 were males with mean age 29 (Figure 1, Tables 1 and 2).

Mean aspartate transaminase levels were markedly increased in ALD (158.3000 ± 71.28084), viral hepatitis (74.6500 ± 49.14883), NAFLD (105.0500 ± 174.87243), and only mildly increased in cholestasis patients (34.4000 ± 12.13992) as compared to control (28.9688 ± 7.12327) (Figure 3).

Mean alanine aminotransferase levels were also markedly elevated in ALD (78.8500 ± 39.71381), viral hepatitis (94.4000 ± 59.87214), NALD (96.1500 ± 174.55998), and only slightly elevated in cholestasis patients (31.2000 ± 13.02817) as compared to control (27.3125 ± 9.09249) [Figure 4].

Mean De Ritis ratio is markedly raised in ALD but decreased in viral hepatitis while slightly increased in patients with NAFLD and cholestasis. The level was found to be 2.1253 ± 0.84766, 0.8006 ± 0.14811, 1.2204 ± 0.17954, and 1.1378 ± 0.18045 as compared to control 1.0934 ± 0.13508 [Figure 5].

The means of AST, ALT, and De Ritis ratio of control and cases were compared simultaneously with one-way ANOVA and the difference was found significant ($p = 0.000$, 0.011, and 0.000 for AST, ALT, and DE Ritis ratio, respectively) [Table 3].

Mean of De Ritis ratio was compared between control and each case separately by independent *t* test. The mean of De Ritis ratio of control and ALD, viral hepatitis and NAFLD was found to be significantly different ($p = 0.000$, 0.000, and 0.005, respectively) while the comparison of mean of De Ritis ratio of control and cholestasis was not significantly different ($p = 0.408$).

Discussion

Aminotransferases are sensitive indicators of hepatocyte injury. The pattern of the aminotransferase elevation, that is, De Ritis ratio can be helpful diagnostically.[3] Viral hepatitis is a leading cause of virus-associated morbidity and mortality, affecting millions of people worldwide. In acute viral hepatitis, ALT is greater than AST. The peak level of aminotransferases has been found to be 400–4,000 U/L or more. De Ritis was the first to describe that ALT is usually higher than AST with the AST/ALT ratio usually well below 1.0 and typically in the range of 0.5–0.7.[3] Reason behind this has been postulated that AST includes mAST isozymes and more time is needed for these isozymes to pass through a second set of membranes to reach plasma in comparison to ALT, which is found in cytoplasm only.[6] When the inflammatory process of acute viral hepatitis especially B and C merges into chronic hepatitis, aminotransferase level falls below 100 U/L and De Ritis ratio changes to ≥1.[4] Diagnosis of viral hepatitis is based on serological tests and polymerase chain reaction, which is expensive and also not available in rural areas of Nepal. Thus, multifold elevation of transaminases and a low De Ritis ratio provides an important clue to the etiology of acute hepatitis. The De Ritis ratio for patients of viral hepatitis in our study was 0.8006 ± 0.14811, which is consistent with the results of De Ritis et al. (1965) and Hasan et al. (2013).[9,10]

High alcohol consumption is one of the most common causes of liver disorder. The prevalence of alcohol consumption among Nepalese adults was 67% in 2006.[11] In alcoholic

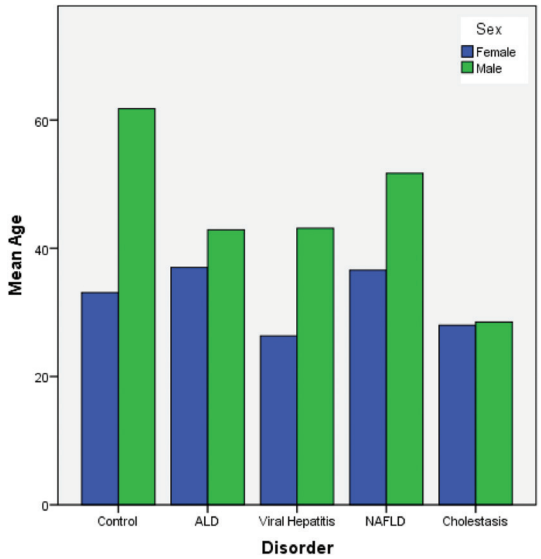

Figure 1: Correlation of age and sex with case and control.

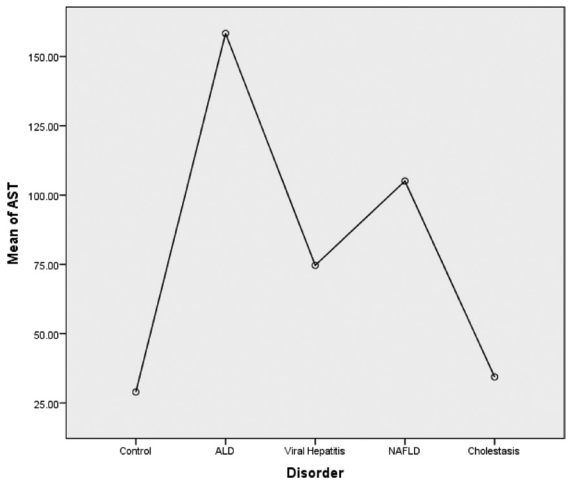

Figure 2: Mean AST level in case and control.

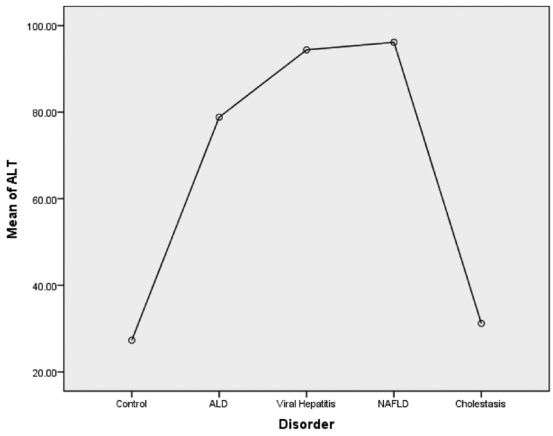

Figure 3: Mean ALT level in case and control.

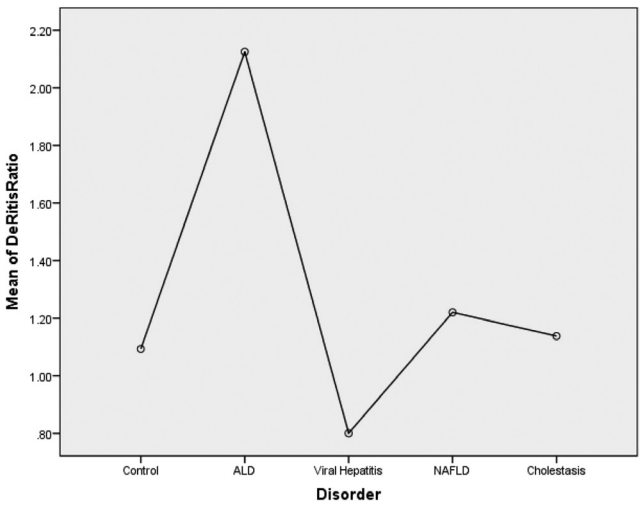

Figure 4: Mean of De Ritis in case and control.

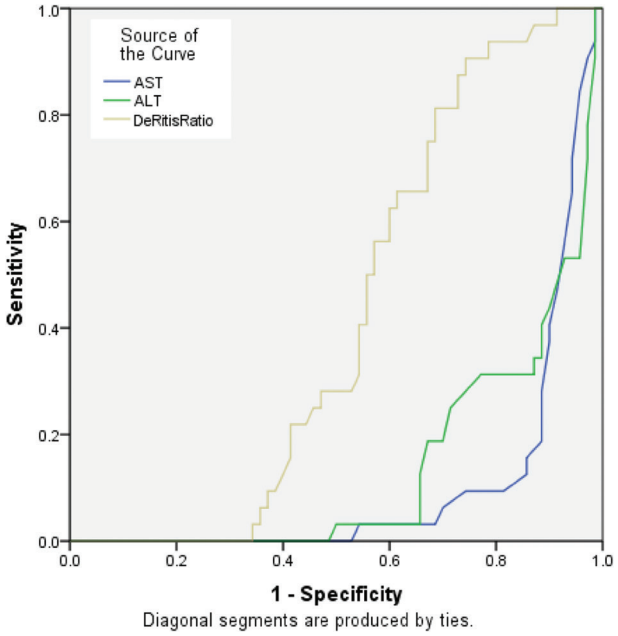

Figure 5: ROC curve.

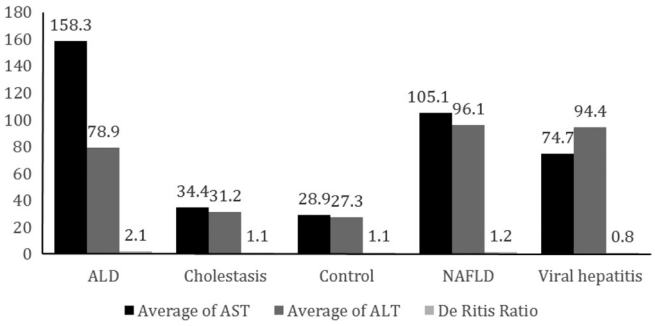

Figure 6: Average AST, ALT, and De Ritis ratio in cases and control.

hepatitis, AST levels are typically higher than ALT with De Ritis ratio greater than 2.[12] The predominance of AST over ALT in alcohol-related disorder was first reported by Harinasuta in 1967.[3] The aminotransferase levels are only moderately elevated in ALD, and ALT levels may even be normal.[4] Reasons for this are multifold. Chronic alcoholics are often deficient in pyridoxal 5'-phosphate (vitamin B_6), which is a necessary coenzyme for both ALT and ALT synthesis. Deficiency of Vitamin B_6 decreases ALT synthesis to a greater extent than AST synthesis.[13] In addition, alcohol itself induces the synthesis and release of mAST, thereby increasing the De Ritis ratio.[4] Next, mAST is found in perivenular area in the liver around the central vein. In ALD, since more perivenular hepatocytes are damaged, mAST is elevated and hence De Ritis ratio gets elevated. This is supported by the finding that normally most of AST activity in serum is the cytosolic isoenzyme; however, in alcoholism, mAST is preferentially released. Cohen and Kaplan evaluated the usefulness of the De Ritis ratio and suggested its diagnostic value as a predictor of ALD. Our study also shows De Ritis ratio to be 2.1253 ± 0.84766 (p = 0.000), which is in accordance with the study of Nyblom et al. (2004) and Hasan and coworkers (2013).[10,14]. Study by Gurung et al. in 2013 further extended the correlation of De Ritis and ALD and suggested that De Ritis is indicative of severity of liver damage due to alcohol.[15]

NAFLD is one of the most frequent complications of obesity. The prevalence of NAFLD is over 20% in developed countries and nearly 10% in developing countries. Pathogenesis of NAFLD is related to obesity, caused by increased lipogenesis in liver. Most of these patients have type 2 diabetes or hyperlipidemia. Other causes of NAFLD are viral hepatitis, medications, toxins, surgical procedures, protein-energy malnutrition, and inborn errors of metabolism.[3] NAFLD causes elevation of serum aminotransferases and liver disease, which could end up in fibrosis, cirrhosis, and eventually hepatic carcinoma. Both AST and ALT increase with body weight and this is more prominent for ALT rather than AST. This is associated with insulin resistance and is considered as the hepatic manifestation of the metabolic syndrome. In several studies, ALT elevation has correlated with the hepatic fat on imaging.[6] De Ritis ratio <0.8 has a 93% predictive value of little or no fibrosis on biopsy while >0.8 increases the likelihood of advanced fibrosis or cirrhosis on biopsy. The finding of De Ritis ratio 1.2204 ± 0.17954 (p = 0.005) in patients with NAFLD in our study suggests the presence of fibrosis or cirrhosis, which is not consistent with the study done by Mittal in 2011 at Manipal College of Medical Sciences, Pokhara, Nepal.[16] The disparity of result because the patient at Manipal Medical College may be in initial stage of NAFLD (steatosis), before advancement of fibrosis and cirrhosis.

In cholestasis, there is accumulation of bile in cells and biliary passages due to reduction in bile flow. The defect in excretion may be within the biliary canaliculi of the hepatocyte and in the microscopic bile ducts (intrahepatic cholestasis) or there may be mechanical obstruction to the extrahepatic biliary excretory apparatus (extrahepatic cholestasis).[1] Serum aminotransferases are not highly increased in this disorder.[2] De Ritis ratio of ≥1.5 suggests intrahepatic cholestasis while values ≤1.5 suggest an extrahepatic process.[6] Our study have shown slight increment of De Ritis ratio (p = 0.408) in comparison to control, which is consistent with the investigations by De Ritis et al. (1965).[9]

Conclusion

The pattern of elevation of aminotransferases, that is, De Ritis ratio is lesser than 1 in viral hepatitis, <1 to 1.5 in NAFLD and cholestasis, and >2 in ALD. Hence, the level of aminotransferases along with De Ritis ratio can be a useful biochemical test to screen the population of liver disorder, which is noninvasive and cost–effective method in less affluent, undeveloped region where people cannot afford battery of liver function test.

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