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Independent Utility of De Ritis Ratio (AST: ALT Ratio) in Alcoholism

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Abstract **Original Research Article**

Because the pattern and degree of elevation of enzyme activity vary with the type of Liver disease, their measurement is extremely helpful in the recognition and differential diagnosis of liver damage. Several factors govern the ability of liver enzymes to assist in diagnosis, including their (1) tissue specificity, (2) subcellular distribution, (3) relative activity of enzyme activity in liver and plasma, (4) patterns of release, and (5) clearance from plasma [1]. One of the typical laboratory abnormalities of alcoholic hepatitis are elevated AST and ALT. Precisely an AST: ALT ratio of more than 2 suggests alcoholism [2]. However pyridoxine deficiency which is common in chronic alcoholics, alter the pattern of ratio as the ALT is more dependent upon pyridoxine rather than AST. ***Aim and Objective:*** The aim is to measure serum AST ALT in persons taking alcohol for long duration and analyze the results statistically in cases and controls by arriving the AST/ALT ratio. ***Materials and methods:*** The study consists of two groups of men of all ages. Both group consume alcohol for longer periods. They are selected by screening them by standard questionnaire for alcoholism and divided in to two groups. Group 1 comprising of persons having AUDIT score of less than 8 and group 2 comprising of persons with AUDIT score 8 and more. An AUDIT score of 8 is generally considered is the cut off score above which alcohol dependency problem usually exists. ***Results:*** Comparisons were made with Mann–Whitney test. Pairwise correlations were calculated with Pearson product-moment correlation coefficients, as required. A P-value <0.05 was considered statistically significant and the overall p value were <0.001(AST); <0.001 (ALT); 0.186 (AST/ALT Ratio) for both groups. ***Conclusion:*** Excessive drinking increases the AST/ALT ratio there by increasing the risk for alcoholic liver diseases. However there is reversal of ratio can occur in alcoholics which would better be studied further.

Keywords: AST, Aspartate aminotransferase; ALT, Alanine amino Transferase; AST/ALT Ratio; AUDIT, Alcohol Use Disorders Identification Tests; Alcohol.

INRODUCTION

The aminotransferses are sensitive indicators of liver cell injury and are most helpful in recognizing acute hepato-cellular disease such as hepatitis. Though AST is found in many cells like kidney, muscle etc apart from liver, ALT is found primarily in liver. The aminotransferses are present in low concentration normally in serum. These enzymes are released into the blood stream when there is injury to the cell membrane resulting in increased permeability. Liver cell necrosis is not at all required for the enzyme release and hence the prognostic value of these enzymes are less [3] as cell injury itself releases the enzymes.

In patients with increased serum aminotransferase activity, the predominance of AST over ALT in alcohol-related liver disease was first reported by Harinasuta *et al*., in 1967. However, it became more widely recognized only with the paper by Cohen and Kaplan in 1979 [4]. But the ratio itself was first described by Fernando De Ritis in 1957 being called as De Ritis Ratio since then.

A possible explanation for high AST/ALT ratio in alcoholic liver disease are

- A decreased hepatic ALT activity [5]
- Pyridoxal 5′-phosphate depletion in the livers of alcoholics [7, 6].
- Mitochondrial damage leading to an increase in serum activity of mitochondrial aspartate in patients with high alcohol consumption [7].

An increased AST/ALT ratio in patients with increased serum aminotransferase activity has also been associated with the development of cirrhosis in Nonalcoholic Steatohepatitis [8] even though a still

higher AST/ALT ratio was observed in a group of non-biopsied patients with alcoholic liver disease. Furthermore, a high AST/ALT ratio in patients with increased serum aminotransferases has been reported in chronic viral hepatitis [21-30] even though reports on relatively low positive predictive values have been published [9].

Abnormality of Plasma enzymes, AST & ALT

ALT is present in several tissues, but increased plasma activities primarily reflect liver injury. AST is found in liver and muscle (cardiac and skeletal), and to a limited extent in red cells. Enzymes are found at different locations within cells. AST, ALT, are cytosolic enzymes. As such, they can be released with cell injury and appear in plasma relatively rapidly. AST and ALT have both mitochondrial and cytosolic isoenzymes in hepatocytes and other cells containing these enzymes. In the case of ALT, the relative amount of mitochondrial isoenzyme is small, and its plasma half-life is extremely short, making it of no diagnostic significance. In the case of AST, the mitochondrial isoenzyme represents a significant fraction of total AST within hepatocytes. For cytoplasmic enzymes, the relative amount of enzyme in the liver relative to plasma is an important determinant of diagnostic sensitivity. The activity of AST within hepatocytes is about twice that of ALT, although plasma activities are similar. Cell injury, the simplest mechanism, appears to allow leakage of cytoplasmic enzymes from cells, but minimal release of other types of enzymes. Thus necro-inflammatory disease leads to release of AST and ALT, but not of mitochondrial isoenzyme of AST. Alcohol appears to induce expression of mitochondrial AST on the surface of hepatocytes.

Clearance of liver enzymes from plasma occurs at variable rates. The half-life of ALT is 47 hours, and of cytosolic AST, 17 hours; thus although more AST is released from the liver, the much longer half-life of ALT leads to higher activities of ALT than AST in most forms of hepatocellular injury. However the half-life is in days in case of GGT and ALP which make sense that when drinking of alcohol is stopped the liver cell thriving to normality is almost possible (Tietz).

MATERIALS AND METHODS

The study population, after obtaining due ethical committee clearance, were selected from the wards of the Stanley Medical College Hospital Chennai who got admitted for various complaints but not related to liver dysfunction but with drinking habits. They were initially screened for alcoholism by the well-known Alcohol Use Disorder Identification Test [10] (AUDIT) screening methods and categorized by AUDIT scoring and divided into two groups; group 1 consists of 50 alcohol drinking persons with AUDIT score 8 above and; group 2 consists of persons with similar drinking behaviour with AUDIT less than 8 irrespective of age. The purpose is to select an AUDIT score above which there is definite chance of alcoholic disorders by asking most of the questions to the respondents. A single traditional bio-marker being used to assess the severity of drinking and only a small group of respondents were selected with a scope to further study comprehensively.

An AUDIT score of 8 is generally considered border line value above which dependence and organ injury is usually expected.

Exclusion Criteria

- Patients with h/o liver disease
- Drugs that elevates liver enzymes like Anti Tuberculosis Drugs, anticonvulsants etc
- Unwilling patients

Sample collection and Analysis: Random venous blood sample of 5 ml was collected; the sample centrifuged; serum separated and analysed for the following;

- AST
- ALT- in fully auto analyzer
- Calculation of AST/ALT ratio

Reference value [11] = AST-less than 35 U/L ALT- less than 45 U/L

STATISTICS

Group Statistics

Table-1:

Group 1 50 persons (AUDIT Score <8)		
No	**Age**	**AST/ALT Ratio Above 2**
1	51	2.428571
2	52	2.272727
3	48	2.733333
4	51	2.612903
5	55	2.052632
6	60	2.205128
7	48	2.129032
8	52	2.166667
9	67	2.075
10	56	2.387097
11	43	2.366667
12	47	3.545455

Percentage: 24 percent

Table-2:

Age Group	AST/ALT	
	above 2	above 3
40-45	1	
46-50	3	1
51-55	5	0
56-60	3	0

Table-3:

Group 2 50 persons (AUDIT≥8)		
No	**Age**	**AST/ALT Ratio Above 2**
1	48	2.315789
2	51	2.358974
3	47	3.454545
4	49	3.153846
5	48	2.290323
6	67	2.186047
7	56	2.441176
8	43	2.170732
9	47	2.333333

Percentage: 18 per cent

Table-4:

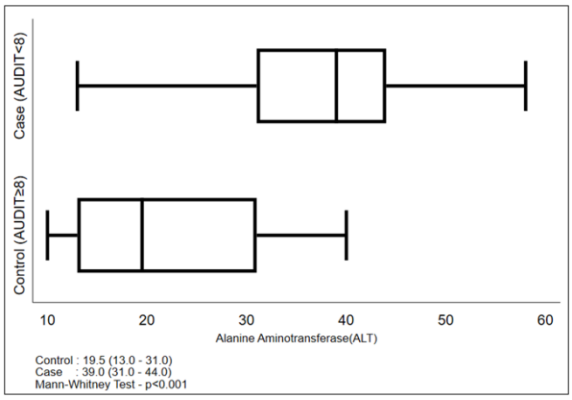
Age Group	AST/ALT	
	above 2	**above 3**
40-45	1	0
46-50	5	2
51-55	1	0
56-60	1	0
Above 60	1	0

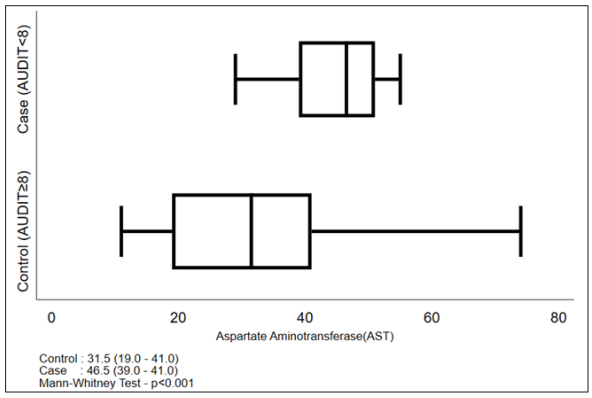
Statistical Method

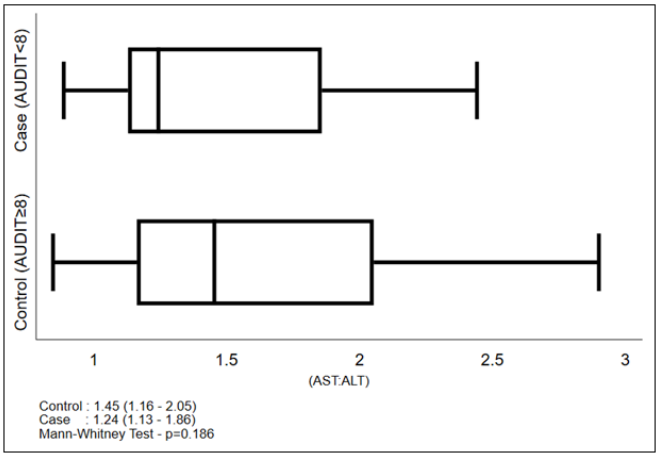
Values are expressed as median, and Quartiles. Comparisons were made with Mann–Whitney test when comparing two groups. Pairwise correlations were calculated with Pearson product-moment correlation coefficients, as required. A *P*-value <0.05 was considered statistically significant.

Table-6: AST, ALT and Ratio (AST: ALT) compared by AUDIT and Age Group

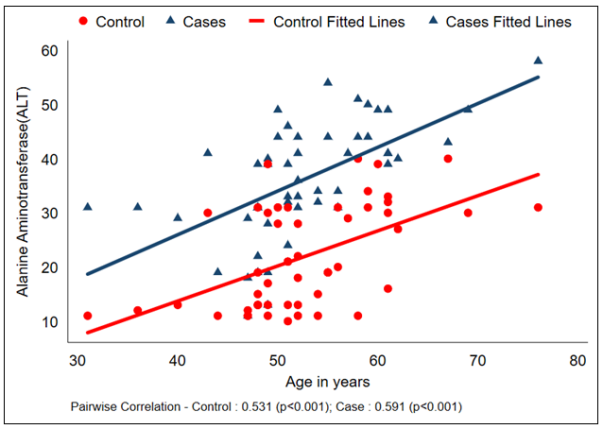
		Group 1 (AUDIT<8)		Group 2 (AUDIT≥8		Overall		p-value
		n	Median (Q1 - Q3)	n	Median (Q1 - Q3)	n	Median (Q1 - Q3)	
AST								
Age	30 - 45	5	39 (33 - 39)	5	18 (18 - 19)	10	31.5 (18 - 39)	0.074
	46 - 55	29	42 (41 - 51)	29	29 (19 - 39)	58	39.5 (29 - 50)	<0.001
	>55	16	51 (49 - 68.5)	16	39.5 (31.5 - 53)	32	49 (39 - 60)	0.012
	Total	50	46.5 (39 - 51)	50	31.5 (19 - 41)	100	41 (31 - 51)	<0.001
ALT								
Age	30 - 45	5	31 (29 - 31)	5	12 (11 - 13)	10	24 (12 - 31)	0.027
	46 - 55	29	33 (28 - 40)	29	17 (13 - 22)	58	26 (15 - 33)	<0.001
	>55	16	43.5 (40.5 - 49)	16	31 (28 - 33.5)	32	39 (31 - 43.5)	<0.001
	Total	50	39 (31 - 44)	50	19.5 (13 - 31)	100	31 (18.5 - 39)	<0.001
AST:ALT								
Age	30 - 45	5	1.34 (1.26 - 1.58)	5	1.64 (1.58 - 1.64)	10	1.58 (1.26 - 1.64)	0.346
	46 - 55	29	1.24 (1.14 - 1.9)	29	1.46 (1.18 - 2.13)	58	1.33 (1.14 - 2.13)	0.397
	>55	16	1.2 (1.06 - 1.56)	16	1.33 (1.13 - 1.77)	32	1.23 (1.09 - 1.75)	0.309
	Total	50	1.24 (1.13 - 1.86)	50	1.45 (1.16 - 2.05)	100	1.29 (1.13 - 1.91)	0.186
	Values were given as median (Q1 - First Quartile - Q3 - Third Quartile); NA - Not available							
	Mann Whitney test was used at 5% level of significance							

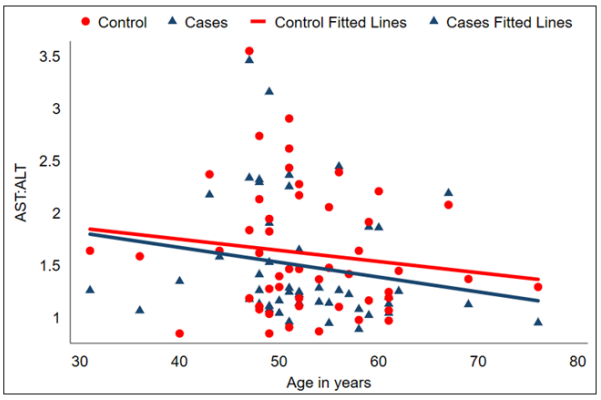


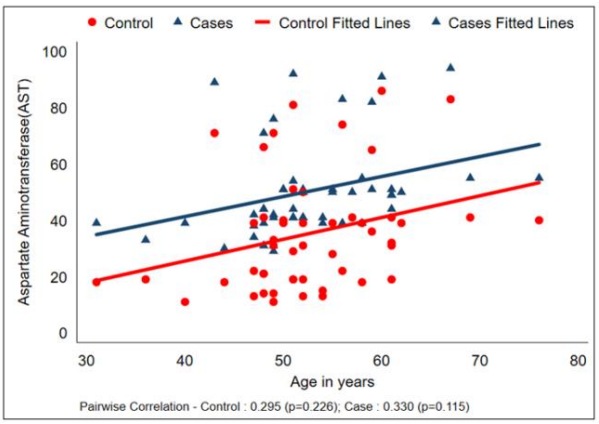




Correlation Table				
		Age	**AST**	**ALT**
Overall	AST	0.287 (0.023)	NA	NA
	ALT	0.458 (<0.001)	0.672 (<0.001)	NA
	AST:ALT	-0.163 (0.633)	0.409 (<0.001)	-0.306 (0.012)
Case	AST	0.330 (0.115)	NA	NA
	ALT	0.591 (<0.001)	0.434 (0.010)	NA
	AST:ALT	-0.190 (>0.950)	0.382 (0.037)	-0.577 (<0.001)
Control	AST	0.295 (0.226)	NA	NA
	ALT	0.531 (<0.001)	0.770 (<0.001)	NA
	AST:ALT	-0.139 (>0.950)	0.571 (<0.001)	-0.006 (>0.950)
NA - Not available				







DISCUSSION

A study by Nyblom *et al.*, showed that high AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking as the mean and maximum ratio for biliary cirrhosis was between 1 and 2 was observed and the AST/ALT ratio decrease rapidly after such patients got admitted [12] there by no chances of drinking. In our study patients yet to develop symptoms of liver damage but the ratio is higher in both the group especially in the age group of 46-55 and above 55 and sooner these persons stop drinking before the development of symptoms of liver disease not later for them to escape from alcoholic liver diseases, ALD.

Nyblom *et al.*, also showed that the ratio rapidly decreased in ALD patients after treatment. This

would suggest the contribution of a direct toxic effect of alcohol on AST/ALT ratio which has been reviewed in a similar study in 2011 by Vidhya *et al.*, [13] shows that had these patients follow abstinence of alcohol the AST/ALT would better be reflected as back to normal from the toxic effects of alcohol, a good sign indeed. Clearance of liver enzymes from plasma occurs at variable rates. The half-life of ALT is 47 hours, and of cytosolic AST, 17 hours; thus although more AST is released from the liver, the much longer half-life of ALT leads to higher activities of ALT than AST in most forms of hepatocellular injury. However the half-life is in days in case of GGT and ALP which make sense that when drinking of alcohol is stopped the liver cell thriving to normality is almost possible (Tietz).

In our study the ratio is >2 in 21 persons in both the groups which show similar views by studies conducted earlier in 2013 by Hyder *et al.*, in which the AST: ALT ratios 1 for normal; 0.65(<1) for viral hepatitis [14] - consistent with DE RITIS *et al*., [17] (>2 for Alcoholic Liver Disease (ALD) [15] which was similar as reported by several other studies conducted earlier (Luis) [18]; and 1.24 in cirrhosis (> 1 but < 2) also documented by Nyblom *et al.*, and others. This helps to differentiate ALD from other liver diseases. When we go by these, patients would have already developed some organ damage waiting only to expose symptom sooner or later especially in the age group 50-55.

One of the opinion from our study is that ALD patients cannot be differentiated from Non-Alcoholic Steato Hepatits (NASH) and acute viral hepatitis with certainty without measuring serum AST/ALT ratio which was also studied earlier by Torkadi *et al*., [16].

And not only that an AST/ALT value less than 0.4 was 99% sensitive for identifying patients with resolving transaminases. This finding may be beneficial to identify patients that have passed the peak AST concentrations and have resolving hepatic injury (Lonnie) [17].

Finally, in this study though patients have no symptoms pertaining to liver now, an updated version on AST/ALT in August 2019 (Daniel & Fogoros) states that a general guideline used to diagnose liver disease are i. an AST/ALT ratio less than 1 is suggestive of non-alcoholic fatty liver disease; ii. a ratio equal to 1 is suggestive of acute viral hepatitis; iii. a ratio higher than 1 is suggestive of cirrhosis and iv. a ratio of more than 2 (21 persons out of 100 in this study) is suggestive of alcoholic liver disease [18] which will throw more light on how to interpret the enzyme values in persons who drinks heavily and the importance of intervention strategy to stop the drinking habits. However pyridoxine deficiency which is common in chronic alcoholics, alter the pattern of ratio as the ALT is more dependent upon pyridoxine rather than AST [19]. So the laboratories which issue results of AST, ALT shall also do issuing the AST/ALT ratio (calculation) since it may provide useful information regarding diagnosis and prognosis of a disease status (Mono Botros) [20] which seems more plausible.

CONCLUSION

Excessive drinking increases the AST/ALT ratio which can independently reveal increasing risk for alcoholic liver diseases. However there is reversal of ratio occur in alcoholics which would better be studied further.

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