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Relation of Transaminase Levels with Severity of Hepatitis A in Children

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Abstract

Objectives: To determine the sensitivity, specificity and diagnostic accuracy of serum alanine transaminase and serum aspartate transaminase in detecting the presence of severe Hepatitis A in children.
Study Design: Cross-sectional validation study.
Place and Duration of Study: Department of Pediatrics, Combined Military Hospital, Rawalpindi Pakistan, Jan to Sep 2022.
Methodology: This study was conducted on 201 patients diagnosed with acute hepatitis A. All patients underwent testing for serum ALT, AST and LDH levels as well for PT/INR. Patients were labelled as suffering from severe hepatitis if INR was greater than 1.5. A 2x2 table was constructed to calculate the sensitivity, specificity and diagnostic accuracy for serum ALT, AST, ALT/AST ratio and ALT/LDH ratio in detecting the presence of severe hepatitis.
Results: The mean age of the sample at the time of the study was 7.47±2.54 years, while 103(51.2%) were female. Serum ALT levels showed a sensitivity of 81.6% and a specificity of 36.0%. Serum AST had a sensitivity and specificity of 86.2% and 27.2% for the same, while the ALT/LDH ratio and the AST/LDH ratio had a sensitivity and specificity of 88.5% and 39.5%, and 100% and 1.7%, respectively for the detection of presence of severe Hepatitis A. Lastly, the ALT/AST ratio had 0% sensitivity and 100% specificity for the detection of severe hepatitis A.
Conclusion: Liver enzyme levels and various associated ratios have low sensitivity and specificity for the detection acute severe hepatitis A.

Keywords: Alanine Transaminase, Aspartate Transaminase, Diagnostic Accuracy, Severe Hepatitis A.

How to Cite This Article: *Mehmood R, Ikram F, Ali B, Sarwar S, Akhtar Z, Munawar B. Relation of Transaminase Levels with Severity of Hepatitis A in Children. Pak Armed Forces Med J 2025; 75(Suppl-4): S578-S582. DOI: https://doi.org/10.51253/pafmj.v75iSUPPL-4.10330*

INTRODUCTION

Acute liver failure is defined as the presence of gross hepatic dysfunction in a patient without any previous history of hepatic disease.[1] Hepatitis A afflicts an estimated 1.5 million people, mostly children, every year, with a global prevalence of 1 case per 100,000 population, according to the World Health Organization (WHO).[2] Less than 1% of cases of hepatitis A develop acute liver failure of whom two-thirds patients improve spontaneously while one-third require liver transplantation if they are to survive.[3] The condition can progress rapidly to a critical phase, and requires strict monitoring for deterioration to prevent morbidity and mortality.[4]

Various modalities have been proposed for the monitoring of liver status in patients with severe Hepatitis A. Traditionally, albumin and prothrombin time have been used as fair indicators of severity of liver disease, however, albumin has a long half-life of twenty-one days, taking an unacceptably long time to demonstrate a fall in levels to be useful for monitoring in some acute settings.[5,6] Prothrombin time is a measure of the extrinsic pathway where the factor with the shortest half-life is Factor VII with a half-life of up to six hours, which is still useful, but hardly optimal.[7] Conversely, liver enzymes such as Alanine Transaminase (ALT), Aspartate Transaminase (AST) and the rather non-specific Lactate Dehydrogenase (LDH) rise quickly, sometimes even precipitously, with liver damage.[8] However, in isolation, the use of any of these serum enzyme levels as accurate means of monitoring for the development of acute liver injury is plagued by lack of sensitivity and diagnostic accuracy.[9] To circumvent this dilemma, various authors have advocated combinations of these enzymes in the form of ratios to detect the presence of severity of acute hepatitis, as a means to monitor the progress of the disease.[10]

This study was conducted with the objective of determining the diagnostic accuracies of different liver enzyme ratios in determining presence of severe acute hepatitis in the paediatric population suffering for Viral Hepatitis A. Doing so will determine the utility of using these ratios in the monitoring the condition of

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Received: 09 May 2023; revision received: 10 Jul 2023; accepted: 12 Jul 2023

these patients suffering from this common infection. If useful, these ratios will give the treating clinician the ability to intensify management or move to transplant where necessary in a timely manner or, conversely, to safely discharge the patient, if indicated, which will help to reduce morbidity, mortality and financial costs of management.

METHODOLOGY

We conducted this research protocol as a cross-sectional validation study between Jan to Sep 2022 in the Department of Pediatrics, Combined Military Hospital, Rawalpindi Pakistan, on 201 patients, whose guardians/parents gave written, informed consent for participation and who were diagnosed as suffering from Acute Hepatitis A, defined as having a positive serum anti-HAV IgM antibody test on admission. All patients were selected via consecutive non-probability sampling. The EPI Tools sample size calculator was used to calculate the sample size keeping an expected sensitivity of 75.0%, expected specificity of 100%, expected prevalence of 48.5.0%, a desired precision of 2 and a confidence level of 95%, figures which were derived from Kotoh et al, using a cut-off of 3.0 for ALT to LDH ratio in predicting whether liver injury was severe or not.[11]

Inclusion Criteria: Patients of both genders, between the ages of 3 and 12 years, diagnosed as suffering from Acute Hepatitis A were included in the study.

Exclusion Criteria: Patients who had a history of alcoholic or nonalcoholic fatty liver disease, chronic hepatitis B or C, heart failure, iron overload, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, autoimmune hepatitis neoplastic disease affecting the liver, or were using hepatotoxic drugs within the past one month were excluded.

All patients underwent a thorough history and clinical examination at the time of inclusion in the study.Diagnosis of acute Hepatitis A was confirmed by testing for serum anti-HAV IgM antibody (Anti-HAV IgM ELISA Kit, Creative Diagnostics; New York, USA) at the time of enrollment. Patients were also tested for serum ALT, AST and LDH levels (POCT Multi-Function Dry Chemistry Analyzer, Wuhan Darppon Medical Technology; Wuhan, China), as well as Prothrombin Time (PT) and International Normalized Ratio (INR) (URIT-610 Coagulation Analyzer, Med Sing Long; Guangzhou, China) on dayof admission. All machines were carefully calibrated and control-tested before testing was conducted. A patient was said to be suffering from severe disease if INR was greater than 1.5.[12] A serum ALT and AST of greater than 500 U/L were considered to be suggestive of severe hepatitis, while an ALT to LDH ratio of 3.0 or more, an ALT to AST ratio of greater than 2.2, or and AST/LDH ratio of greater than 2.4 where indicative of the same.[11-14]

Data was analyzed using the Statistical Package for the Social Sciences version 26.0. Mean and SD was calculated for quantitative variables specifically age, duration of illness,serum ALT levels, serum AST levels, serum LDH levels, PT/INR, ALT/LDH ratio, AST/LDH ratio and ALT/AST ratio. Qualitative variables like gender and presence of severe disease according to INR, as well as according to serum ALT levels, serum AST levels, ALT/LDH ratio, AST/LDH ratio and ALT/AST ratio were recorded in terms of frequency and percentage. A 2x2 table was constructed to calculate the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of serum ALT, AST, ALT/LDH ratio, AST/LDH ratio and ALT/AST ratio in detecting the presence of severe hepatitis.

RESULTS

Our study sample was composed of a total of 201 patients, with a mean age of 7.47±2.54 years. Females and males were almost equally present: 103(51.2%) versus 98(48.8%), respectively. The mean duration of illness was 3.85±1.84 days. The mean serum ALT levels were 1137.62±669.08 U/L, while mean AST and LDH levels were 1330.00±822.71 U/L and 310.97±210.65 IU/L, respectively.The mean INR for the sample was 1.70±0.62. Table-I shows the patient data distributed according to gender.

Table-I: Results According to Gender (n=201)

Variable	Male (n=103)	Female (n=98)	*p*-value
Gender	98(48.8%)	103(51.2%)	-
Age (years)	7.60±2.48	7.34±2.61	0.460
Illness Duration (Days)	3.76±1.94	3.93±1.75	0.497
Serum ALT Levels (U/L)	1102.22±671.58	1171.29±668.22	0.466
Serum AST Levels (U/L)	1290.90±831.35	1367.21±816.72	0.512
Serum LDH Levels (IU/L)	304.84±215.40	316.81±206.91	0.688
INR	1.62±0.52	1.78±0.70	0.067

We constructed a 2x2 table to determine the test characteristics for serum ALT and AST, where we found that the two enzymes appeared to have results that were similar to each other as shown in Table-II.

A second 2x2 table was constructed for the three ratios under study, specifically to determine their test characteristics was also constructed as displayed in Table-III.

Table-II: 2x2 Table for ALT and AST

2 x 2 Table		Presence of Severe Acute Hepatitis A according to INR		Total
		Yes	No	
Presence of Severe Acute Hepatitis A according to ALT	Yes	True Positive: 71	False Positive: 73	144
	No	False Negative: 16	True Negative: 41	57
Total		**87**	**114**	**201**
Presence of Severe Acute Hepatitis A according to AST	Yes	True Positive: 75	False Positive: 83	158
	No	False Negative: 12	True Negative: 31	43
Total		**87**	**114**	**201**

Table-III: 2x2 Table for ALT/LDH, AST/LDH and ALT/AST Ratios

2 x 2 Table		Presence of Severe Acute Hepatitis A according to INR		Total
		Yes	No	
Presence of Severe Acute Hepatitis A according to ALT/LDH Ratio	Yes	True Positive: 77	False Positive: 69	146
	No	False Negative: 10	True Negative: 45	55
Total		**87**	**114**	**201**
Presence of Severe Acute Hepatitis A according to AST/LDH Ratio	Yes	True Positive: 87	False Positive: 110	197
	No	False Negative: 0	True Negative: 4	4
Total		**87**	**114**	**201**
Presence of Severe Acute Hepatitis A according to ALT/AST Ratio	Yes	True Positive: 0	False Positive: 0	0
	No	False Negative: 87	True Negative: 114	201
Total		**87**	**114**	**201**

The sensitivity, specificity, positive and negative predictive values, as well as diagnostic accuracy for each test are displayed in Table-IV. While serum ALT, AST and ALT/LDH ratio had a good degree of sensitivity, their specificity was low, and the AST/LDH range appeared to be very non-specific. None of the tests appeared to have a good diagnostic accuracy. Additionally, the ALT/AST ratio failed to detect any cases of severe disease.

Table-IV: Test Characteristics (n=201)

Test	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Diagnostic Accuracy
ALT	81.6%	36.0%	49.3%	71.9%	55.7%
AST	86.2%	27.2%	47.5%	72.1%	52.7%
ALT/LDH Ratio	88.5%	39.5%	52.7%	81.8%	60.7%
AST/LDH Ratio	100%	1.7%	44.2%	100%	45.3%
ALT/AST Ratio	0%	100%	0%	56.7%	56.7%

DISCUSSION

Predicting the development of severe disease in paediatric patients with viral Hepatitis A is of paramount importance, particularly in patients who go on to develop fulminant hepatic failure and may require more intensive management or even liver transplant. The levels of enzymes such as ALT, AST and LDH rise in serum, as more and more hepatocytes undergo cell death, releasing their contents into the blood stream and, therefore, can serve as potential markers for severity of injury.

Our study demonstrated that Hepatitis A does not appear to have gender predilection: both males and females are equally affected. This finding is in keeping with existing literature such as Michaelis et aland Choe et al, who shared our conclusion.[15,16] Our study showed that the mean age of patients presenting with acute Hepatitis A had a mean age of 7.47±2.54 years. Kumar *et al.,* carried out a similar study and reported that the mean age of children presenting with Hepatitis A was 7.85±3.40 years in their study, which was similar to our results.[17] In addition, Akman et al noted that the majority of cases in their study of the epidemiology of Hepatitis A were aged below 11 years.[18]

Our study showed that serum ALT levels with a cut-off of 500 U/L had a sensitivity of 81.6%, a specificity of 36.0% and a diagnostic accuracy of 55.7% in the detection of severe hepatitis, while serum AST levels with a cut-off of 500 U/L had a sensitivity of 86.2%, a specificity of 27.2% and a diagnostic accuracy of 52.7%.While we were unable to find a study that looked at serum ALT and AST in a similar manner despite an extensive literature search, Schaefer *et al.,* noted that levelsof both enzymes greater than 500 U/L were associated with severe disease.[12] Breu *et al.,* noted that levels of both enzymes greater than 1000 U/L were associated most commonly with three causes: acute viral hepatitis, drug-induced injury and ischaemic injury.[19] Through our study, we determined that while serum ALT and AST were good indicators of liver injury, they correlated poorly with severity of injury.

The ALT/LDH ratio with a cut-off of 3.0 had a sensitivity of 88.5%, a specificity of 39.5%, and a diagnostic accuracy of 60.7% in our research. Kotoh *et al.,* determined that this ratio, with a cut-off of 3.0, had a sensitivity of 50.0% and specificity of 52.9% and a diagnostic accuracy of 51.5% on the day of presentation for the detection of severity that was similar to our study, however, they also reported that the test parameters improved on day 3 of admission: with a sensitivity of 75.0%, a specificity of 100% and a diagnostic accuracy of 87.9%, and concluded that the ratio could be a useful indicator of severity of hepatic

hypoxia.[11] It is pertinent to note here that we did not study the role of delayed testing in our study. Additionally, Kuwano *et al.*, reported that a ratio of greater than 1.5 was indicative of severe viral hepatitis, while lower ratios were associated with ischaemic insults.[20]

Our research showed that AST/LDH ratio with a cut-off of 2.4 carried a sensitivity of 100%, a specificity of 1.7% and a diagnostic accuracy of 45.3%. Kalas *et al.*, noted that a ratio of higher than 1.5 was associated with viral hepatitis, while those lower than 1.5 were more likely to be due to ischaemic injury,[21] however, the study did not report that it correlated well with the severity of injury.

Lastly, the ALT/AST ratio, with a cut-off of 2.2 had sensitivity of 0%, a specificity of 100%, and a diagnostic accuracy of 56.7% in the detection severe disease in acute Hepatitis A. This ratio has been traditionally been useful in association with alcoholic hepatitis, where AST levels are increased to a greater level as compared to ALT levels, and ratios less than 1.5 are indicative of severe liver damage, but correlates poorly with other forms of hepatitis such as of viral etiology, which was also demonstrated in our study.[5,22]

LIMITATION OF STUDY

Our research was limited by the fact that we conducted it in a tertiary care center: this resulted in many patients presenting late for study, and the liver enzyme levels were at variable degrees, entirely dependent upon the time of presentation, and since each enzyme follows its own timeline for rise, peak and fall, this may have produced confounding within the results. Secondly, since the patients received healthcare elsewhere and presented late, a larger proportion had severe disease than is necessarily reflective of the natural history of Hepatitis A in the population. Lastly, liver mass to body mass varies with age, with younger children having a larger liver size as compared to their body, even minor damage in these children will result in higher circulating levels of liver enzymes as compared to older children, which may have resulted in confounding.

CONCLUSION

Liver enzymes are useful indicators of whether liver damage has occurred or not, but are not accurate in determining the extent of liver damage in children suffering from Hepatitis A, both when employed in isolation, or when combined with other enzymes in the form of ratios. Use of these tests in predicting the presence of severe viral Hepatitis A in the paediatric population should be done with caution. A combination of these enzymes with various other parameters such as bilirubin or electrolyte levels may improve their diagnostic utility, which may serve as the focus of future research, however, till such as time as new recommendations can be drawn for said research, the clinician will have to rely on traditional markers for severity such as prothrombin time and serum albumin levels.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

RM & FI: Conception, study design, drafting the manuscript, approval of the final version to be published.

BA & SS: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

ZA & BM: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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