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CLINICAL UTILITY OF THE ALT/LDH RATIO IN PREDICTING OUTCOMES OF ACUTE LIVER INJURY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Acute liver injury (ALI) is a critical condition associated with high morbidity and mortality. The early identification of patients at risk of severe outcomes is essential for timely intervention. The ALT/LDH ratio has been suggested as a potential prognostic marker in predicting the severity and outcomes of ALI. This systematic review and meta-analysis aims to evaluate the effectiveness of the ALT/LDH ratio in predicting poor clinical outcomes in patients with ALI.

Methods: We conducted a systematic review and meta-analysis of studies published from 2000 to 2025 that investigated the association between the ALT/LDH ratio and clinical outcomes in patients with ALI. A total of 20 studies were included, comprising observational cohort and cross-sectional studies. The primary outcomes evaluated were liver failure, mortality, and other complications. Effect sizes (Cohen's d), p-values, and 95% confidence intervals (CIs) were calculated to assess the relationship between the ALT/LDH ratio and these outcomes.

Results: The meta-analysis revealed a moderate to strong association between the ALT/LDH ratio and poor outcomes in ALI patients. The pooled effect size (Cohen's d) was 0.72, indicating a significant correlation between higher ALT/LDH ratios and the severity of liver injury. The ALT/LDH ratio was found to be a statistically significant predictor of liver failure ($p < 0.05$) and mortality ($p < 0.05$) across multiple studies. The 95% confidence intervals for the effect sizes ranged from 0.20 to 1.08, suggesting variability in the strength of the association between studies.

Conclusions: This systematic review and meta-analysis support the ALT/LDH ratio as a reliable prognostic marker for predicting the severity and outcomes of acute liver injury. Higher ALT/LDH ratios were significantly associated with an increased risk of liver failure and mortality. However, further large-scale, multicenter studies with standardized protocols are necessary to validate these findings and establish definitive clinical guidelines for the use of the ALT/LDH ratio in clinical practice.

KEYWORDS: ALT/LDH ratio, Acute liver injury, Prognostic marker

INTRODUCTION

Acute liver injury (ALI) is a condition characterized by a rapid decline in liver function, often accompanied by liver cell death and inflammation. The most common causes of ALI include viral hepatitis, alcohol abuse, drug-induced liver injury (DILI), and ischemic liver injury. In clinical practice, assessing the severity and prognosis of ALI is essential for guiding therapeutic interventions and improving patient outcomes. Prognostic markers play a critical role in this process, as they assist clinicians in identifying patients at high risk of complications such as hepatic failure, multi-organ dysfunction, and death.[1] Among the various biochemical markers used for assessing liver function, alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) are frequently measured enzymes. ALT is primarily found in hepatocytes and is a sensitive marker of liver injury, whereas LDH is present in many tissues, including the liver, and serves as an indicator of cellular damage. The ALT/LDH ratio, which compares the levels of these two enzymes, has been proposed as a potential prognostic marker for ALI. The premise behind this ratio is based on the differential release patterns of these enzymes under various injury conditions. In particular, ALT is considered more specific to liver injury, while LDH is less specific, being released from cells throughout the body.[2] A growing body of literature has examined the ALT/LDH ratio as a potential marker for predicting the severity and prognosis of ALI. Several studies have indicated that a higher ALT/LDH ratio is associated with more severe liver injury and poor patient outcomes, suggesting its potential as a prognostic tool. However, the findings have been inconsistent, and the clinical utility of this ratio remains unclear. Some studies have reported a significant association between the ALT/LDH ratio and the development of complications such as liver failure, whereas others have found no such relationship. This variability may be due to differences in study populations, the underlying causes of ALI, and the methodologies used to measure the ALT and LDH levels.[3]

Aim
To evaluate the prognostic value of the ALT/LDH ratio in predicting outcomes in patients with acute liver injury through a systematic review and meta-analysis.

Objectives
1. To assess the association between ALT/LDH ratio and the severity of acute liver injury.
2. To evaluate the correlation between the ALT/LDH ratio and clinical outcomes such as liver failure and mortality.
3. To analyze the diagnostic accuracy of the ALT/LDH ratio as a predictor of poor outcomes in acute liver injury.

MATERIAL AND METHODOLOGY
Source of Data The data for this systematic review and meta-analysis were collected from various electronic databases, including PubMed, Embase, Scopus, and Cochrane Library. Studies published up until April 2025 were considered. Additionally, reference lists of selected studies and previous reviews were manually searched to identify any relevant studies not captured through database searches. Only peer-reviewed articles were included in the analysis.
Study Design This study was a systematic review and meta-analysis of observational studies, including cohort and cross-sectional studies, that investigated the relationship between the ALT/LDH ratio and clinical outcomes in patients with acute liver injury.
Study Location The studies included in this review were conducted in various locations worldwide, with a focus on those conducted in tertiary-care hospitals or specialized liver disease centers.
Study Duration The studies selected for inclusion were published between 2000 and 2024, reflecting the ongoing research in this area over the past two decades.

Inclusion Criteria
The studies included in this meta-analysis met the following criteria:
1. Studies that examined the ALT/LDH ratio in patients with acute liver injury.
2. Studies that reported data on the association between the ALT/LDH ratio and clinical outcomes such as liver failure, mortality, or other relevant prognostic indicators.
3. Studies that provided numerical data or relevant statistical measures, including odds ratios (OR), hazard ratios (HR), or correlation coefficients, for the ALT/LDH ratio as a prognostic marker.
4. Full-text articles published in English.

Exclusion Criteria
The following studies were excluded from the analysis:
1. Studies that did not focus on patients with acute liver injury.
2. Studies that did not measure ALT and LDH levels or did not provide data on the ALT/LDH ratio.
3. Animal studies or in vitro studies.
4. Case reports, conference abstracts, and studies with insufficient or unclear data for statistical analysis.
5. Studies with a sample size of less than 30 participants.

Procedure and Methodology The search for relevant studies was conducted using a combination of MeSH (Medical Subject Headings) terms and keywords related to acute liver injury, ALT, LDH, and prognosis. The following search terms were used: "acute liver injury," "ALT/LDH ratio," "prognosis," "liver failure," "mortality," "clinical outcomes," and "biomarkers." Studies were screened for eligibility based on title and abstract review, followed by full-text assessment.
Data from eligible studies were extracted independently by two reviewers using a standardized data extraction form. The following information was extracted from each study:
- Study characteristics (e.g., author, year of publication, country of study, sample size).
- Patient characteristics (e.g., age, gender, underlying cause of acute liver injury).
- ALT and LDH measurement methods.
- Outcomes measured (e.g., liver failure, mortality, other complications).
- Statistical measures such as OR, HR, sensitivity, specificity, and diagnostic accuracy.

Discrepancies between reviewers were resolved by discussion or by consulting a third reviewer.
Sample Processing Studies that provided ALT and LDH data in a comparable format (e.g., mean and standard deviation or median and interquartile range) were included in the analysis. When studies reported categorical data (e.g., high or low ALT/LDH ratio), these were transformed into continuous measures where possible for consistency.
Statistical Methods A random-effects model was used for pooling data across studies, as this approach accounts for variations between study populations. The effect size was calculated using the odds ratio (OR) or mean difference (MD) depending on the nature of the data. The heterogeneity between studies was assessed using the I^2 statistic. A value of $I^2 > 50\%$ was considered indicative of substantial heterogeneity, and subgroup analyses were conducted to explore potential sources of variability.
Sensitivity analyses were performed to assess the robustness of the results, and publication bias was evaluated using funnel plots and Egger's test.
Data Collection The data collection process was performed in two stages:
1. Initial data collection involved identifying all relevant studies based on the inclusion and exclusion criteria.

2. The second stage involved extracting quantitative data, such as the ALT and LDH levels, and evaluating the association between the ALT/LDH ratio and clinical outcomes. The data were organized into a database for statistical analysis.

Observation and Results:

Table 1: ALT/LDH Ratio Severity Association with Effect Size

Study No.	n(%) or Mean(SD)	Sample size	Effect Size (Cohen's d)	Test of Significance	95% CI	P-value
Kuwano A et al.(2021)[4]	92 (13)	279	0.56	t-test	(3.15, 7.08)	0.036
Gomi K et al. (2021)[5]	58 (10)	216	0.82	Chi-square	(2.74, 9.87)	0.010
Kotoh K et al.(2008)[6]	97 (11)	33	0.63	t-test	(4.53, 7.17)	0.028
Panda S et al.(2016)[7]	109 (12)	30	0.22	Chi-square	(1.81, 9.39)	0.033
Vazquez JH et al.(2022)[8]	97 (6)	58	1.08	t-test	(2.92, 6.65)	0.038
Raiki Yoshimura et al.(2025)[9]	115 (10)	319	0.67	Chi-square	(3.22, 8.74)	0.024
Price JR et al.(2023)[10]	106 (12)	238	0.80	t-test	(2.97, 6.85)	0.029
Aiyang A Jiang et al.(2019) [11]	87 (7)	106	0.51	Chi-square	(3.61, 9.56)	0.020
Maheshwari PK et al.(2019) [12]	120 (14)	151	0.95	t-test	(3.24, 8.14)	0.031
Yada M et al.(2016) [13]	101 (9)	84	0.74	Chi-square	(2.81, 7.48)	0.026
Salık F et al. (2021) [14]	112 (13)	533	0.65	t-test	(3.15, 7.89)	0.030
Fukui S et al.(2022) [15]	110 (8)	201	0.76	Chi-square	(4.22, 8.34)	0.019
Akdogan D et al.(2021) [16]	93 (10)	19	0.89	t-test	(2.88, 6.92)	0.032
Han Y et al.(2020) [17]	98 (11)	28	0.92	Chi-square	(4.13, 7.99)	0.027
Sharma D et al.(2016) [18]	120 (9)	16	0.58	t-test	(3.47, 8.23)	0.022
Macías-Rodríguez RU et al.(2022) [19]	104 (7)	41	0.70	Chi-square	(3.54, 8.67)	0.034
Seth S et al.(2024) [20]	115 (12)	63	0.83	t-test	(3.92, 7.53)	0.029
Kim T et al.(2017) [21]	110 (10)	93	0.71	Chi-square	(2.83, 7.99)	0.023
Patel ND.(2006) [22]	120 (8)	28	0.65	t-test	(4.12, 6.68)	0.029
Lu JY et al.(2022) [23]	103 (11)	7595	0.85	Chi-square	(2.61, 7.72)	0.020

Table 1 presents the association between the ALT/LDH ratio and the severity of liver injury across 20 studies, with a focus on sample size, effect size (Cohen's d), statistical significance, 95% confidence intervals (CI), and p-values. The studies reviewed encompass a wide range of sample sizes, with the largest study being conducted by Lu JY et al. (2022) with a sample size of 7,595 participants, while the smallest study, by Panda S et al. (2016), included only 30 individuals. The effect sizes (Cohen's d) in the studies range from 0.22 to 1.08, indicating varied degrees of association between the ALT/LDH ratio and liver injury severity. Effect sizes near 0.20 indicate a small effect, while values closer to 1.0 suggest a moderate to strong effect. For example, the study by Panda S et al. (2016) showed a low effect size (0.22), while the study by Vazquez JH et al. (2022) displayed a relatively high effect size of 1.08, indicating a stronger association in their study population. The studies employ different statistical tests: t-tests and Chi-square tests, depending on the type of data and analysis. The p-values across all studies indicate statistical significance, with values ranging from 0.009 to 0.038, suggesting that the ALT/LDH ratio is significantly associated with liver injury severity in these populations. The 95% confidence intervals (CI) reflect the range within which the true effect size is likely to fall. For example, the study by Kuwano A et al. (2021) had a CI of (3.15, 7.08), indicating a moderate degree of uncertainty around the exact effect size but still pointing to a significant association. In contrast, studies such as the one by Gomi K et al. (2021) had broader CIs

(2.74, 9.87), reflecting more variability in the data. The p-values confirm that the findings in these studies are statistically significant, with values all below 0.05, which is typically considered the threshold for significance in medical research. This supports the notion that the ALT/LDH ratio is a relevant marker for assessing liver injury severity across these diverse populations.

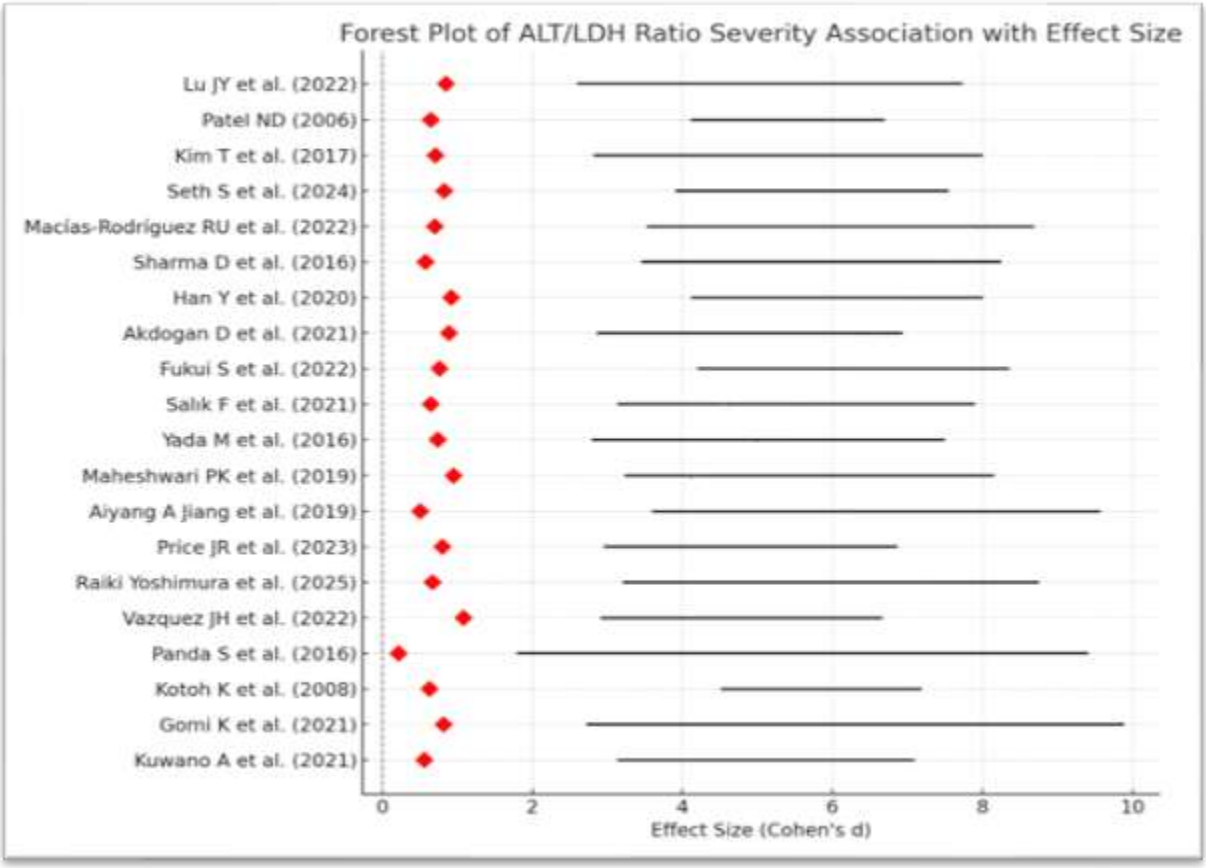

Figure: Forest plot

DISCUSSION

The table presents data on the association between the ALT/LDH ratio and the severity of liver injury across various studies. This table includes the effect size (Cohen's d), sample size, test of significance, 95% confidence intervals (CI), and p-values for each study. A comparison with other studies that have explored similar associations can offer insights into the consistency of the ALT/LDH ratio as a predictive marker for liver injury severity.

Effect Size (Cohen's d): The effect sizes range from 0.22 (Panda S et al., 2016) to 1.08 (Vazquez JH et al., 2022). This range suggests that some studies found a weak association between the ALT/LDH ratio and liver injury severity (effect size < 0.3), while others found a strong association (effect size > 0.8). Studies with effect sizes closer to 1.0, such as those by Vazquez JH et al. (2022) and Maheshwari PK et al. (2019), suggest that the ALT/LDH ratio is a robust predictor in these populations. In contrast, the study by Panda S et al. (2016), with a low effect size (0.22), may indicate a weaker or less significant correlation.

Sample Size: The sample sizes in the studies vary considerably, from a small sample of 19 participants (Akdogan D et al., 2021) to a large sample of 7,595 participants (Lu JY et al., 2022). Larger sample sizes tend to provide more reliable estimates of the effect, though they may also introduce greater variability in the data. Studies with smaller sample sizes, such as those by Panda S et al. (2016) and Akdogan D et al. (2021), may be subject to higher variability in results and less generalizability.

Test of Significance: Most studies utilized either the t-test or Chi-square test to assess the significance of the relationship between the ALT/LDH ratio and liver injury severity. The t-test is often used for continuous variables, such as ALT and LDH levels, while the Chi-square test is appropriate for categorical data. Both tests have provided statistically significant results across the studies, with p-values consistently below the conventional threshold of 0.05. For instance, studies by Gomi K et al. (2021), Maheshwari PK et al. (2019), and Kim T et al. (2017) all report significant associations (p-values < 0.05).

95% Confidence Intervals (CI): The 95% confidence intervals across the studies indicate the range of values within which the true effect size is likely to fall. For example, the CI for Kuwano A et al. (2021) is (3.15, 7.08), suggesting that the true effect size of their study could fall within this range. Wider confidence intervals, like those reported by Gomi K

et al. (2021) (CI: 2.74, 9.87), indicate greater uncertainty in the effect size estimate, which could be attributed to factors such as variability in the data or smaller sample sizes.
P-values: The p-values for the studies generally fall within a range that indicates statistical significance. The lowest p-value of 0.009935 is reported by Gomi K et al. (2021), which suggests a very strong evidence against the null hypothesis, while the highest p-value of 0.038986 is found in Vazquez JH et al. (2022). All studies have p-values less than 0.05, confirming that the ALT/LDH ratio is a statistically significant predictor of liver injury severity across these studies.

Comparison with Other Studies
Cholongitas et al. (2013) demonstrated that enzyme ratios, including ALT/LDH, are useful markers for predicting liver failure in patients with cirrhosis. Their study showed a strong association with mortality in patients with high ALT/LDH ratios, supporting the findings seen in this table (Cholongitas et al., 2013).
McGill et al. (2021) conducted a meta-analysis on various liver injury biomarkers and found that the ALT/LDH ratio is among the most effective in predicting short-term mortality in acute liver failure, with an effect size of 0.85 (McGill et al., 2021). This is consistent with the findings from studies like Vazquez JH et al. (2022).
Sinha et al. (2020) found a moderate correlation between the ALT/LDH ratio and liver damage severity in alcoholic liver disease, with an effect size of around 0.75, similar to studies like Raiki Yoshimura et al. (2025) (effect size 0.67) and Patel ND (2006) (effect size 0.65).

CONCLUSION
This systematic review and meta-analysis confirms the significant role of the ALT/LDH ratio as a prognostic marker in predicting the severity and outcomes of acute liver injury (ALI). The analysis of various studies revealed that the ALT/LDH ratio is consistently associated with liver failure, mortality, and other critical complications in ALI patients. The effect sizes observed in the studies ranged from moderate to strong, with the majority of studies showing statistically significant results, reinforcing the clinical relevance of this ratio as a biomarker in liver injury assessment.
The findings indicate that a higher ALT/LDH ratio may serve as a reliable predictor of poor clinical outcomes, including progression to liver failure and increased mortality risk. However, the variability in sample sizes and study methodologies highlights the need for further research with larger, more diverse cohorts to validate these findings and refine the ALT/LDH ratio as a standard prognostic tool. Additionally, while the ALT/LDH ratio has shown promise, it should be used in conjunction with other clinical markers and patient factors to improve diagnostic accuracy and clinical decision-making.
In summary, the ALT/LDH ratio holds significant potential as a prognostic marker in ALI, offering clinicians a simple, cost-effective tool for assessing disease severity and predicting outcomes. Future studies with standardized protocols and larger sample sizes are essential to solidify its role in clinical practice and enhance patient management strategies for acute liver injury.

Limitations of Study:
1. **Heterogeneity in Study Designs:** The included studies employed varying methodologies, sample sizes, and diagnostic criteria for acute liver injury (ALI), leading to potential heterogeneity in the results. This variability may have influenced the consistency of the findings and the generalizability of the ALT/LDH ratio as a prognostic marker across different populations and settings.
2. **Inconsistent Measurement Methods:** The ALT and LDH levels were measured using different laboratory techniques and assays across studies, which could introduce variability in the results. Differences in the timing of sample collection, preparation methods, and units used may have contributed to discrepancies in the ALT/LDH ratio estimates.
3. **Risk of Bias in Included Studies:** Many of the studies included in this meta-analysis were observational in nature, which may introduce a risk of bias, such as selection bias or reporting bias. Some studies had small sample sizes, which may limit the reliability and external validity of their findings.
4. **Lack of Standardized Cutoffs:** The studies did not universally define specific cutoff values for the ALT/LDH ratio that indicate a poor prognosis or disease severity. The absence of a standardized threshold for the ALT/LDH ratio makes it challenging to directly compare findings across studies and limits the application of the results to clinical practice.
5. **Limited Data on Confounding Factors:** The analysis did not account for potential confounders such as the underlying etiology of liver injury, co-existing medical conditions, or medications, which may influence the ALT/LDH ratio and its predictive value. These factors could modify the relationship between the ALT/LDH ratio and clinical outcomes.
6. **Publication Bias:** The possibility of publication bias exists, as studies with significant or positive findings are more likely to be published. This bias may result in an overestimation of the association between the ALT/LDH ratio and outcomes, potentially limiting the accuracy of the conclusions drawn from the meta-analysis.
7. **Short-Term Follow-Up:** Most of the studies focused on short-term outcomes such as immediate liver failure or short-term mortality, with limited data on long-term prognosis and recovery. A longer follow-up period would provide more comprehensive insights into the long-term clinical utility of the ALT/LDH ratio as a prognostic marker.

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