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Nonlinear association between AST/ALT ratio and 28-day all-cause mortality following ICU admission in critically ill cirrhotic patients: a retrospective cohort study

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Abstract

Background The AST/ALT ratio is a biochemical marker associated with poor clinical outcomes in various patients, but its role in severe cirrhosis is unclear. This study investigated the relationship between the AST/ALT ratio and mortality in the intensive care unit (ICU) patients with cirrhosis.

Methods This retrospective cohort study analyzed 2,090 liver cirrhosis patients from the MIMIC-IV database, focusing on their first ICU admission between 2008 and 2019. The AST/ALT ratio, measured within 24 h of admission, was the exposure variable, and the main outcome was 28-day mortality. A multivariable logistic regression model evaluated the link between the AST/ALT ratio and mortality. Nonlinear relationships were explored using smooth curve fitting and saturation effect analyses. Stratified analyses and interaction tests were also performed based on demographic and clinical characteristics.

Results The study involved 2,090 critically ill liver cirrhosis patients, averaging 59.1 years old, with 65% male and a 28-day post-ICU admission mortality rate of 29%. The AST/ALT ratio was linked to mortality risk (adjusted odds ratio (OR) 1.1, 95% confidence interval (CI) 1.0–1.2; $p = 0.015$), showing a nonlinear pattern with a critical point at 3.6. Below this, each unit increase raised mortality risk by 40% (adjusted OR 1.4, 95% CI 1.2–1.6, $p < 0.001$), but the effect plateaued beyond this level (adjusted OR 1.0, 95% CI 0.8–1.1, $p = 0.600$). Subgroup analyses confirmed the consistent association, with interaction *P* values over 0.05.

Conclusions The AST/ALT ratio is an independent predictor of 28-day mortality in critically ill cirrhotic patients, with a nonlinear relationship (risk increases up to a ratio of ~ 3.6, then plateaus). This marker could enhance ICU risk stratification and inform clinical decision-making.

Keywords Cirrhosis, AST/ALT ratio, ICU mortality, Prognosis, Nonlinear association

Introduction

Globally, chronic liver cirrhosis poses a grave and growing public health threat [1, 2]. Recent research has demonstrated that in 2019, approximately 1.47 million individuals worldwide succumbed to cirrhosis and other chronic liver diseases, representing a 63.5% increase compared with 1990 [3]. In intensive care units (ICUs), patients suffering from cirrhosis generally exhibit more

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complex conditions and higher mortality rates compared to other ICU patients [4, 5]. Studies show that the ICU in-hospital mortality rate for cirrhosis patients can be as high as 52%. Reported ICU mortality rates for cirrhotic patients range from about 35% [6, 7] to as high as 42% within the ICU and 54% by hospital discharge in some studies [8]. These findings underscore the challenges of managing cirrhosis in intensive care settings. Cirrhosis is marked by fibrosis and nodule formation due to ongoing hepatocellular damage, significantly impairing liver structure and function [9]. As the disease advances, patients may experience severe complications, including portal hypertension, liver failure, and hepatic encephalopathy [10, 11]. These complications have a significant impact on patients'quality of life and result in a considerable increase in the requirement for intensive care treatment, particularly during acute decompensation [12].

The Child–Pugh and Model for End-stage Liver Disease (MELD) scores are commonly used to assess the prognoses of cirrhotic patients, but their effectiveness in ICUs is debated. Research findings suggest that the prognosis of cirrhotic patients in ICUs is influenced by complex, multifactorial interactions [13–15], emphasizing the necessity for more comprehensive assessment methods [16]. This highlights the need for additional research into prognostic markers for patients with advanced cirrhosis [17]. Recent studies have explored the integration of novel biomarkers and clinical parameters to increase prognostic accuracy [18, 19].

The aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio is a significant prognostic marker for liver diseases [20–22], with recent studies highlighting its association with poor outcomes in cirrhosis patients. This highlights its utility in assessing liver fibrosis and predicting outcomes in chronic liver disease cases [23].

Despite extensive literature on outpatients and general inpatients, the relationship between the AST/ALT ratio and short-term prognosis in cirrhotic patients in ICUs requires further study. Therefore, we utilized the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, a widely used public resource for intensive care research [24], to examine the association between the AST/ALT ratio and 28-day mortality following ICU admission in critically ill cirrhotic patients.

Materials and methods

Data source

This study utilized data from the MIMIC-IV, version 2.2, a publicly accessible database containing clinical information on over 52,000 patients admitted to Beth Israel Deaconess Medical Center between 2008 and 2019. Before accessing the database, scholars completed the Protecting Human Research Participants training program (certificate number 61979179) to ensure compliance with ethical standards in human subject research. The MIMIC-IV database employed rigorous deidentification protocols, safeguarding patient privacy and confidentiality.

Study population

This single-center retrospective cohort study analyzed 2,090 patients with liver cirrhosis admitted to the ICU for the first time. The liver cirrhosis diagnosis utilized ICD codes (Supplementary Table S1) from the MIMIC-IV database. Exclusion criteria included (1) liver cancer or other malignancies, (2) ICU stays under 24 h, (3) age below 18, and (4) missing outcome data or data for ALT or AST. Liver cirrhosis diagnosis was determined using ICD codes from the MIMIC-IV database. The data collection process utilized SQL to extract patient demographics, lab results, diagnoses, and treatment details from the MIMIC-IV database.

Variables

The exposure variable, the AST/ALT ratio, was derived from initial measurements taken within 24 h of ICU admission. Standard biochemical procedures were utilized to measure AST and ALT. The AST/ALT ratio was analyzed as a continuous variable and divided into tertiles for analysis. The main outcome assessed was 28-day all-cause mortality, defined as death from any cause within 28 days of ICU admission, regardless of whether the death occurred in the ICU, after transfer to a regular ward, or following hospital discharge. All patients were followed for at least 28 days or until death, whichever came first. For patients discharged from the hospital within the 28-day window, survival status was determined through the hospital's follow-up records in the MIMIC-IV database. Mortality status was ascertained through a comprehensive review of electronic health records in the MIMIC-IV database. The analysis incorporated the following covariates: age, sex, race, white blood cell (WBC) count, platelet count, hemoglobin, sodium, chloride, hypertension, acute kidney injury, mechanical ventilation, continuous renal replacement therapy (CRRT), Sequential Organ Failure Assessment (SOFA) score, MELD score, and the use of diuretics and vasoactive drugs. The selection of these covariates was informed by a comprehensive review of the extant literature and their clinical relevance to the prognosis of liver cirrhosis. It should be noted that while AST and ALT were measured within the first 24 h of ICU admission, intervention-related covariates (mechanical ventilation, vasopressors, CRRT) reflected treatments initiated at any point during the ICU stay. We acknowledged this temporal ambiguity might have resulted in adjusting for potential mediators

rather than solely confounders. Definitions and measurements of the aforementioned covariates followed standard procedures as outlined in the MIMIC-IV database.

Ethical

Approval for the study was obtained from the Institutional Review Boards of BIDMC and MIT. Due to its retrospective design and use of deidentified data, informed consent was waived. The research adhered to the Declaration of Helsinki, ensuring compliance with medical ethics in human subject research. The study design and reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to ensure the methodological and transparent presentation of observational research results.

Statistical analysis

We utilized the median with interquartile range (IQR) or the mean with standard deviation (SD), depending on data distribution, to analyze continuous variables. Categorical variables were presented as counts and percentages. Differences across AST/ALT ratio tertiles were analyzed using one-way ANOVA or the Kruskal–Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as applicable.

This study evaluated the relationship between the AST/ALT ratio and 28-day mortality following ICU admission using multivariable logistic regression models. The analysis employed three models: 1) an unadjusted model, 2) a model with minimal adjustments (considering age, sex, and race), and 3) a model with full adjustments. The fully modified model was selected based on clinical relevance and a > 10% change in the AST/ALT OR criterion. The selection of covariates was informed by the fully modified model. The ultimate model included these covariates: age, gender, ethnicity, heart rate, respiratory rate, high blood pressure, acute kidney injury, hepatorenal syndrome, ventilation, CRRT, vasoactive agents, diuretics, WBC count, hemoglobin, platelet count, potassium, sodium, chloride, SOFA score, and MELD score. ORs with 95% CIs were used to present the results. Multicollinearity among predictors was assessed using variance inflation factors (VIF), with values below 5 considered acceptable. The VIF analysis showed no significant multicollinearity issues among the selected covariates, with the highest VIF value of 3.8 observed for MELD score.

The AST/ALT ratio was analyzed as both a continuous and categorical variable to investigate potential nonlinear relationships. The dose–response relationship between the AST/ALT ratio and mortality was assessed to determine the cumulative effect of each parameter (Fig. 2). Furthermore, a saturation effect analysis was conducted using a two-piecewise logistic regression model. The optimal inflection point for the AST/ALT ratio was determined by adjusting the trial inflection point within a defined range (3.0–4.2) to maximize model likelihood through exploratory analysis. A log-likelihood ratio test was conducted to compare the single-line and two-piecewise logistic regression models. To ensure the robustness of our findings, we performed sensitivity analyses by varying the inflection points (3.0, 3.2, 3.4, 3.6, 3.8, 4.0 and 4.2) and comparing the model fit and effect estimates across different thresholds. Subgroup analyses were conducted to evaluate the consistency of relationships across different patient variables. For variables with 5–20% missing data, repeated imputation was employed. Statistical significance was determined at $P < 0.05$ for each analysis. All analyses were performed using Empower Stats (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) and R software version 3.6.3 (http://www.r-project.org).

Results

Baseline characteristics

The present study comprised 2,090 participants (Fig. 1), who were divided into three tertiles according to the AST/ALT ratio: low ($n = 697$), middle ($n = 696$), and high ($n = 697$). Table 1 provided a description of the baseline characteristics. The high AST/ALT ratio group was significantly younger (56.6 ± 11.8 years) and had a higher percentage of females (37.6%, 262/697) compared to the bottom tertile group (60.9 ± 12.5 years, 31.0% females, 216/697), with $p < 0.001$ and $p = 0.023$, respectively. Laboratory findings revealed lower hemoglobin and platelet counts ($p < 0.004$) in the high tertile group but higher INR, total bilirubin, and creatinine levels (all $p < 0.001$). Furthermore, a notable correlation was found between elevated disease severity scores (SOFA and MELD) and a high AST/ALT ratio ($p < 0.001$). The low tertile exhibited a higher prevalence of diabetes and hypertension, while the high tertile demonstrated an augmented incidence of hepatorenal syndrome (all $p < 0.05$). The two groups had notably different treatment needs, with the high AST/ALT ratio group having demonstrated a higher prevalence of CRRT and vasoactive agents ($p < 0.001$). With regard to the utilisation of diuretics, the middle tertile demonstrated the highest level of use ($p = 0.002$). 28-day mortality following ICU admission increased progressively across the three AST/ALT ratio categories, with rates of 20.1% (140 of 697), 29.2% (203 of 696), and 37.7% (263 of 697) ($p < 0.001$). These findings corresponded to an overall 28-day mortality rate of 29.0% (606/2,090) in our entire cohort of 2,090 patients, showing the stratification of mortality risk across different AST/ALT ratio levels.

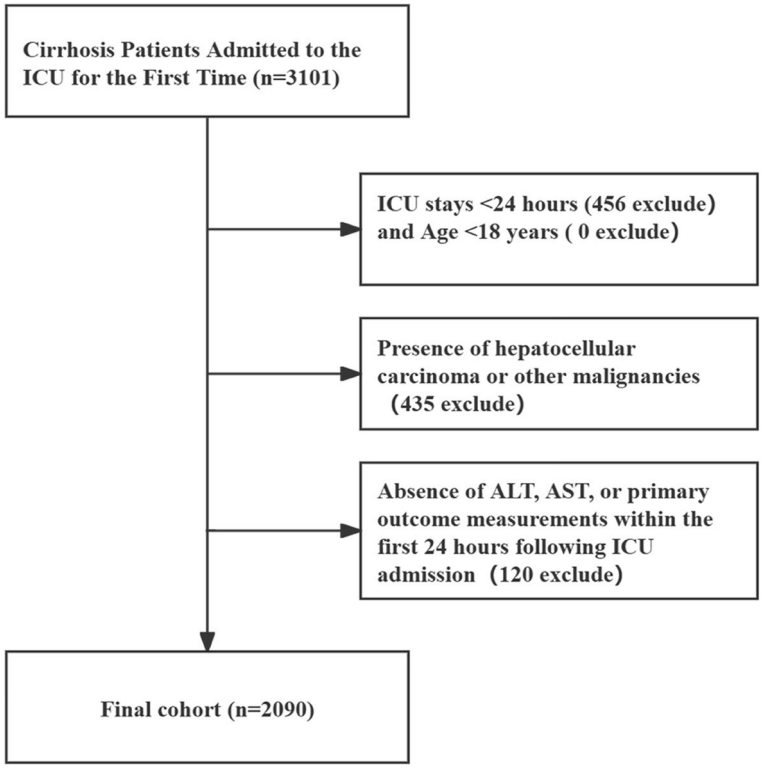

Fig. 1 Study selection process flowchart

Association between AST/ALT ratio and 28-day mortality following ICU admission

This study investigated the relationship between the AST/ALT ratio and clinical outcomes. The unadjusted continuous variable analysis indicated a 20% higher risk of the outcome event per unit increase in the AST/ALT ratio (OR = 1.2, 95% CI 1.1–1.3). Following the implementation of basic factor adjustment, this association exhibited marginal strengthening (OR = 1.3, 95% CI: 1.2–1.4). However, subsequent to further confounder adjustment, the association underwent attenuation yet retained its significance (OR = 1.1, 95% CI: 1.0–1.3). Tertile analysis revealed a nonlinear relationship. The findings of the study indicated that the middle and highest tertiles exhibited significantly elevated ORs (T2: OR = 1.6, 95% CI: 1.2–2.1; T3: OR = 2.0, 95% CI: 1.5–2.7) in comparison to the lowest tertile. The trend test was statistically significant across all models (p for trend < 0.001), supporting the hypothesis that there was an increasing risk with increasing AST/ALT ratios (see Table 2 for details). This association persisted after multiple adjustments, suggesting the AST/ALT ratio's potential as a prognostic indicator.

AST/ALT ratio and ICU mortality: a nonlinear saturation effect

The analysis of the saturation effect revealed a non-linear relationship between the AST/ALT ratio and 28-day mortality following ICU admission (Fig. 2). The initial linear model (Model I) revealed a modest yet statistically significant association (OR: 1.1, 95% CI: 1.0–1.3, $p = 0.002$). A piecewise logistic model (Model II) identified a more complex relationship, highlighted a turning point at an AST/ALT ratio of 3.6. The findings revealed a significant correlation for AST/ALT ratio below 3.6 (OR 1.4, 95% CI 1.2–1.6, $p < 0.001$), while no significant correlation was found for AST/ALT ratio above 3.6 (OR 1.0, 95% CI 0.8–1.1, $p = 0.600$). The log-likelihood ratio test ($p = 0.011$) indicated that Model II provided a significantly better fit, indicating a nonlinear connection with a saturation effect when the AST/ALT ratio reaches 3.6 (Table 3). Sensitivity analyses with varying inflection points (2.5, 3.0, 3.6, 4.0, and 4.5) consistently demonstrated a significant association between AST/ALT ratio and 28-day mortality following ICU admission below the threshold, with effect attenuation above the threshold (Supplementary Table S2). Among all tested inflection

Table 1 Baseline Characteristics of the Study Participants ($N = 2090$)

Characteristic	AST/ALT ratio tertiles				*P*
	Total ($N = 2090$)	**T1: < 1.6 ($n = 697$)**	**T2:1.6–2.4 ($n = 696$)**	**T3: > 2.4 ($n = 697$)**	
Demographics					
Age, years, mean ± SD	59.1 ± 12.1	60.9 ± 12.5	59.9 ± 11.5	56.6 ± 11.8	< 0.001
Male sex, n (%)	1450 (65.0%)	481 (69.0%)	443 (63.6%)	435 (62.4%)	0.023
Ethnicity, n (%)					0.154
White	1374 (65.7%)	459 (65.9%)	472 (67.8%)	443 (63.6%)	
Black	160 (7.7%)	48 (6.9%)	55 (7.9%)	57 (8.2%)	
Hispanic	129 (6.2%)	38 (5.5%)	50 (7.2%)	41 (5.9%)	
Other	427 (20.4%)	152 (21.8%)	119 (17.1%)	156 (22.4%)	
Comorbidities, n (%)					
Hypertension	1026 (49.1%)	370 (53.1%)	338 (48.6%)	318 (45.6%)	0.019
Diabetes	681 (32.6%)	280 (40.2%)	226 (32.5%)	175 (25.1%)	< 0.001
Congestive heart failure	184 (8.8%)	73 (10.5%)	60 (8.6%)	51 (7.3%)	0.113
Chronic kidney disease	419 (20.0%)	163 (23.4%)	122 (17.5%)	134 (19.2%)	0.019
Acute kidney injury	1746 (83.5%)	570 (81.8%)	575 (82.6%)	601 (86.2%)	0.059
Hepatorenal syndrome	298 (14.3%)	65 (9.3%)	112 (16.1%)	121 (17.4%)	< 0.001
Disease severity scores					
SOFA score, median [IQR]	8.0 [5.0–11.0]	7.0 [4.0–10.0]	8.0 [6.0–11.0]	9.0 [7.0–12.0]	< 0.001
MELD score, median [IQR]	18.2 [11.3–27.2]	14.8 [9.3–23.0]	18.3 [11.5–27.7]	21.2 [14.0–29.7]	< 0.001
Treatment modalities, n (%)					
Mechanical ventilation	1677 (80.2%)	554 (79.5%)	558 (80.2%)	565 (81.1%)	0.759
CRRT	274 (13.1%)	66 (9.5%)	88 (12.6%)	120 (17.2%)	< 0.001
Vasoactive agents	1067 (51.1%)	306 (43.9%)	355 (51.0%)	406 (58.2%)	< 0.001
Diuretics	763 (36.5%)	221 (31.7%)	283 (40.7%)	259 (37.2%)	0.002
Laboratory values					
WBC, × 10^9/L, median [IQR]	9.1 [6.0–14.3]	9.2 [6.0–14.4]	8.9 [6.0–13.5]	9.4 [5.9–14.9]	0.307
Hemoglobin, g/dL, median [IQR]	9.5 [8.2–10.9]	10.0 [8.6–11.5]	9.4 [8.1–10.7]	9.1 [7.7–10.4]	< 0.001
Platelets, × 10^9/L, median [IQR]	101.0 [65.0–155.0]	110.0 [70.5–168.0]	96.0 [64.0–148.0]	95.0 [60.0–146.0]	0.004
AST, U/L, median [IQR]	67.0 [39.0–146.0]	52.0 [31.0–124.0]	60.0 [39.0–113.0]	100.0 [56.0–202.0]	< 0.001
ALT, U/L, median [IQR]	34.0 [20.0–71.0]	42.0 [25.0–112.0]	30.0 [20.0–57.0]	30.0 [17.0–59.0]	< 0.001
Sodium, mEq/L, mean ± SD	136.7 ± 6.5	137.6 ± 6.0	136.7 ± 6.2	135.8 ± 7.1	< 0.001
Chloride, mEq/L, mean ± SD	102.5 ± 7.7	103.6 ± 7.1	102.9 ± 7.3	101.0 ± 8.5	< 0.001
INR, mean ± SD	1.9 ± 0.9	1.7 ± 1.0	1.9 ± 0.8	2.0 ± 0.9	< 0.001
Total bilirubin, mg/dL, median [IQR]	2.7 [1.2–6.9]	1.8 [0.9–4.2]	2.7 [1.3–6.5]	4.2 [1.8–9.7]	< 0.001
Creatinine, mg/dL, median [IQR]	1.2 [0.8–2.1]	1.1 [0.8–1.8]	1.2 [0.8–2.0]	1.3 [0.8–2.4]	0.004
Albumin, g/dL, mean ± SD	3.0 ± 0.7	3.0 ± 0.7	3.0 ± 0.7	3.0 ± 0.7	0.107
Outcome, n (%)					
28-day mortality following ICU admission	606 (29.0%)	140 (20.1%)	203 (29.2%)	263 (37.7%)	< 0.001

Abbreviations: *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *WBC* white blood cell, *INR* International Normalized Ratio, *SOFA* Sequential Organ Failure Assessment, *MELD* Model for End-stage Liver Disease, *CRRT* Continuous Renal Replacement Therapy

points, 3.6 yielded the optimal model fit based on log-likelihood ratio tests, confirming the robustness of our primary findings.

Subgroup analysis of the AST/ALT ratio and ICU mortality

In a large retrospective study of 2,090 critically ill cirrhotic patients from the MIMIC-IV database, the AST/ALT ratio was identified as a significant predictor of 28-day mortality following ICU admission. A positive correlation was found between the AST/ALT ratio and mortality risk, where each unit increase was associated with a 10% higher odds of 28-day mortality following ICU admission after adjusting for confounding factors. The identification of a novel nonlinear relationship,

Table 2 Correlation between aspartate aminotransferase to alanine aminotransferase (AST/ALT) ratio and 28-day mortality following intensive care unit (ICU) admission

Variable	Non-Adjusted OR, 95%CI, *p* value	Model 1 OR,95%CI, *p* value	Model 2 OR,95%CI, *p* value
AST/ALT ratio	1.2 (1.1, 1.3) < 0.001	1.3 (1.2, 1.4) < 0.001	1.1 (1.0, 1.3) 0.002
AST/ALT ratio tertile			
T1	Ref	Ref	Ref
T2	1.6 (1.3, 2.1) < 0.001	1.8 (1.4, 2.3) < 0.001	1.6 (1.2, 2.1) 0.003
T3	2.4 (1.9, 3.1) < 0.001	2.8 (2.1, 3.5) < 0.001	2.0 (1.5, 2.7) < 0.001
P for trend	< 0.001	< 0.001	< 0.001

Nonadjusted: Crude model without adjustment

Model 1: Adjusted for age, gender, and ethnicity

Model 2: Adjusted for age, sex, race, hypertension, acute kidney injury, hepatorenal syndrome, ventilation, CRRT, vasoactive agents, diuretics, WBC count, hemoglobin, platelet count, sodium, chloride, SOFA score, and MELD score

Abbreviations: *OR* odds ratio, *CI* confidence interval, *Ref* reference, *SOFA* Sequential Organ Failure Assessment, *MELD* Model for End-stage Liver Disease

marked by a saturation effect at an AST/ALT ratio of 3.6, is particularly significant. Below this threshold, the association was particularly pronounced, with each unit increase corresponding to a 40% higher mortality risk, whereas the relationship attenuated above this cutoff point. Stratified analyses (Fig. 3) suggested the AST/ALT ratio holds prognostic value across various subgroups (e.g., males, non-white patients, those with hypertension or MELD ≥ 18), although no significant interactions were found. Overall, our findings support that AST/ALT ratio is an independent prognostic marker in critically ill cirrhotic patients, one that could enhance risk assessment when combined with patient-specific factors.

Discussion

In this large retrospective analysis of 2,090 critically ill cirrhotic patients from the MIMIC-IV database, the AST/ALT ratio emerged as a significant predictor of 28-day mortality following ICU admission. After adjustment for confounding factors, each unit increase was associated with 10% higher mortality odds. We identified a nonlinear relationship characterized by a saturation effect at an AST/ALT ratio of 3.6. Below this threshold, each unit increase corresponded to 40% higher mortality risk, whereas the association attenuated above this cutoff. Stratified analyses demonstrated consistent prognostic significance across all examined subgroups, including sex, race, comorbidities, and disease severity, with no significant interaction effects observed. These findings enhance mortality risk assessment in critically ill cirrhotic patients, suggesting the AST/ALT ratio as a valuable prognostic marker when considered alongside patient-specific factors.

Previous research has established that elevated AST/ALT ratios predict increased mortality across various clinical conditions. Patients with acute myocardial infarction demonstrate higher mortality risks in both short and

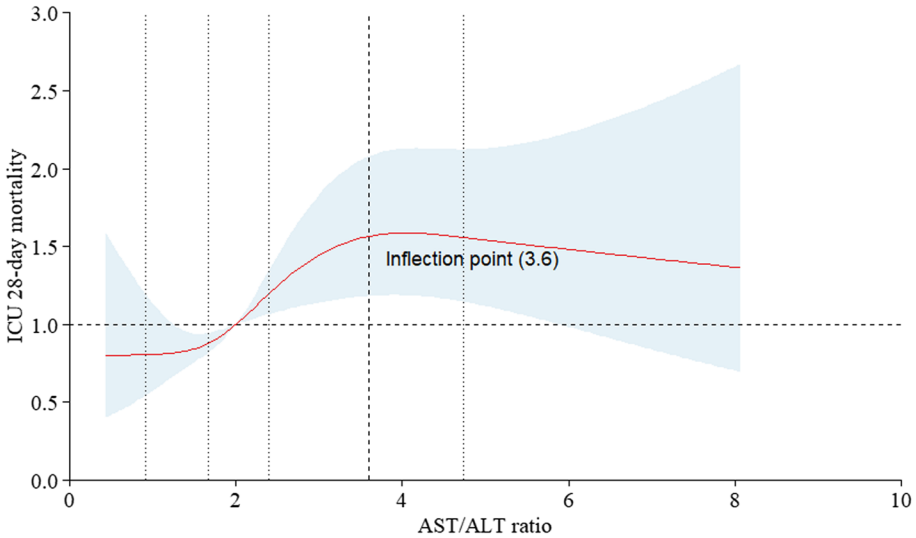

Fig. 2 Smooth curve fitting for the relationship between AST/ALT ratio and 28-day mortality following ICU admission. The red line represents the estimated probability of mortality, and the green lines indicate the 95% CIs. The analysis identified an inflection point at an AST/ALT ratio of 3.6 (indicated by the vertical dotted line), where the relationship between AST/ALT ratio and mortality risk changes significantly. Below this threshold, each unit increase in AST/ALT ratio was associated with a 40% increase in mortality risk (odds ratio [OR] = 1.4, 95% confidence interval [CI] 1.2–1.6, $p < 0.001$), while above 3.6, the relationship attenuated substantially (OR = 1.0, 95% CI 0.8–1.1, $p = 0.600$)

Table 3 Analysis of the saturation effect of the AST/ALT ratio on 28-day mortality following ICU admission

Model	OR (95% CI)	*P* value
Model I: Linear	1.1 (1.0, 1.3)	0.002
Model II: Piecewise Linear		
Inflection point of the AST/ALT ratio	3.6	
≤ 3.6	1.4 (1.2, 1.6)	< 0.001
> 3.6	1.0 (0.8, 1.1)	0.600
Log-likelihood ratio test	-	0.011

Model II was adjusted for demographic factors (age, gender, ethnicity) and clinical variables including hypertension, acute kidney injury, hepatorenal syndrome, ventilation status, CRRT, use of vasoactive agents and diuretics, as well as laboratory and scoring parameters such as WBC count, hemoglobin, platelet count, sodium, chloride, SOFA score, and MELD score

Abbreviations: *OR* odds ratio, *CI* confidence interval, *Ref* reference, *SOFA* Sequential Organ Failure Assessment, *MELD* Model for End-stage Liver Disease

long-term periods [25, 26]. Lu et al. [27] established that elevated AST/ALT ratios independently predict mortality in cardiac arrest patients during ICU stay and hospitalization. Similarly, Schupp et al. [28] documented associations between higher AST/ALT ratios and increased 30-day mortality in sepsis patients. Investigations by Liu [29] and Nakajima [30] confirmed strong correlations between AST/ALT ratios and mortality in hypertensive and elderly populations, respectively.

Despite these findings, limited evidence exists regarding the prognostic value of AST/ALT ratio in critically ill cirrhotic patients. Our investigation identified a significant nonlinear relationship between this ratio and 28-day mortality in first-time ICU-admitted cirrhotic patients, with a critical threshold of 3.6. Below this threshold, each unit increase corresponded to 40% higher mortality risk (OR = 1.4, 95% CI 1.2–1.6, $p < 0.001$), whereas the association attenuated above this value (OR = 1.0, 95% CI 0.8–1.1, $p = 0.600$). Sensitivity analyses confirmed this nonlinear relationship with an optimal threshold range of 2.5–4.5, enabling risk stratification and suggesting differential treatment approaches based on ratio values.

Although the specific mechanisms connecting a higher AST/ALT ratio to increased mortality risk remain unclear, the current findings highlight several significant potential pathways. It is important to acknowledge that AST is present in multiple tissues beyond the liver, including cardiac and skeletal muscle. In critically ill patients, AST elevation might result from non-hepatic causes such as myocardial or skeletal muscle injury. Biomarkers such as creatine kinase (CK) and troponin can help differentiate between hepatic and non-hepatic sources of AST elevation. The absence of these differentiating biomarkers in our analysis is a limitation that should be considered when interpreting the prognostic value of the AST/ALT ratio. Despite this limitation, elevated AST/ALT ratios indicate mitochondrial dysfunction and increased oxidative stress [31], contributing to multiorgan injury in critically ill patients [32, 33]. Furthermore, AST/ALT levels correlate positively with inflammatory markers including CRP, IL-4, IL-6, and TNF-α [34, 35], potentially amplifying inflammatory responses.

The observed nonlinear relationship reflects differential enzyme distribution and release kinetics [36, 37].

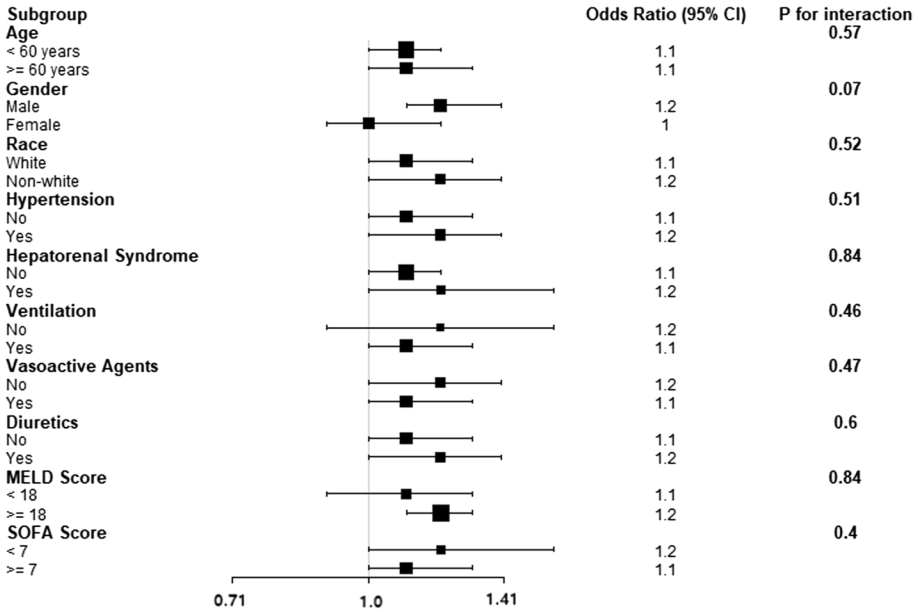

Fig. 3 Analysis of the correlation between the AST/ALT ratio and intensive care unit (ICU) mortality across different subgroups. Abbreviations: OR (odds ratio), CI (confidence interval), MELD (Model for End-stage Liver Disease), SOFA (Sequential Organ Failure Assessment)

AST exists in both cytosolic (20%) and mitochondrial (80%) forms across multiple organs, whereas ALT is predominantly cytosolic and liver-specific [37]. In early liver injury (AST/ALT ratio < 3.6), membrane permeability changes primarily release cytosolic enzymes [38]. As injury progresses, mitochondrial damage releases mitochondrial AST [39], representing transition to extensive necro-inflammatory damage [40].

The attenuated mortality correlation beyond the 3.6 threshold likely results from hepatocyte exhaustion, enzyme clearance saturation, and cellular trans-differentiation [41]. At higher ratios, extrahepatic factors including multiorgan failure become primary mortality determinants [42], with complications such as hepatorenal syndrome and coagulopathy predominating [43, 44].

Alternative biomarkers demonstrated significant elevations in the highest AST/ALT tertile, including INR (2.0 ± 0.9 vs 1.7 ± 1.0, $p < 0.001$), total bilirubin (4.2 vs 1.8 mg/dL, $p < 0.001$) [45, 46], and creatinine (1.3 vs 1.1 mg/dL, $p = 0.004$) [47]. MELD and SOFA scores were also significantly higher in this tertile [48], confirming that multi-organ assessment becomes increasingly important beyond the established threshold. Importantly, AST elevations may partially reflect extra-hepatic tissue injury rather than solely hepatic dysfunction, potentially confounding observed associations.

Our study presents several notable strengths. First, this large-scale retrospective cohort study utilizing the MIMIC-IV database encompassed 2,090 cirrhotic patients with first-time ICU admission. The substantial sample size enhances statistical reliability and provides comprehensive real-world data. Second, we employed multivariable logistic regression models with thorough adjustment for confounding factors, including demographics, laboratory results, comorbidities, and treatment modalities, strengthening the validity of our findings. Third, our application of piecewise logistic regression analysis identified a nonlinear relationship between the AST/ALT ratio and mortality risk, identifying a critical threshold of 3.6. Fourth, we performed extensive subgroup analyses to assess the AST/ALT ratio's predictive value across diverse populations, providing insights for personalized risk assessment.

However, several limitations warrant consideration. Our strict inclusion criteria, while strengthening internal validity, may limit generalizability. The exclusion of patients with liver cancer and other malignancies affects applicability to these populations, while inclusion of only patients with ICU stays exceeding 24 h might underestimate mortality in those with brief ICU stays. An important limitation is our reliance on single AST/ALT ratio measurements within 24 h of ICU admission, which may not capture temporal changes in liver function throughout ICU stay. Future studies incorporating serial measurements could provide valuable insights into how biomarker changes relate to prognosis. Additionally, identification of cirrhotic patients through ICD codes represents a significant limitation, as coding practices vary across institutions, clinicians, and time periods. Potential misclassification might have influenced our study population characteristics, and patients with early or compensated cirrhosis might not be accurately captured, potentially biasing our sample toward more severe cases.

Furthermore, our analysis based on data from a single US medical center may not be broadly generalizable to other geographic and demographic settings. This retrospective observational study identifies correlation, not causation, between the AST/ALT ratio and 28-day mortality following ICU admission. Despite adjustments for known confounders, unmeasured variables may influence results. Genetic polymorphisms affecting hepatic enzymes may modify AST/ALT-mortality relationships [49]. Prior liver function status represents another potential confounder, as baseline hepatic reserve affects outcomes but may not be fully captured in the database [50]. Concurrent infections may independently elevate transaminases while increasing mortality risk [51]. Nutritional status and sarcopenia, significant predictors of survival in cirrhosis, could also confound observed associations [52]. Moreover, medication history and alcohol consumption may affect both AST/ALT ratios and outcomes [53].

A notable limitation is our inability to account for cirrhosis etiology (alcoholic, viral, or NASH), which may independently influence both baseline AST/ALT ratios and mortality risk. For instance, alcoholic liver disease often elevates AST/ALT ratio regardless of disease severity, potentially confounding our observed association. The study's exclusive focus on short-term outcomes, rather than long-term prognosis, represents an additional limitation.

A critical limitation is the non-specificity of the AST/ALT ratio as a liver marker. While interpreted primarily as an indicator of liver dysfunction or fibrosis, AST may be elevated due to injury in various organs including muscle, heart, and other tissues. In critically ill patients with potential multi-organ dysfunction, conditions such as acute myocardial injury or rhabdomyolysis could contribute to elevated AST levels independently of liver status. Ideally, specific biomarkers such as CK (for muscle injury) and troponin (for cardiac injury) would help differentiate the source of AST elevation. Future prospective studies should incorporate these biomarkers to better isolate liver-specific AST elevation and thus provide more precise interpretation of the

AST/ALT ratio's prognostic value in cirrhotic patients. Despite this limitation, our findings in a confirmed cirrhotic population suggest that the AST/ALT ratio remains a valuable prognostic tool, though clinicians should consider potential extrahepatic sources of AST elevation when interpreting individual cases. Our dataset did not permit isolation of liver-origin AST from other sources. Therefore, the prognostic value observed might partially reflect overall illness severity or extrahepatic organ injury, both independently associated with increased mortality risk.

Furthermore, our study spans 2008–2019, during which ICU management strategies for cirrhosis evolved, including potential changes in vasopressor protocols, renal support approaches, and complication treatments. We did not adjust for admission year or analyze temporal trends, representing a limitation as practice changes could influence outcomes. Additionally, the MIMIC-IV database may incompletely capture certain comorbidities like heart failure and diabetes, potentially affecting our multivariable analysis. Despite including comprehensive clinical variables and severity scores to mitigate this limitation, future prospective studies with more complete clinical data are needed to validate our findings.

Conclusions

In This single-center study suggests a nonlinear relationship between the AST/ALT ratio and 28-day all-cause mortality in critically ill cirrhotic patients, with a potential inflection point at 3.6. While these findings indicate the possible prognostic significance of the AST/ALT ratio, they require validation in independent external cohorts before clinical application.

Abbreviations

AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
CI	Confidence Interval
ICU	Intensive Care Unit
CRRT	Continuous Renal Replacement Therapy
IQR	Interquartile Range
INR	International Normalized Ratio
MIMIC-IV	Medical Information Mart for Intensive Care IV
MELD	Model for End-stage Liver Disease
OR	Odds Ratio
Ref	Reference
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
WBC	White Blood Cell

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

XZG designed the study, extracted the data, performed the statistical analyses, and drafted the manuscript. XBH critically reviewed and approved the final version of the manuscript for submission. All authors read and approved the final manuscript.

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Data availability

The datasets presented in the current study are available in the MIMIC-IV database (https://physionet.org/content/mimiciv/).

Declarations

Ethics approval and consent to participate

The investigation complied with the Helsinki Declaration's guidelines. The review committees at Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology approved the use of the MIMIC-IV database. The MIMIC-IV database makes the data freely available, hence this study did not require an informed consent form or an ethical approval declaration.
The requirement for individual patient consent was waived as this study utilized the de-identified MIMIC-IV database. The original database received consent during its establishment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019;70:151–71. https://doi.org/10.1016/j.jhep.2018.09.014.
2. Liu ZP, Ouyang GQ, Huang GZ, Duan TY, Chen L, Cai JG. Global burden of cirrhosis and other chronic liver diseases due to nonalcoholic fatty liver disease, 1990–2019. World J Hepatol. 2023;15:1210–25. https://doi.org/10.4254/wjh.v15.i11.1210.
3. Wang Y, Wang M, Liu C, Shi XD, Zhang YN, Wang X. Global burden of liver cirrhosis 1990–2019 and 20 years forecast: results from the global burden of disease study 2019. Ann Med. 2024;56:2328521. https://doi.org/10.1080/07853890.2024.2328521.
4. Dong V, Karvellas CJ. Acute-on-chronic liver failure: Objective admission and support criteria in the intensive care unit. JHEP Rep. 2019;1:44–52. https://doi.org/10.1016/j.jhepr.2019.02.005.
5. Majeed A, Bailey M, Kemp W, Bellomo R, Pilcher D, Roberts SK. Improved survival of cirrhotic patients with infections in Australian and New Zealand ICUs between 2005 and 2017. Liver Int. 2023;43:49–59. https://doi.org/10.1111/liv.15285.
6. Huang YF, Lin CS, Cherng YG, Yeh CC, Chang CL, Fan SZ, et al. A population-based cohort study of mortality of intensive care unit patients with liver cirrhosis. BMC Gastroenterol. 2020;20:15. https://doi.org/10.1186/s12876-020-1163-1.
7. Chebl RB, Tamim H, Sadat M, Qahtani S, Dabbagh T, Arabi YM. Outcomes of septic cirrhosis patients admitted to the intensive care unit: A retrospective cohort study. Medicine (Baltimore). 2021;100:e27593. https://doi.org/10.1097/MD.0000000000027593.

8. Lindenmeyer CC, Flocco G, Sanghi V, Lopez R, Kim AJ, Niyazi F, et al. LIV-4: A novel model for predicting transplant-free survival in critically ill cirrhotics. World J Hepatol. 2020;12:298–311. https://doi.org/10.4254/wjh.v12.i6.298.
9. Das PP, Medhi S. Role of inflammasomes and cytokines in immune dysfunction of liver cirrhosis. Cytokine. 2023;170:156347. https://doi.org/10.1016/j.cyto.2023.156347.
10. Zhu Q, Chen D, Lou Y, Zhang L, Yan Z, Zhang W, et al. Baseline ALBI Grade Predicts Benefits After Splenectomy for Cirrhosis-Related Hypersplenism. J Gastrointest Surg. 2023;27:1130–40. https://doi.org/10.1007/s11605-023-05610-2.
11. Manning C, Elzubeir A, Alam S. The role of pre-emptive Transjugular Intrahepatic Portosystemic Shunt in acute variceal bleeding: a literature review. Ther Adv Chronic Dis. 2021;12:2040622321995771. https://doi.org/10.1177/2040622321995771.
12. Nagel M, Labenz C, Wörns MA, Toenges G, Sprinzl MF, Nguyen-Tat M, et al. Impact of acute-on-chronic liver failure and decompensated liver cirrhosis on psychosocial burden and quality of life of patients and their close relatives. Health Qual Life Outcomes. 2020;18:10. https://doi.org/10.1186/s12955-020-1272-0.
13 Smith TN, Gallo de Moraes A, Simonetto DA. Cirrhosis management in the intensive care unit. Semin Liver Dis. 2023;43:117–32. https://doi.org/10.1055/a-2015-1290.
14. Gao F, Lin MT, Yang XY, Yao SY, Liu LH, Yao LT, et al. Metabolic acidosis in critically ill patients with cirrhosis: Epidemiology and short-term mortality risk factors. Turk J Gastroenterol. 2019;30:883–91. https://doi.org/10.5152/tjg.2019.18813.
15. Kamran M, Khalid AB, Siddiqui HAB, Aftab A, Azmat R. Predictors of outcome of cirrhotic patients requiring invasive mechanical ventilation: Experience from a non-transplant tertiary care hospital in Pakistan. Cureus. 2022;14:e21517. https://doi.org/10.7759/cureus.21517.
16. Karagiannakis DS, Stefanaki K. Spleen stiffness: a predictive factor of dismal prognosis in liver cirrhosis. Clin J Gastroenterol. 2023;16:121–9. https://doi.org/10.1007/s12328-023-01782-3.
17. Mitra LG, Rajput G, Saluja V, Kumar G. EEG abnormality as a prognostic factor in cirrhotic patients with Grade III-IV hepatic encephalopathy requiring mechanical ventilation: A retrospective analysis. J Clin Transl Res. 2021;7:467–72. https://doi.org/10.18053/jctres.07.202104.003.
18. Ferrarese A, Frigo AC, Mion MM, Pinto A, Burra P, Russo FP. Diagnostic and prognostic role of presepsin in patients with cirrhosis and bacterial infection. Clin Chem Lab Med. 2021;59:775–82. https://doi.org/10.1515/cclm-2020-1212.
19. Chen SH, Wan QS, Wang T, Zhang KH. Fluid biomarkers for predicting the prognosis of liver cirrhosis. Biomed Res Int. 2020;2020:7170457. https://doi.org/10.1155/2020/7170457.
20. Xu J, Xia Y, Li S, Xu Y, Zhang JF, Zhou J, et al. A retrospective pilot study to examine the potential of aspartate aminotransferase to alanine aminotransferase ratio as a predictor of postoperative acute kidney injury in patients with hepatocellular carcinoma. Ann Clin Biochem. 2019;56:357–66. https://doi.org/10.1177/0004563218817797.
21. Shen J, Dai J, Zhang Y, Ma Q, Tian R, Zhang D, et al. Baseline HBV-DNA load plus AST/ALT ratio predicts prognosis of HBV-related hepatocellular carcinoma after hepatectomy: A multicentre study. J Viral Hepat. 2021;28:1587–96. https://doi.org/10.1111/jvh.13606.
22. Huo RR, Pan LX, Wu PS, Chen HZ, Zheng JL, Yao HC, et al. Prognostic value of aspartate aminotransferase/alanine aminotransferase ratio in hepatocellular carcinoma after hepatectomy. BJS Open. 2024;8:zrad155. https://doi.org/10.1093/bjsopen/zrad155.
23. Liu HM, Li H, Deng GH, Pan CL, Sheng JH, Yin B, et al. Association of AST/ALT ratio with 90-day outcomes in patients with acute exacerbation of chronic liver disease: a prospective multicenter cohort study in China. Front Med (Lausanne). 2024;11:1307901. https://doi.org/10.3389/fmed.2024.1307901.
24. Johnson AEW, Bulgarelli L, Shen L, Gayles A, Shammout A, Horng S, et al. MIMIC-IV, a freely accessible electronic health record dataset. Sci Data. 2023;10:1. https://doi.org/10.1038/s41597-022-01899-x.
25. Steininger M, Winter MP, Reiberger T, Koller L, El-Armouche A, Bartko PE, et al. De-Ritis ratio improves long-term risk prediction after acute myocardial infarction. J Clin Med. 2018;7:474. https://doi.org/10.3390/jcm7120474.
26. Ndrepepa G, Holdenrieder S, Kastrati A. Prognostic value of De Ritis ratio in patients with acute myocardial infarction. Clin Chim Acta. 2022;535:75–81. https://doi.org/10.1016/j.cca.2022.08.019.
27. Lu Z, Ma G, Chen L. De-Ritis ratio is associated with mortality after cardiac arrest. Dis Markers. 2020;2020:8826318. https://doi.org/10.1155/2020/8826318.
28. Schupp T, Weidner K, Rusnak J, Kaier K, Hammer M, Findeisen P, et al. Diagnostic and prognostic value of the AST/ALT ratio in patients with sepsis and septic shock. Scand J Gastroenterol. 2023;58:392–402. https://doi.org/10.1080/00365521.2022.2131331.
29. Liu H, Ding C, Hu L, Wang X, Jiang Y, Zhang Y, et al. The association between AST/ALT ratio and all-cause and cardiovascular mortality in patients with hypertension. Medicine (Baltimore). 2021;100:e26693. https://doi.org/10.1097/MD.0000000000026693.
30. Nakajima K, Yuno M, Tanaka K, Nakamura T. High aspartate aminotransferase/alanine aminotransferase ratio may be associated with all-cause mortality in the elderly: A retrospective cohort study using artificial intelligence and conventional analysis. Healthc (Basel). 2022;10:692. https://doi.org/10.3390/healthcare10040692.
31. Botezelli JD, Cambri LT, Ghezzi AC, Dalia RA, Voltarelli FA, de Mello MAR. Fructose-rich diet leads to reduced aerobic capacity and to liver injury in rats. Lipids Health Dis. 2012;11:78. https://doi.org/10.1186/1476-511X-11-78.
32. Li Y, Tao Y, Xu J, Zhou L, Deng J, Zhao S, et al. Hyperoxia provokes time- and dose-dependent gut injury and endotoxemia and alters gut microbiome and transcriptome in mice. Front Med (Lausanne). 2021;8:732039. https://doi.org/10.3389/fmed.2021.732039.
33. Dresen E, Pimiento JM, Patel JJ, Heyland DK, Rice TW, Stoppe C. Overview of oxidative stress and the role of micronutrients in critical illness. JPEN J Parenter Enteral Nutr. 2023;47:170–83. https://doi.org/10.1002/jpen.2421.
34. Wang J, Li J, Ren Y, Xia J, Zhang X, Zhao Y, et al. Association between alanine aminotransferase/aspartate aminotransferase ratio (AST/ALT ratio) and coronary artery injury in children with Kawasaki disease. Cardiol Res Pract. 2020;2020:8743548. https://doi.org/10.1155/2020/8743548.
35. Xu J, Shi X, Pan Y. The association of aspartate aminotransferase/alanine aminotransferase ratio with diabetic nephropathy in patients with type 2 diabetes. Diabetes Metab Syndr Obes. 2021;14:3831–7. https://doi.org/10.2147/DMSO.S330741.
36. Smith AK, Ropella GEP, McGill MR, Krishnan P, Dutta L, Kennedy RC, et al. Contrasting model mechanisms of alanine aminotransferase (ALT) release from damaged and necrotic hepatocytes as an example of general biomarker mechanisms. PLoS Comput Biol. 2020;16:e1007622. https://doi.org/10.1371/journal.pcbi.1007622.
37. Giannini EG, Testa R, Savarino V. Mechanisms of liver enzyme abnormalities in patients with cirrhosis. Clin Liver Dis. 2017;9:138–40. https://doi.org/10.1002/cld.617.
38. Botros M, Sikaris KA. The De Ritis ratio: the test of time. Clin Biochem Rev. 2013;34:117–30.
39. Contreras-Zentella ML, Hernández-Muñoz R. Is liver enzyme release really associated with cell necrosis induced by oxidant stress? Oxid Med Cell Longev. 2016;2016:3529149. https://doi.org/10.1155/2016/3529149.
40. Bessone F, Dirchwolf M, Rodil MA, Razori MV, Roma MG. The severity of DILI according to baseline liver disease: is chronic liver disease a risk factor for severe DILI? Expert Opin Drug Metab Toxicol. 2022;18:223–33. https://doi.org/10.1080/17425255.2022.2032253.
41. Woolbright BL, Jaeschke H. Mechanisms of inflammatory liver injury and drug-induced hepatotoxicity. Curr Pharmacol Rep. 2018;4:346–57. https://doi.org/10.1007/s40495-018-0147-0.
42. Téllez L, Guerrero A. Management of liver decompensation in advanced liver disease (renal impairment, liver failure, adrenal insufficiency, cardiopulmonary complications). Clin Drug Investig. 2022;42(Suppl 1):15–23. https://doi.org/10.1007/s40261-022-01149-3.
43. Clària J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis. Hepatology. 2016;64:1249–64. https://doi.org/10.1002/hep.28740.
44. Piano S, Tonon M, Angeli P. Management of ascites and hepatorenal syndrome. Hepatol Int. 2018;12(Suppl 1):122–34. https://doi.org/10.1007/s12072-017-9815-0.
45. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011;365:147–56. https://doi.org/10.1056/NEJMra1011170.

46. Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Ginès P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol. 2014;61:1038–47. https://doi.org/10.1016/j.jhep.2014.06.012.
47. Angeli P, Garcia-Tsao G, Nadim MK, Parikh CR. News in pathophysiology, definition and classification of hepatorenal syndrome: A step beyond the International Club of Ascites (ICA) consensus document. J Hepatol. 2019;71:811–22. https://doi.org/10.1016/j.jhep.2019.07.002.
48. Arroyo V, Moreau R, Jalan R. Acute-on-Chronic Liver Failure. N Engl J Med. 2020;382:2137–45. https://doi.org/10.1056/NEJMra1914900.
49. Valenti L, Rametta R, Dongiovanni P, Maggioni M, Fracanzani AL, Zappa M, et al. Genetic variants regulating insulin receptor signalling are associated with the severity of liver damage in patients with non-alcoholic fatty liver disease. Gut. 2010;59:267–73. https://doi.org/10.1136/gut.2009.190801.
50. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144:1426–37. https://doi.org/10.1053/j.gastro.2013.02.042.
51. Wong F, O'Leary JG, Reddy KR, Patton H, Kamath PS, Fallon MB, et al. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. Gastroenterology. 2013;145:1280–8. https://doi.org/10.1053/j.gastro.2013.08.051.
52. Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, et al. Muscle wasting is associated with mortality in patients with cirrhosis. Clin Gastroenterol Hepatol. 2012;10:166–73. https://doi.org/10.1016/j.cgh.2011.08.028.
53. Liangpunsakul S, Chalasani N. Treatment of alcoholic liver disease: Is it time for nutritional support and herbal remedies? Hepatology. 2019;70:1520–2. https://doi.org/10.1002/hep.30798.

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