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Association between aspartate aminotransferase to alanine aminotransferase ratio and mortality in critically ill patients with end stage renal disease

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The aspartate aminotransferase to alanine aminotransferase (AST/ALT) ratio has been extensively studied in relation to mortality, yet its specific association with intensive care unit (ICU) mortality in end stage renal disease (ESRD) patients remains underexplored. The study investigated this relationship in critically ill ESRD patients. This multicenter retrospective cohort study analyzed data from ESRD patients admitted to 208 ICUs across the United States between 2014 and 2015 using the eICU Collaborative Research Database. Smooth curve fitting with Generalized Additive Model and two-piecewise linear regression analyses were utilized to examine nonlinear relationships. Among the 3005 patients (mean age 62.68 ± 14.16 years; 54.48% male), 252 (8.39%) died in the ICU. A significant nonlinear relationship between the AST/ALT ratio and ICU mortality was identified with an inflection point of 1.59. For AST/ALT ratios ≤ 1.59, each unit increase was associated with a 2.02-fold higher risk of ICU mortality (OR 2.02, 95% CI 1.22–3.33, *P* = 0.0059). For AST/ALT ratios > 1.59, no significant association with mortality was observed (OR 1.07, 95% CI 0.86–1.33, *P* = 0.5348). Sensitivity analyses confirmed the robustness of these findings. In critically ill ESRD patients, a nonlinear relationship exists between AST/ALT ratio and ICU mortality.

Keywords Aspartate aminotransferase, Alanine aminotransferase, Mortality, End stage renal disease, Cohort

Abbreviations

AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ICU	Intensive care unit
ESRD	End stage renal disease
eICU-CRD	eICU Collaborative Research Database
BUN	Blood urea nitrogen
APACHE-IV	Acute physiology and chronic health evaluation-IV
ACS	Acute coronary syndrome
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
OR	Odds ratio
CI	Confidence intervals

End stage renal disease (ESRD), defined as chronic kidney disease (CKD) stage 5 with an estimated glomerular filtration rate (eGFR) below 15 mL/min/1.73 m^2, represents the final stage of renal function decline requiring renal replacement therapy[1]. In 2018, ESRD prevalence in the United States reached 2,242 cases per million people,

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with approximately 131,000 new diagnoses annually[2]. Despite modern hemodialysis techniques, mortality rates in ESRD patients remain high, ranging from 20 to 50%[3,4]. While research has established diabetes, hypertension, glomerulonephritis, obesity, age, and specific medications as primary ESRD causes[3–7], these underlying conditions frequently overlap in intensive care unit (ICU) patients with ESRD. Consequently, researchers have increasingly focused on identifying biomarkers to monitor ESRD progression[8,9]. Liver comorbidities commonly occur in ESRD patients, with a significant proportion exhibiting hepatic dysfunction or abnormal liver enzyme profiles, necessitating careful monitoring of liver function tests, particularly transaminase levels[10–14].

Aspartate aminotransferase (AST) is distributed in both mitochondria and cytoplasm of various tissues, including the liver, kidney, brain, heart, and skeletal muscle, whereas alanine transaminase (ALT) is predominantly found in liver cytoplasm[15]. While ALT primarily indicates liver dysfunction, AST may also reflect mitochondrial dysfunction caused by oxidative stress in other organs, albeit to a lesser extent[15]. The AST/ALT ratio is calculated by dividing serum AST by ALT levels, both enzymes crucial for amino acid metabolism that are released into the bloodstream during hepatocyte damage[16–18]. Although elevated AST/ALT ratios correlate with severe liver fibrosis and decreased hepatic function[19], they are also associated with systemic conditions including ischemic-reperfusion injury, inflammatory responses, and increased oxidative stress[20,21]. Higher AST/ALT ratios have been linked to worse outcomes across multiple conditions, including diabetes, congestive heart failure (CHF), hypertension, acute myocardial infarction (AMI), sepsis, and cancer[22–27].

However, limited research exists on the relationship between AST/ALT levels and mortality in ESRD patients. The AST/ALT ratio in ESRD patients may be confounded by multiple factors, including liver dysfunction, inflammatory states and sepsis[8,14,26]. To examine the association between baseline AST/ALT ratio (measured within 24 h of ICU admission) and the ICU mortality among critically ill ESRD patients, we conducted a multicenter retrospective cohort study using the eICU Collaborative Research Database (eICU-CRD) v2.0.

Methods

Study design

In this multicenter retrospective cohort study, we examined baseline AST/ALT ratio as the independent variable and ICU mortality in ESRD patients as the dependent variable (categorized as death or survival).

Data source

The eICU-CRD is an open-access, multicenter resource designed for critical care research[28]. This database contains comprehensive clinical data from 200,859 patients admitted to ICUs across 208 US hospitals between 2014 and 2015[28]. It includes essential clinical information such as diagnoses, vital signs, disease severity scores, nursing care plans, and treatment interventions. Researchers can access this data after registration, following the MIT Ethics Committee's requirements (Record ID: 63069214) and in accordance with the Declaration of Helsinki principles.

Study population

In the current study, ESRD was defined according to international guidelines[1,2] as either an eGFR < 15 mL/min/1.73 m^2 (CKD stage 5) or the requirement for chronic renal replacement therapy (hemodialysis or peritoneal dialysis). ESRD patients were identified from the eICU-CRD using International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) codes. This study was selected by particular exclusion criteria: (1) non-ESRD patients; (2) Age < 18 years; (3) ICU stay time < 24 h; (4) Missing ICU outcome; (5) Missing AST; (6) Missing ALT; (6) Extreme AST/ALT values (three standard deviations below or above the mean). After applying these criteria, 3,005 individuals participated in the analysis. Figure 1 depicts the participant selection procedure.

Variables

We first measured baseline AST/ALT ratio (measured within 24 h of ICU admission) as a continuous quantity. It was then classified into tertiles. The study's endpoint was all-cause ICU mortality following admission to the ICU.

Covariates

The selection of covariates was guided by clinical experience and previous research[4,8,29–33]. The variables included were: (1) categorical variables: gender, ethnicity, hypertension, chronic obstructive pulmonary disease (COPD), acute coronary syndrome (ACS), CHF, diabetes, sepsis, cancer, anticoagulants, antiplatelet, vancomycin, levofloxacin, glucocorticoids, carbapenems, vasopressor, dialysis, and mechanical ventilation; (2) continuous variables: creatinine, blood urea nitrogen (BUN), age, albumin, platelet, hemoglobin, body mass index (BMI) and Acute Physiology and Chronic Health Evaluation-IV score (APACHE-IV score)[34]. All baseline values were obtained within the first 24 h after ICU admission.

Missing data processing

Missing data in our study included: BUN (1, 0.03%), Creatinine (2, 0.07%), Platelet (13, 0.43%), Albumin (23, 0.77%), BMI (119, 3.96%), and APACHE-IV score (405, 13.48%). Multiple imputations were employed to address missing covariate data[35–38]. The imputation model incorporated gender, age, ethnicity, hypertension, COPD, ACS, CHF, diabetes, sepsis, cancer, anticoagulant, antiplatelet, hemoglobin, vancomycin, levofloxacin, glucocorticoid, carbapenem, dialysis, vasopressor, and mechanical ventilation.

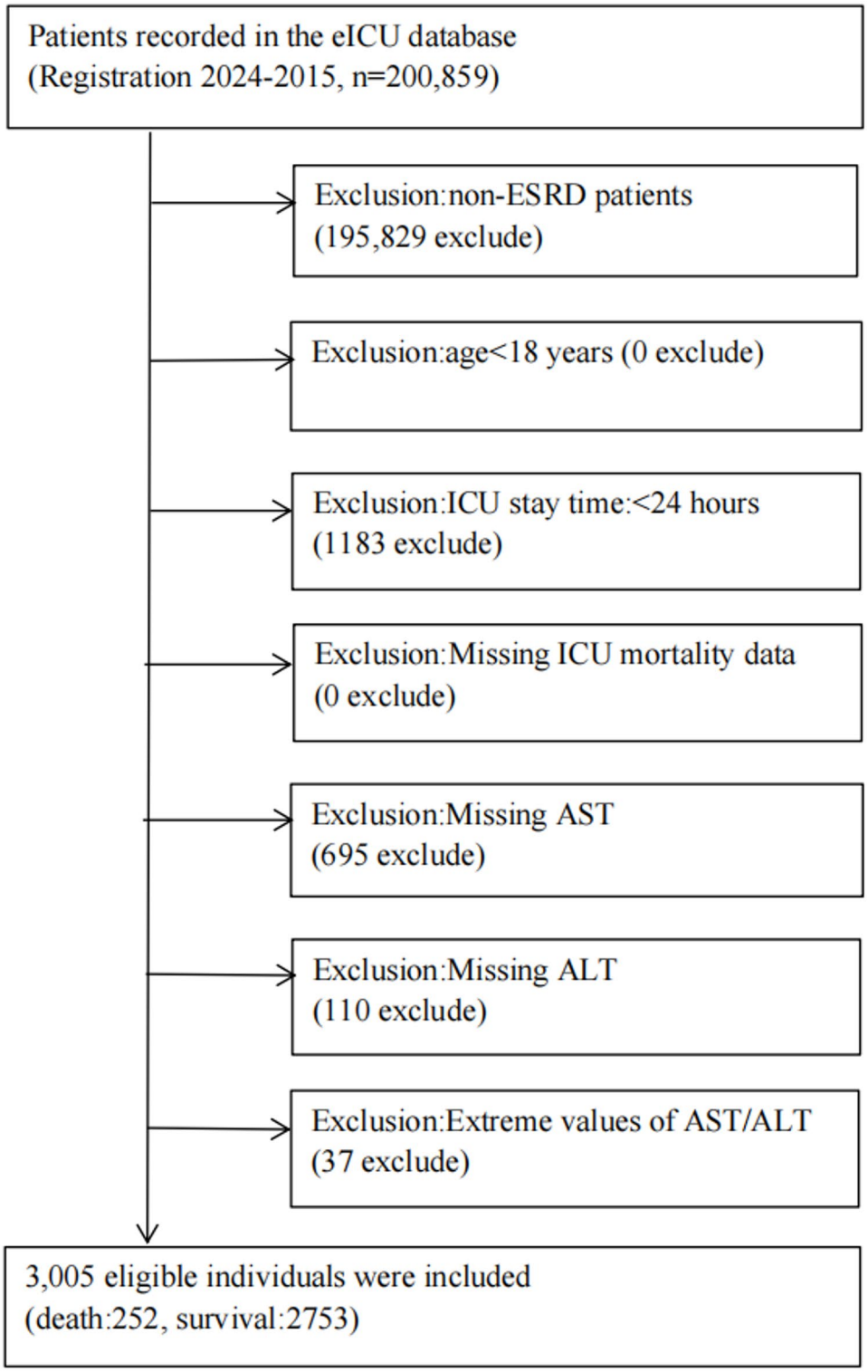

Fig. 1. Flowchart of study participants.

Statistical analysis

Continuous variables were presented as mean ± SD (normal distribution) or median (Q1-–Q3), and categorical variables as n (%). Between group comparisons used Student's t-test (normal distribution), χ^2 test (categorical variables), or Mann–Whitney U test (skewed distribution).

Multivariate linear regression models were used to investigate the relationship between AST/ALT and ICU mortality. Covariates were selected if they altered odds ratios (OR) by ≥ 10%[39]. Effect estimates were recorded with 95% confidence interval (CI). We constructed three models: Crude model: No adjustments. Model I: Adjusted

for age, gender, and ethnicity. Model II: Adjusted for creatinine, gender, BUN, age, ethnicity, albumin, platelet, hypertension, COPD, ACS, CHF, diabetes, sepsis, cancer, APACHE-IV, anticoagulant, antiplatelet, hemoglobin, vancomycin, levofloxacin, glucocorticoid, carbapenem, vasopressor, mechanical ventilation, dialysis, and BMI.

Potential nonlinearity was assessed using Generalized Additive Model with smooth curve fitting[40]. When nonlinearity was detected, we identified inflection points using recursive algorithms and constructed two-piecewise linear models, comparing them with standard linear models using likelihood ratio tests[40]. Robustness was validated through sensitivity analyses, including stratified regression models with interaction testing and E-value calculation[41] to assess unmeasured confounding potential.

All analyses followed STROBE guidelines[39] and were performed using R (version 4.2.0) and EmpowerStats (version 4.2), with significance set at $P < 0.05$.

Results

Characteristics of participants

Continuous data were presented as mean ± SD or median (Q1-–Q3), and categorical data as n (%). AST aspartate aminotransferase, ALT alanine aminotransferase, BUN blood urea nitrogen, APACHE-IV acute physiology and chronic health evaluation-IV, ACS acute coronary syndrome, CHF congestive heart failure, COPD chronic obstructive pulmonary disease, CRP C-reactive protein.

Figure 2 shows AST/ALT ratios ranging from 0.12 to 5.67 (median 1.29). Table 1 displays the baseline characteristics. Among 3005 participants (mean age 62.68 ± 14.16 years, 54.48% male), ICU mortality was 8.39% (252/3005). AST/ALT ratio was classified into tertiles (Table 1). T3 had the oldest patients, lowest male proportion, poorest parameters (lowest BMI, platelet, albumin, BUN), and highest mechanical ventilation rates, APACHE-IV scores, and mortality. T1 showed highest COPD, diabetes, hypertension, and glucocorticoid use (Table 1). Mortality increased across tertiles: T1: 49 (4.91%), T2: 81 (8.12%), T3: 122 (12.08%) (Fig. 3).

Multivariate analyses results using the logistic regression model

Table 2 demonstrates associations between AST/ALT ratio and ICU mortality across three models. As a continuous variable, each unit increase in AST/ALT ratio was associated with significantly higher mortality odds in all models: 46% in the Crude model (OR 1.46, 95% CI 1.29–1.66, $P < 0.0001$), 46% in Model I (OR 1.46, 95% CI 1.28–1.66, $P < 0.0001$), and 25% in Model II (OR 1.25, 95% CI 1.07–1.45, $P = 0.0041$). When analyzed by tertiles, compared to T1, both T2 and T3 showed increased mortality across three models (Table 2).

Sensitivity analysis

Sensitivity analyses confirmed the robustness of our findings (Table 3). After adjusting for confounders, AST/ALT ratio remained significantly associated with ICU mortality in subgroups without diabetes (OR 1.22, 95% CI 1.01–1.47), without sepsis (OR 1.30, 95% CI 1.06–1.58), and without ACS (OR 1.29, 95% CI 1.10–1.52) (Table 3).

Nonlinear relationship

We identified a nonlinear relationship between AST/ALT ratio and ICU mortality (Fig. 4; Table 4). Two-piecewise linear regression analysis revealed an inflection point at AST/ALT = 1.59 (Table 4). Below this inflection point, each unit increase in AST/ALT was associated with significantly higher ICU mortality (OR 2.02, 95% CI 1.22–3.33, $P = 0.0059$), while no significant association was observed above this inflection point (OR 1.07, 95% CI 0.86–1.33, $P = 0.5348$) (Table 4).

Subgroup analysis

Stratified analyses across various subgroups demonstrated consistent associations between AST/ALT ratio and ICU mortality, with no statistically significant interactions detected (Fig. 5).

We calculated the E-value to assess unmeasured confounding. Our findings remain robust unless an unmeasured confounder exists with an OR exceeding 3.46.

Discussion

This study investigated the association between the AST/ALT ratio and ICU mortality in critically ill patients with ESRD. In our multicenter retrospective cohort of 3005 participants, a nonlinear relationship between AST/ALT ratio and ICU mortality was identified with an inflection point at 1.59. Below this threshold, each unit increase in AST/ALT ratio was associated with a 2.02-fold higher risk of ICU mortality (95% CI 1.22–3.33, $P = 0.0059$). These findings provide important insights into the relationship between the AST/ALT ratio and mortality risk in critically ill ESRD patients.

The AST/ALT ratio, also known as the De Ritis ratio, serves as a valuable biomarker for assessing mortality risk across diverse patient populations, including those with critical illnesses. Multiple studies have demonstrated a clear association between elevated AST/ALT ratio and increased mortality. Yang et al. found a nonlinear relationship between the AST/ALT ratio and in-hospital mortality with a saturation effect at 1.8 in critically ill elderly patients[32]. Liu et al. observed similar patterns in patients with stable coronary artery disease, where an AST/ALT ratio ≥ 1.40 correlated with higher all-cause and cardiovascular mortality[42]. Additionally, research by Drácz et al. revealed that an AST/ALT ratio ≥ 1.218 is significantly associated with mortality in COVID-19 patients[31]. The relationship between the AST/ALT ratio and ICU mortality in critically ill ESRD patients remains an important yet understudied area, particularly considering the complex interactions between liver function, renal impairment, and overall prognosis. Our study contributes valuable evidence by confirming a strong correlation between elevated AST/ALT ratio and increased mortality risk in ESRD populations, while also establishing a nonlinear relationship with a specific inflection point.

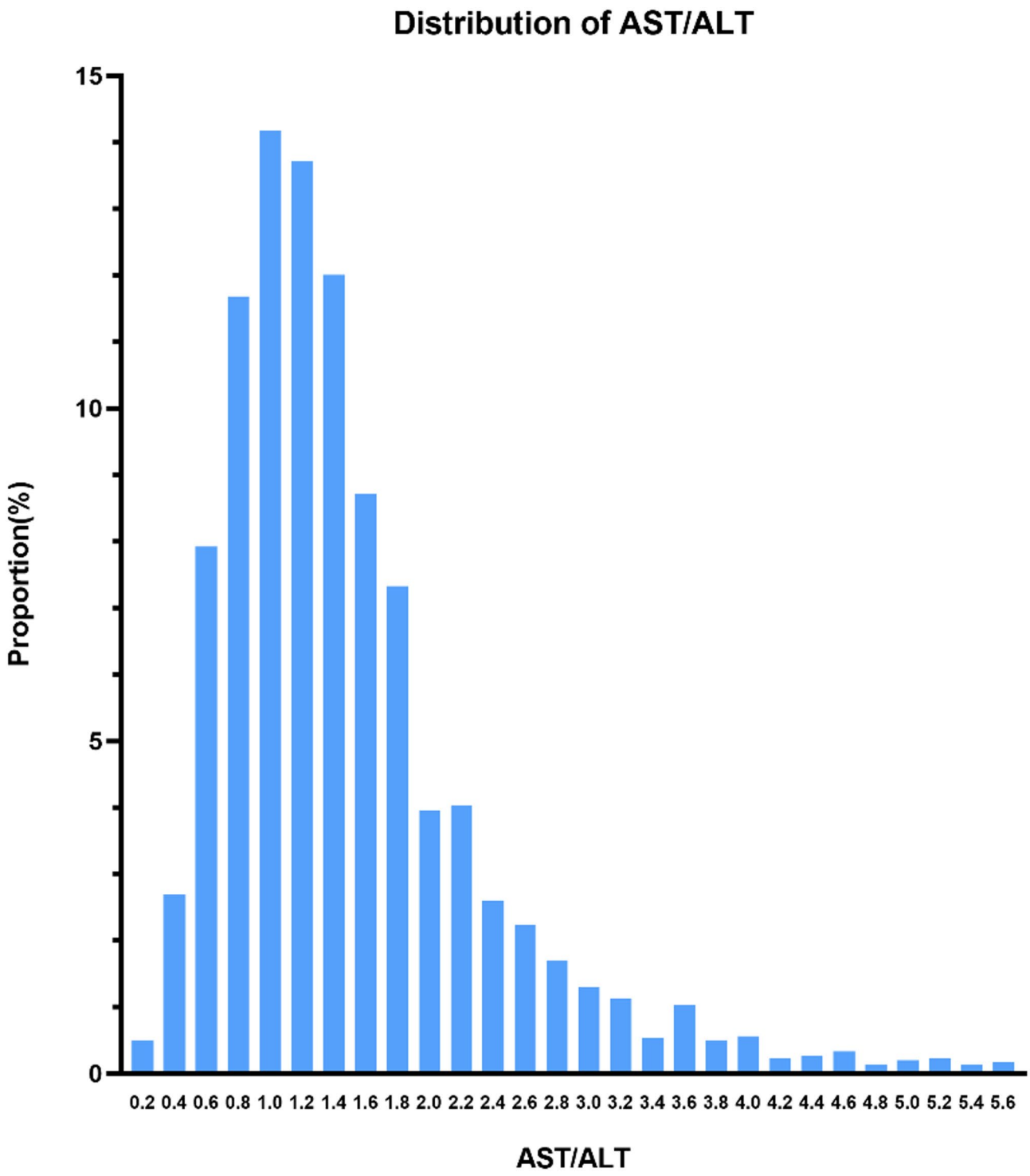

Fig. 2. Distribution of AST/ALT ratio. It displayed a distribution ranging from 0.12 to 5.67, with a median of 1.29.

Multiple confounding factors may influence the AST/ALT ratio in ESRD patients, including liver dysfunction, inflammatory states, and sepsis[8,14,26]. Sensitivity analyses consistently demonstrated the robustness of our findings. The nonlinear relationship between the AST/ALT ratio and ICU mortality remained significant after adjusting for liver conditions (cirrhosis, liver failure) and inflammatory markers (CRP) (Table S1). Additionally, this nonlinear relationship persisted even when including patients with extreme AST/ALT ratios, with a similar inflection point (Fig. S1 and Table S2). We systematically controlled for conditions associated with inflammatory states, particularly sepsis, which directly correlates with inflammatory marker elevation. Notably, sensitivity analysis (Table 3) excluding sepsis patients still revealed a significant association between AST/ALT ratio and

Characteristic	Total	AST/ALT ratio			P
		T1 (0.12–1.04)	T2 (1.05–1.59)	T3 (1.60–5.67)	
N	3005	997	998	1010	
Age (years)	62.68 ± 14.16	61.69 ± 14.77	62.97 ± 14.04	63.37 ± 13.61	0.021
Gender					< 0.001
Male	1637 (54.48%)	598 (59.98%)	531 (53.21%)	508 (50.30%)	
Female	1368 (45.52%)	399 (40.02%)	467 (46.79%)	502 (49.70%)	
Ethnicity					< 0.001
African American	836 (27.82%)	233 (23.37%)	270 (27.05%)	333 (32.97%)	
Caucasian	1619 (53.88%)	576 (57.77%)	541 (54.21%)	502 (49.70%)	
Other	550 (18.30%)	188 (18.86%)	187 (18.74%)	175 (17.33%)	
BMI (kg/m^2)	28.84 ± 8.32	29.53 ± 8.69	28.87 ± 8.39	28.14 ± 7.83	0.001
Hemoglobin (g/dL)	10.06 ± 2.04	10.13 ± 2.08	10.11 ± 2.02	9.94 ± 2.00	0.075
Platelet ($\times 10^9$ /L)	190.00 (138.00–255.25)	197.00 (148.00–257.00)	190.00 (137.00–256.00)	182.00 (131.00–250.75)	0.020
Albumin (g/dL)	2.98 ± 0.71	3.07 ± 0.67	3.03 ± 0.71	2.85 ± 0.74	< 0.001
BUN (mg/dL)	45.00 (30.00–65.00)	50.00 (33.00–72.00)	46.00 (30.00–64.00)	40.00 (27.00–57.00)	< 0.001
Creatinine (mg/dL)	5.66 (3.90–8.09)	5.90 (4.14–8.55)	5.81 (4.10–8.23)	5.20 (3.59–7.46)	< 0.001
CRP (mg/dL)	14.40 (7.00–30.90)	10.61 (4.63–157.35)	14.70 (7.46–21.40)	18.50 (9.20–31.77)	0.478
AST (IU/L)	25.00 (17.00–42.00)	20.00 (14.00–32.00)	23.50 (17.00–39.00)	33.00 (21.00–57.75)	< 0.001
ALT(IU/L)	20.00 (13.00–33.00)	27.00 (19.00–43.00)	19.00 (13.00–30.00)	15.00 (10.00–25.75)	0.641
AST/ALT ratio	1.29 (0.93–1.80)	0.81 (0.64–0.93)	1.29 (1.17–1.42)	2.11 (1.79–2.71)	< 0.001
Liver failure	67 (2.23%)	18 (1.81%)	19 (1.90%)	30 (2.97%)	0.326
Cirrhosis	91 (3.03%)	21 (2.11%)	26 (2.61%)	44 (4.36%)	0.036
ACS	283 (9.42%)	80 (8.02%)	95 (9.52%)	108 (10.69%)	0.122
CHF	590 (19.63%)	208 (20.86%)	201 (20.14%)	181 (17.92%)	0.224
COPD	271 (9.02%)	119 (11.94%)	86 (8.62%)	66 (6.53%)	< 0.001
Diabetes	1009 (33.58%)	371 (37.21%)	332 (33.27%)	306 (30.30%)	0.004
Hypertension	779 (25.92%)	314 (31.49%)	253 (25.35%)	212 (20.99%)	< 0.001
Sepsis	792 (26.36%)	217 (21.77%)	267 (26.75%)	308 (30.50%)	< 0.001
Cancer	27 (0.90%)	7 (0.70%)	11 (1.10%)	9 (0.89%)	0.638
Antiplatelet	282 (9.38%)	108 (10.83%)	82 (8.22%)	92 (9.11%)	0.126
Anticoagulant	149 (4.96%)	49 (4.91%)	44 (4.41%)	56 (5.54%)	0.502
Glucocorticoid	226 (7.52%)	93 (9.33%)	71 (7.11%)	62 (6.14%)	0.021
Carbapenem	78 (2.60%)	28 (2.81%)	32 (3.21%)	18 (1.78%)	0.117
Levofloxacin	86 (2.86%)	28 (2.81%)	30 (3.01%)	28 (2.77%)	0.945
Vancomycin	393 (13.08%)	123 (12.34%)	140 (14.03%)	130 (12.87%)	0.519
Mechanical ventilation	856 (28.49%)	230 (23.07%)	307 (30.76%)	319 (31.58%)	< 0.001
Dialysis	2227 (74.11%)	745 (74.72%)	744 (74.55%)	738 (73.07%)	0.648
Hemodialysis	2034 (67.69%)	679 (68.10%)	680 (68.14%)	675 (66.83%)	
Peritoneal dialysis	193 (6.42%)	66 (6.62%)	64 (6.41%)	63 (6.24%)	
Vasopressor	28 (0.98%)	8 (0.85%)	11 (1.16%)	9 (0.93%)	0.776
APACHE-IV	71.30 ± 25.19	66.95 ± 23.11	71.32 ± 24.50	75.43 ± 27.02	< 0.001
ICU stay (days)	2.80 (1.79–5.02)	2.60 (1.76–4.56)	2.83 (1.74–5.12)	2.97 (1.88–5.41)	0.915
ICU mortality	252 (8.39%)	49 (4.91%)	81 (8.12%)	122 (12.08%)	< 0.001

Table 1. Baseline characteristics of participants.

mortality (OR 1.30, 95% CI 1.06–1.58, $P = 0.0098$). Furthermore, the effect of AST/ALT ratio on ICU mortality remained consistent across all examined subgroups, including those with and without sepsis (Fig. 5), with no significant interactions detected, strengthens the validity of our findings.

In patients with ESRD, an elevated AST/ALT ratio likely indicates systemic inflammation and oxidative stress, both prevalent in this population. Research demonstrates that elevated AST levels can indicate liver dysfunction while simultaneously reflecting damage in extrahepatic tissues, particularly the heart and kidneys[42,43]. AST is less specific to liver injury than ALT, which primarily resides in the liver; therefore, a high AST/ALT ratio often indicates multi-organ dysfunction rather than isolated hepatic injury[31]. Cardiovascular diseases, prevalent comorbidities in ESRD patients, are often characterized by elevated AST levels, establishing a mechanistic link between increased AST/ALT ratio and cardiovascular mortality risk[24]. The relationship between AST/ALT ratio and mortality may also involve metabolic dysregulation. The Warburg effect, characterized by increased aerobic glycolysis in cancer cells, has been proposed as a mechanism for poor survival outcomes in patients with

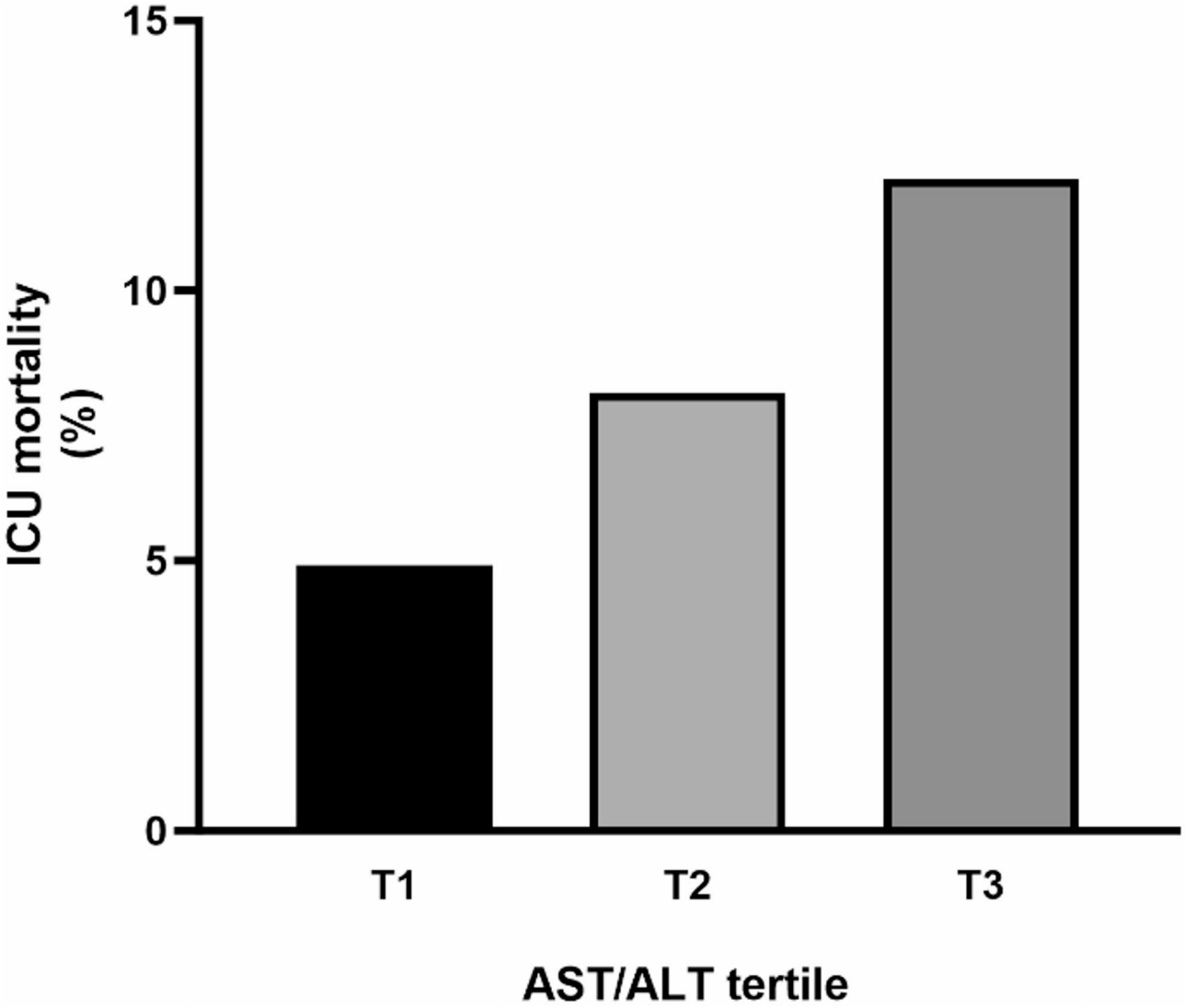

Fig. 3. ICU mortality across AST/ALT tertile.

Exposure	Crude model (OR, 95% CI, *P*)	Model I (OR, 95% CI, *P*)	Model II (OR, 95% CI, *P*)
AST/ALT	1.46 (1.29, 1.66) < 0.0001	1.46 (1.28, 1.66) < 0.0001	1.25 (1.07, 1.45) 0.0041
AST/ALT tertile			
T1	1.0	1.0	1.0
T2	1.71 (1.18, 2.46) 0.0041	1.70 (1.18, 2.46) 0.0046	1.31 (0.89, 1.95) 0.1729
T3	2.66 (1.88, 3.75) < 0.0001	2.65 (1.87, 3.75) < 0.0001	1.71 (1.17, 2.49) 0.0059
P for trend	< 0.0001	< 0.0001	0.0051

Table 2. Relationship between AST/ALT ratio and ICU mortality in different models. Crude model: No adjustments. Model I: Adjusted for age, gender, and ethnicity. Model II: Adjusted for creatinine, gender, BUN, age, ethnicity, albumin, platelet, hypertension, COPD, ACS, CHF, diabetes, sepsis, cancer, APACHE-IV, anticoagulant, antiplatelet, hemoglobin, vancomycin, levofloxacin, glucocorticoid, carbapenem, vasopressor, mechanical ventilation, dialysis, and BMI.

elevated AST/ALT ratios[43]. This metabolic shift increases the production of reactive oxygen species, contributing to oxidative stress and cellular damage, which is particularly harmful in patients with compromised renal function[44]. Additionally, the inflammatory response associated with elevated AST levels can worsen renal injury and accelerate ESRD progression, further increasing mortality risk[45].

Exposure	Model I (OR, 95% CI, *P*)	Model II (OR, 95% CI, *P*)	Model III (OR, 95% CI, *P*)
AST/ALT	1.22 (1.01, 1.47) 0.0362	1.30 (1.06, 1.58) 0.0098	1.29 (1.10, 1.52) 0.0017
AST/ALT tertile			
T1	1.0	1.0	1.0
T2	1.24 (0.76, 2.03) 0.3929	1.58 (0.94, 2.67) 0.0835	1.41 (0.93, 2.15) 0.1035
T3	1.66 (1.04, 2.66) 0.0349	1.95 (1.17, 3.26) 0.0104	1.82 (1.21, 2.74) 0.0038
P for trend	0.0277	0.0114	0.0035

Table 3. Relationship between AST/ALT ratio and ICU mortality in different sensitivity analyses. Model I was sensitivity analysis in participants without diabetes ($N = 1996$). Adjusted for creatinine, gender, BUN, age, ethnicity, albumin, platelet, hypertension, COPD, ACS, CHF, sepsis, cancer, APACHE-IV, anticoagulant, antiplatelet, hemoglobin, vancomycin, levofloxacin, glucocorticoid, carbapenem, vasopressor, mechanical ventilation, dialysis, and BMI. Model II was sensitivity analysis in participants without sepsis ($N = 2213$). Adjusted for creatinine, gender, BUN, age, ethnicity, albumin, platelet, hypertension, COPD, ACS, CHF, diabetes, cancer, APACHE-IV, anticoagulant, antiplatelet, hemoglobin, vancomycin, levofloxacin, glucocorticoid, carbapenem, vasopressor, mechanical ventilation, dialysis, and BMI. Model III was sensitivity analysis in participants without ACS ($N = 2722$). Adjusted for creatinine, gender, BUN, age, ethnicity, albumin, platelet, hypertension, COPD, CHF, diabetes, sepsis, cancer, APACHE-IV, anticoagulant, antiplatelet, hemoglobin, vancomycin, levofloxacin, glucocorticoid, carbapenem, vasopressor, mechanical ventilation, dialysis, and BMI.

Our analysis revealed a nonlinear relationship between the AST/ALT ratio and ICU mortality with a critical inflection point at 1.59. This threshold effect has important clinical implications. For AST/ALT ratios below 1.59, each unit increase was associated with a 2.02-fold higher risk of ICU mortality (95% CI 1.22–3.33, $P = 0.0059$), demonstrating that even slight elevations within this range significantly impact patient outcomes. Conversely, above 1.59, further increases in AST/ALT showed no significant association with mortality risk (OR 1.07, 95% CI 0.86–1.33, $P = 0.5348$), indicating a saturation effect. This inflection point provides clinicians with a precise reference value for identifying high-risk ESRD patients who might benefit from intensified monitoring and intervention, particularly when their AST/ALT ratio approaches but remains below 1.59—the range where the association with mortality is pronounced.

The AST/ALT ratio has important clinical implications for identifying ICU mortality risk in critically ill patients with ESRD. First, it is a simple and readily available biochemical indicator that can be obtained immediately upon ICU admission, providing clinicians with a rapid assessment tool. Second, our finding of a significant increase in ICU mortality with rising AST/ALT ratios below 1.59 provides clinicians with a specific reference value to more accurately identify high-risk patients. Third, our subgroup analyses excluding comorbidities such as diabetes and sepsis revealed that the AST/ALT ratio maintained its significant association with ICU outcomes, suggesting it reflects fundamental pathophysiological mechanisms worthy of further investigation.

Study strengths and limitations

Key strengths of this study include: (1) A large-scale multicenter retrospective cohort design with substantial sample size and high representativeness, focusing specifically on ICU patients with ESRD, a population not extensively investigated in this context before. (2) Application of sophisticated statistical methods, including nonlinear relationship exploration and comprehensive sensitivity analyses, yielding robust results. (3) Implementation of multiple imputation techniques to handle missing data, reducing potential bias and enhancing statistical power. (4) Validation of findings through rigorous subgroup analyses and E-value calculations to assess potential unmeasured confounding.

Our study has several limitations. First, our cohort included only American ESRD patients treated in ICUs, limiting generalizability to other geographical and cultural populations. Validation studies across diverse populations are needed, including ESRD patients not requiring ICU admission. Second, the observational design precludes establishing definitive causal relationships between AST/ALT ratio and ICU mortality. Third, our database lacks information on ESRD etiology classification. This limitation prevents comprehensive investigation of relationships between AST/ALT ratio and specific ESRD subtypes. Future research should include multi-ethnic prospective studies exploring the prognostic value of AST/ALT ratio across different ESRD subtypes.

Conclusions

In this multicenter retrospective cohort study including 3005 participants from the eICU-CRD database, we identified a nonlinear relationship between AST/ALT ratio and ICU mortality in critically ill ESRD patients. Below the inflection point of 1.59, each unit increase in AST/ALT ratio was significantly associated with higher ICU mortality risk. This inflection point provides clinicians with a precise reference value for identifying high-risk ESRD patients. Future research should explore this relationship across different ethnic populations and in various ESRD subtypes through prospective studies.

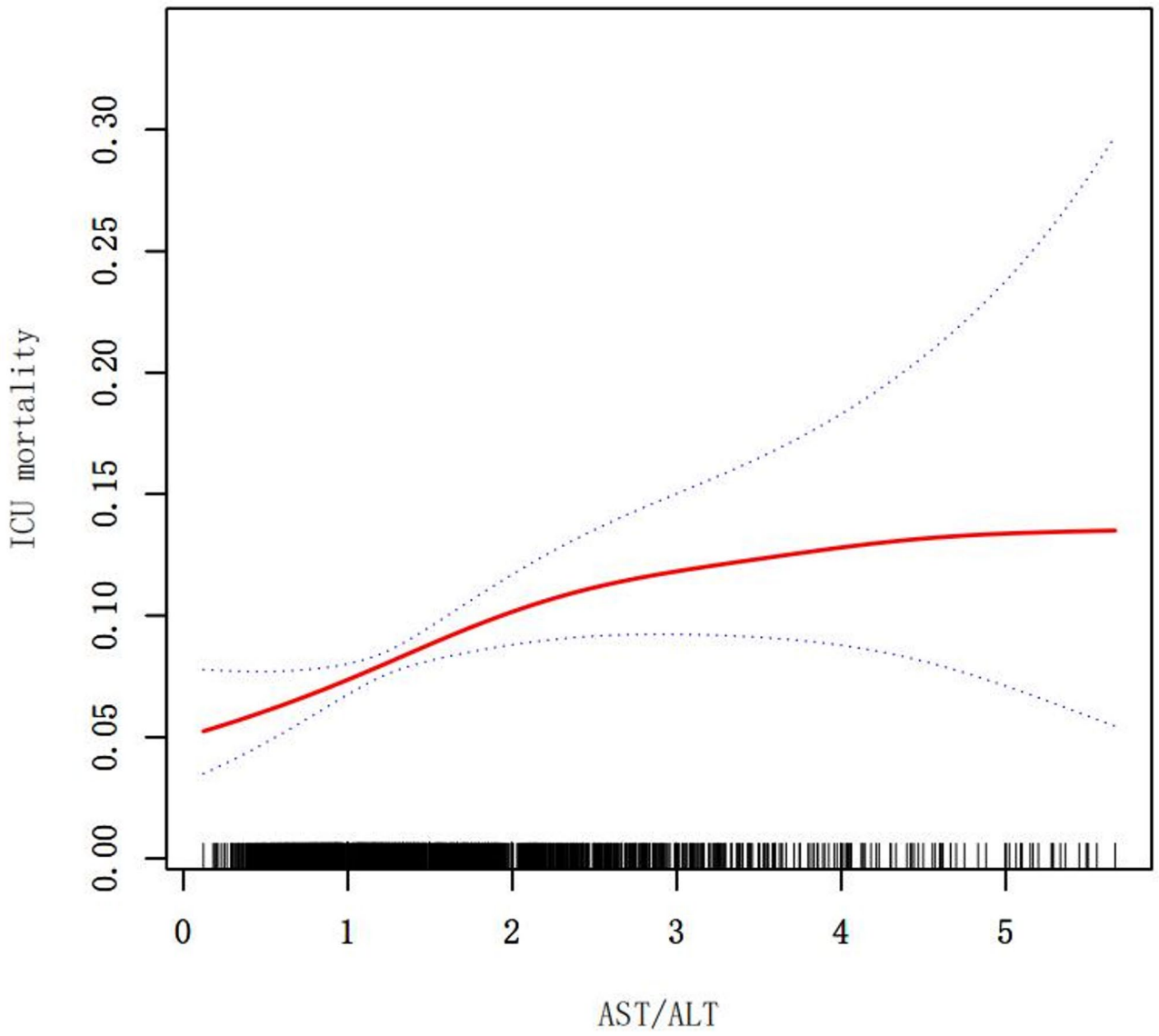

Fig. 4. The nonlinear relationship between AST/ALT ratio and ICU mortality using the generalized additive model. Adjusted for creatinine, gender, BUN, age, ethnicity, albumin, platelet, hypertension, COPD, ACS, CHF, diabetes, sepsis, cancer, APACHE-IV, anticoagulant, antiplatelet, hemoglobin, vancomycin, levofloxacin, glucocorticoid, carbapenem, vasopressor, mechanical ventilation, dialysis, and BMI.

ICU mortality	OR, 95% CI, *P*
Fitting model by standard linear regression	1.25 (1.07, 1.45) 0.0041
Fitting model by two-piecewise regression	
Inflection point of AST/ALT	1.59
≤ 1.59	2.02 (1.22, 3.33) 0.0059
> 1.59	1.07 (0.86, 1.33) 0.5348
P for log-likelihood ratio test	0.043

Table 4. Association between AST/ALT and ICU mortality by two-piecewise linear regression model. Adjusted for creatinine, gender, BUN, age, ethnicity, albumin, platelet, hypertension, COPD, ACS, CHF, diabetes, sepsis, cancer, APACHE-IV, anticoagulant, antiplatelet, hemoglobin, vancomycin, levofloxacin, glucocorticoid, carbapenem, vasopressor, mechanical ventilation, dialysis, and BMI.

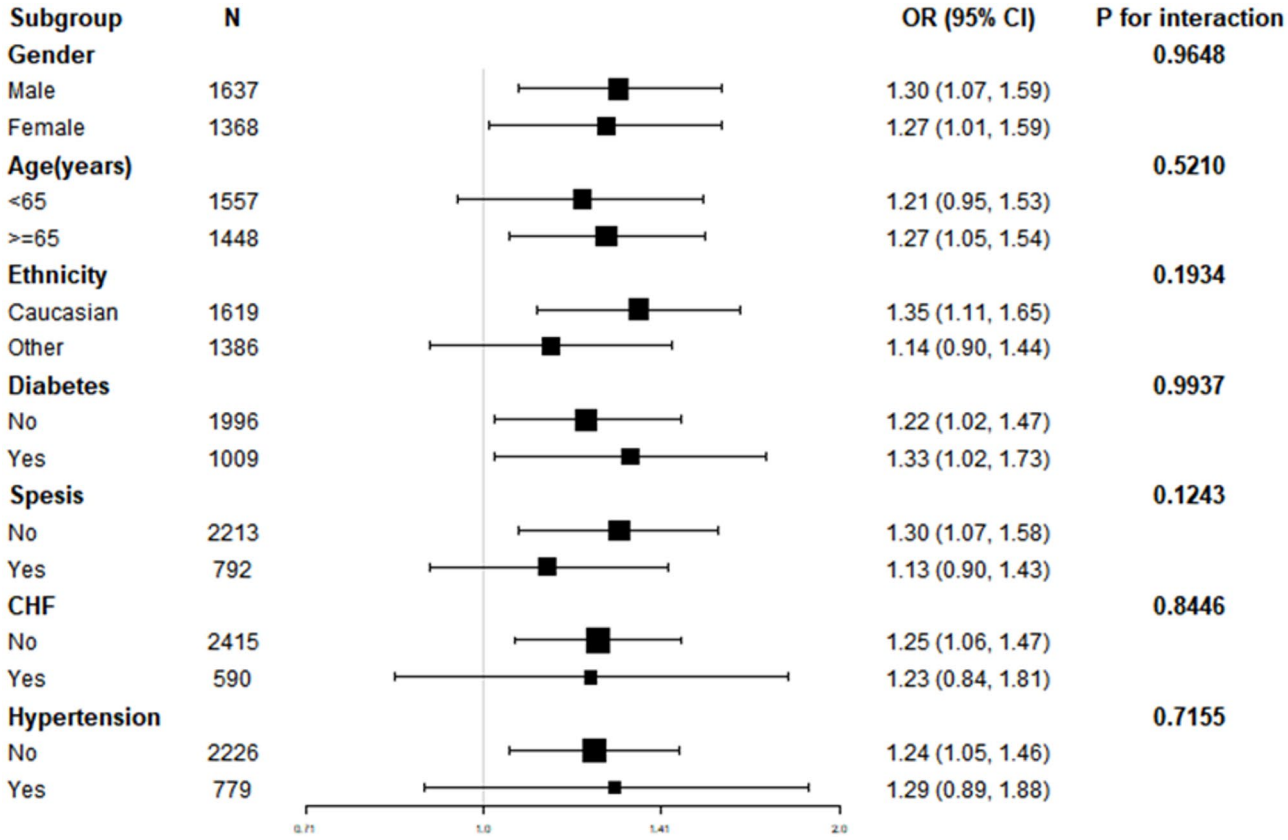

Fig. 5. Effect size of AST/ALT ratio on ICU mortality in prespecified and exploratory subgroups. The model above is adjusted for creatinine, gender, BUN, age, ethnicity, albumin, platelet, hypertension, COPD, ACS, CHF, diabetes, sepsis, cancer, APACHE-IV, anticoagulant, antiplatelet, hemoglobin, vancomycin, levofloxacin, glucocorticoid, carbapenem, vasopressor, mechanical ventilation, dialysis, and BMI, but not adjusted for stratification variables.

Data availability

The data were completely available at https://eicu-crd.mit.edu/.

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Study designing, data gathering, and manuscript writing: X.L. Statistical analysis: Q.W., K.L., and X.L. Manuscript editing: S.G., Y.L., and Z.X. The final manuscript has been read and approved by all of the authors.

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Declarations

Ethics approval and consent to participate
Data was retrieved from eICU-CRD in compliance with the data usage agreement (our record ID: 63069214) by the MIT Ethics Committee. This was a retrospective analysis conducted on an anonymized database for researchers, and the MIT Ethics Committee waived the informed consent.

Competing interests
The authors declare no competing interests.

Additional information
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