Ma et al. BMC Gastroenterology (2025) 25:112
https://doi.org/10.1186/s12876-025-03686-5

BMC Gastroenterology

RESEARCH Open Access

Association between lactate-to-albumin ratio and all-cause mortality in critically ill cirrhotic patients with sepsis: a retrospective analysis of the MIMIC-IV database

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Abstract

Background The impact of lactate-to-albumin ratio (LAR) on mortality of critically ill cirrhotic patients with sepsis is scant.

Methods Critically ill cirrhotic patients with sepsis were obtained from the MIMIC-IV database (v3.0). Cox regression models alone and in combination with restricted cubic splines, generalized additive models and smoothed curve fitting were used to investigate the relationship between LAR and all-cause mortality.

Results A total of 1864 patients were included. The 30-day, 90-day, and 180-day all-cause mortality rates were 38.0%, 46.3%, and 49.5%, respectively. Higher LAR were significantly and nonlinearly associated with higher risks of 30-day, 90-day, and 180-day all-cause mortality (all adjusted HR = 1.17, $P < 0.001$). L-shaped associations between LAR and 30-day, 90-day, and 180-day all-cause mortality were observed, with an inflection point of 1.05 (P for log-likelihood ratio < 0.01). Compared with patients with LAR < 1.05, patients with LAR ≥ 1.05 had higher risks of 30-day, 90-day, and 180-day all-cause mortality (adjusted HR (95% CI): 1.48 (1.27–1.72), 1.44 (1.25–1.66), and 1.38 (1.21–1.57), respectively). No potential modifiers were found in the relationship between LAR and mortality.

Conclusions LAR was positively and nonlinearly associated with all-cause mortality in critically ill cirrhotic patients with sepsis. Thus, it could be used as a prognostic biomarker.

Keywords Liver cirrhosis, Sepsis, Mortality, Intensive care, Risk factor, Lactate-to-albumin ratio

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Introduction

The deterioration of cirrhosis from asymptomatic compensation to decompensation is characterized by the development of distinct clinical symptoms, such as ascites, gastrointestinal bleeding, encephalopathy, and jaundice [1]. Infections in cirrhotic patients would trigger the deterioration, leading to decompensation of liver function and progression to acute-on-chronic liver failure (ACLF). In the end, it adversely affects survival of patients, and results in removal from the transplant waitlist [2]. Previous study reported that infection increased mortality by 4-fold: 30% of patients died within one month and another 30% died within one year [3]. The occurrence of bacterial infection has been considered a feature of critically ill as well as an important basis for staging cirrhosis [3, 4]. Unfortunately, although active critical care management has evolved over time in critically ill cirrhotic patients with sepsis, their mortality remains high. The disease severity and prognosis evaluation of liver cirrhosis can be measured using scoring systems such as Child-Turcotte-Pugh score [5], CLIF-C ACLF score [6], and MELD score and its derivative scoring system [7–9], which integrate clinical features, extrahepatic organ function, and laboratory parameters. However, these scoring systems seem not effective enough when infection happens. Sepsis-3, a criterion which has been proven relatively accurate in predicting the severity of infections in cirrhotic patients, helps to some degree. Quick sequential organ failure assessment (qSOFA), another useful bedside tool to assess risk for worse outcomes, is also applicable in these patients [10]. Although these tools are helpful in identifying critically ill cirrhotic patients with sepsis and their prognosis, their performance remains sub-optimal. Laboratory markers that can directly predict outcome of critically ill cirrhotic patients with sepsis are still not universally recognized [2].

Elevated lactate levels can occur under tissue hypoxia, accelerated glycolysis, reduced lactate clearance due to renal or liver insufficiency and so on. In patients with sepsis, lactate level is a reliable parameter in guiding diagnosing, making treatment decisions, and predicting prognosis [11]. Several studies have reported that hyperlactacidemia in cirrhotic patients or in patients with ACLF is positively related to disease severity and poor prognosis [12–17]. Serum albumin is one of the acute phase protein that reflects the severity of inflammation [18]. Serum albumin levels are sharply decreased in cirrhotic patients hospitalized for acute decompensation, which is closely related to their disease severity and prognosis [19]. Excluding the potential confounding effect from exogenous albumin administration, low serum albumin levels are also associated with an increased mortality risk in patients with severe sepsis [20]. Combining the two parameter, a newly discovered biomarker, the lactate-to-albumin ratio (LAR), is generated to evaluate prognosis and is positively associated with the disease severity and increased short-term mortality in sepsis patients [21–25]. LAR is superior or at least equivalent to lactate alone in predicting the outcome of sepsis patients [23, 24]. However, limited research has focused on the performance of LAR in cirrhotic patients with sepsis. To better predict prognosis and determine the potential applicability of LAR in cirrhotic patients with sepsis, we conducted this retrospective cohort study to investigate the relationship between LAR and all-cause mortality in critically ill cirrhotic patients with sepsis.

Materials and methods

Study design and patients

A retrospective analysis was conducted to investigate the association between LAR and outcome based on the Medical Information Mart for Intensive Care IV (MIMIC-IV) database (v3.0), which contains comprehensive and high-granularity information about well-defined and characterized patients admitted to intensive care unit (ICU) at Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2022 [26–28]. One author obtained access to the database and was responsible for data extraction (certification number 64735113). Because only third-party anonymized publicly available data were used, the Institutional Review Board at BIDMC granted a waiver of informed consent and approved the sharing of the research resource. This study was reported in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement.

Critically ill adult patients with liver cirrhosis admitted to ICU for the first time were screened (Fig. 1). Patients with hospital length of stay less than one day, or ICU length of stay less than one day or more than 100 days were excluded. Patients diagnosed with sepsis according to Sepsis-3 [29] were further screened (Supplemental file 1: Supplemental Methods). Patients were excluded if the sepsis occurred 48 h before or 24 h after ICU admission. At last, patients had missing values of lactate or albumin were excluded.

Variable extraction and data collection

The following data were extracted from the MIMIC-IV database (v3.0) using the first value on the first day of ICU admission: age, sex, height, weight, race, marital status, insurance, ICU type (Supplemental file 1: Table S1), severity of illness (acute physiology score III (APS III), simplified acute physiology score II (SAPS II), systemic inflammatory response syndrome (SIRS), Oxford acute severity of illness score (OASIS), Glasgow Coma Scale, sequential organ failure assessment (SOFA) score, and

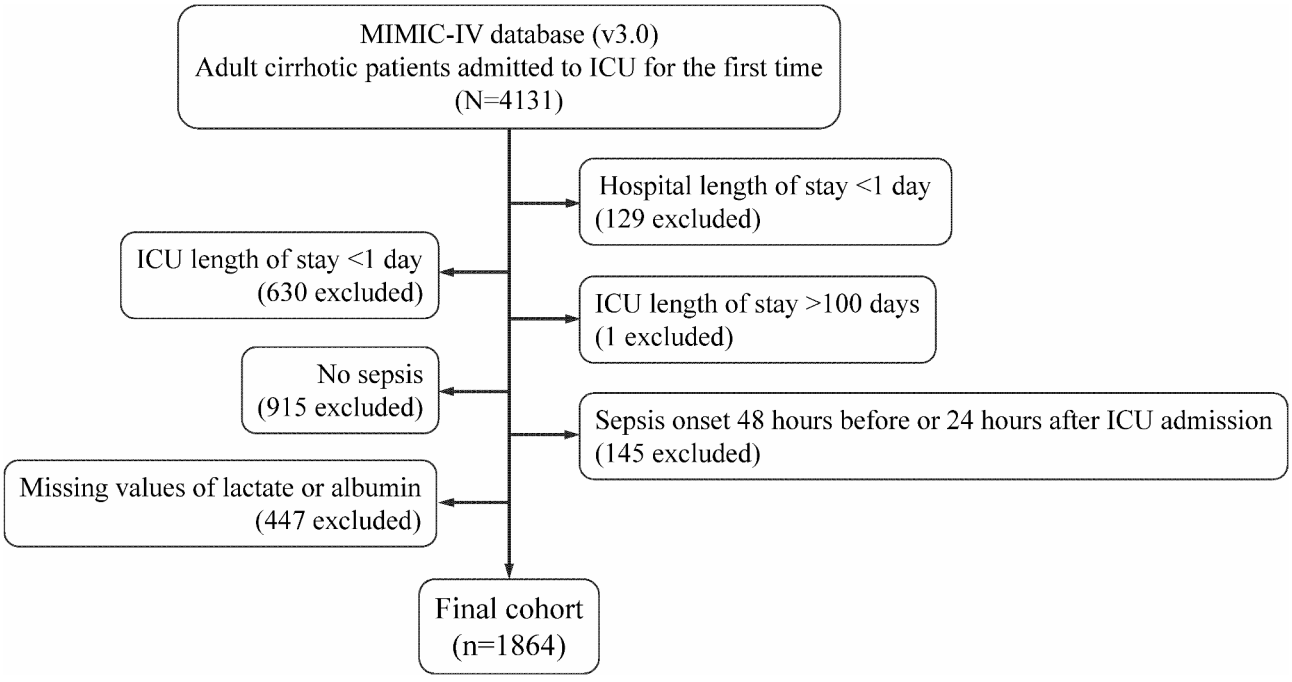

Fig. 1 Flow chart of patient selection

each component of the SOFA score), vital signs and laboratory measurements (blood cell analysis, coagulation function, liver and kidney function, electrolyte, blood gas analysis, etc.). The outcome and Charlson comorbidity index (CCI) were obtained too. We identified liver cirrhosis and infection sites based on the ICD-9-CM and ICD-10-CM codes available at discharge (Supplemental file 1: Table S2). With respect to the infection sites, we focused on the presence or absence of abdominal infections, lung infections, and blood stream infections, which are the main sites or severe type in cirrhotic patients [1, 30].

ACLF was diagnosed according to the CLIF-C ACLF criteria [31]. The severity of ACLF and sepsis were rated according to CLIF-C ACLF score and SOFA score, respectively [6, 29].

Variables with more than 60% missing values were excluded from the analysis (Supplemental file 1: Supplemental Methods, and Table S3). Multiple imputation by chained equation was adopted to generate values for those with less than 60% missing values using the observed data of all patients. A Gaussian imputation model was used for multiple imputation, involving five iterations and one dataset. The *"mice"* was employed to impute the data [32].

LAR and outcomes

The LAR was defined as follows: LAR = lactate (mmol/L) / albumin (g/dL) [21].

All patients were retrieved on the day of ICU admission and were followed up for 180 days after enrollment, or incident of death. The outcomes were 30-day, 90-day, and 180-day all-cause mortality.

Statistical analysis

Quantitative data were represented as means (standard deviation, SD) (normally distributed data) or medians (P_{25}-P_{75}) (non-normally distributed data), and were analyzed with one-way analysis of means (not assuming equal variances) or Kruskal-Wallis rank sum test. Qualitative data were represented as frequencies (proportions) and analyzed with the Pearson's Chi-squared test.

Patients were stratified to quartile 1–4 according to the LAR quartile. Cox proportional hazards models were applied to investigate the relationship between LAR and all-cause mortality in cirrhotic patients with sepsis. The proportional hazards assumption was checked using the Schoenfeld residuals, and the scaled Schoenfeld residuals were visually inspected; in some instances, the assumption was violated, we therefore interpreted the hazard ratios (HRs) as weighted averages of the time-varying HRs over the entire follow-up period [33]. Model 1 was adjusted for none. Model 2 was partially adjusted for age (years), sex (female vs. male), height (cm), weight (kg), race (Black vs. Hispanic vs. White vs. Others), marital status (Married vs. Single vs. Others), insurance (Medicare vs. Medicaid vs. Private vs. Others), and CCI. Model 3 was fully adjusted for variables used in Model 2 and ICU type (MICU vs. MICU/SICU vs. SICU/TSICU),

infection site (blood stream infection, lung infection, abdominal infection), disease severity of liver cirrhosis (CLIF-C ACLF score), and disease severity of sepsis (SOFA score). Tests for linear trend were performed by entering the median value of each category as a continuous variable. Variance inflation factor was used for multicollinearity analysis.

To investigate whether the association between LAR and all-cause mortality was nonlinear, Cox proportional hazards models (Model 3) were developed using restricted cubic splines (RCS) (knots at the 10th, 50th, and 90th percentiles) and generalized additive models and smoothed curve fitting. If the relationship was nonlinear, the inflection point was identified, and a two-segment Cox proportional hazards models were used on both sides of the inflection point to investigate the association between LAR and all-cause mortality. The inflection point was determined through the following steps [34]: (1) Divide the variable into 20 equal intervals, thereby creating multiple smaller segments. (2) Conduct a separate Cox regression analysis for each segment of the variable. (3) Compute the log-likelihood values of the regression models for adjacent segments. (4) Identify the boundary point between two adjacent segments that exhibits the greatest difference in log-likelihood as the inflection point.

Stratified analysis was conducted based on ICU type, age (< 60 vs. ≥60 years), sex, race, insurance, marital status, CCI (1–3 vs. 4–6 vs. ≥7), SOFA score (1–6 vs. 7–12 vs. ≥13), CLIF-C ACLF (yes vs. no), blood stream infection (yes vs. no), lactate (< 2 vs. 2–4 vs. ≥4 mmol/L), albumin (< 2.5 vs. 2.5-3.0 vs. ≥3.0 g/dL).

The receiver operating characteristic curve (ROC) and the area under the ROC (AUC) were utilized to evaluate and compare the predictive performance of LAR relative to lactate and albumin. Additionally, the combined predictive performance of LAR with the MELD score ($MELDs_{LAR}$) and LAR with the CLIF-C ACLF score (CLIF-C $ACLFs_{LAR}$) was evaluated and compared to the standalone MELD score [7] and CLIF-C ACLF score [6], respectively.

Data processing and analysis were performed using DecisionLinnc v1.0.9 [35]. DecisionLinnc is a platform that integrates multiple programming language environments and enables data processing, data analysis, and machine learning through a visual interface. Statistical significance was set at $P < 0.05$.

Results

Patient characteristics

A total of 1864 critically ill cirrhotic patients with sepsis were retrieved in the final cohort (Fig. 1). The median age was 59.0 (52.0–67.0) years, 36.4% patients were female, and 42.2% patients had CLIF-C ACLF (Table 1). The mean CLIF-C ACLF score and median SOFA score were 45.8 (8.5), and 9.0 (7.0–12.0), respectively. The median lactate, albumin, and LAR were 2.5 (1.7-4.0) mmol/L, 2.9 (2.4–3.3) g/dL, 0.9 (0.6–1.5), respectively. During the follow-up period, a total of 52 (2.8%) patients underwent liver transplantation. The 30-day, 90-day, and 180-day all-cause mortality rates were 38.0%, 46.3%, and 49.5%, respectively.

Patients with higher LAR were more likely to be obese and CLIF-C ACLF, and had lower albumin and higher lactate, CLIF-C ACLF score and SOFA score (all $P < 0.01$) (Table 1). The rates of liver transplantation across the quartiles of LAR did not differ significantly ($P = 0.123$). Patients with higher LAR had worse prognosis at 30, 90, and 180 days after ICU admission (all $P < 0.001$).

Relationship between LAR and mortality

During 30, 90, 180 days of follow-up, 708 (38.0%), 863 (46.3%), and 922 (49.5%) all-cause deaths occurred. The Kaplan-Meier survival curves indicated that the survival probability differed significantly between the four groups (LAR quartile 1–4) (all log-rank $P < 0.001$; Fig. 2A, B and C). Patients with higher LAR quartile had lower survival probability during the 30-day, 90-day, and 180-day follow-up. We designed three Cox regression models to investigate the independent role of LAR in mortality among critically ill cirrhotic patients with sepsis (Table 2). After multivariable adjustment (Model 3), the adjusted HRs (aHRs) (95% confidence intervals (CIs)) from LAR quartile 1 to quartile 4 categories were 1.00 (reference), 1.15 (0.91–1.46), 1.45 (1.15–1.81), and 1.76 (1.41–2.20), respectively, for 30-day all-cause mortality (P for trend < 0.001); 1.00 (reference), 1.10 (0.89–1.36), 1.40 (1.15–1.71), and 1.65 (1.35–2.02), respectively, for 90-day all-cause mortality (P for trend < 0.001); and 1.00 (reference), 1.11 (0.91–1.36), 1.37 (1.13–1.66), and 1.66 (1.37–2.01), respectively, for 180-day all-cause mortality (P for trend < 0.001). Similarly, the aHRs (95% CIs) of LAR for 30-day, 90-day, and 180-day all-cause mortality in Model 3 were 1.17 (1.11–1.23), 1.17 (1.12–1.23), and 1.17 (1.12–1.23), respectively (all $P < 0.001$).

The variance inflation factors of the covariates used in this study were all less than 2, indicating that the multicollinearity was weak and the multivariable adjustment models were robust (Supplemental file 1: Table S4).

Detection of nonlinear relationship between LAR and mortality

By adjusted RCS models, we discovered the nonlinear associations between LAR and 30-day, 90-day, and 180-day all-cause mortality in critically ill cirrhotic patients with sepsis (all P for overall < 0.001, all P for nonlinear < 0.05) (Fig. 3A and B, and 3 C). Based on adjusted RCS models, and adjusted generalized additive models

Table 1 Characteristics and outcomes of critically ill cirrhotic patients with sepsis categorized by lactate-to-albumin ratio

Variables	Overall (*N* = 1,864)	Quartile 1 (*n* = 469)	Quartile 2 (*n* = 465)	Quartile 3 (*n* = 464)	Quartile 4 (*n* = 466)	*P*
Age (years)	59.0 (52.0–67.0)	59.0 (51.0–68.0)	59.0 (53.0–67.0)	61.0 (52.0–68.0)	59.0 (51.0–65.0)	0.154
Weight (kg)	82.9 (70.3–99.3)	79.4 (68.0-96.4)	83.3 (70.0-98.7)	84.0 (70.4–100.0)	85.0 (72.8–100.0)	0.008
Height (cm)	173.0 (168.0-180.0)	173.0 (168.0-180.0)	173.0 (168.0-180.0)	173.0 (168.0-180.0)	173.0 (168.0-180.0)	0.533
Sex						0.127
Female	678 (36.4%)	183 (39.0%)	178 (38.3%)	167 (36.0%)	150 (32.2%)	
Male	1,186 (63.6%)	286 (61.0%)	287 (61.7%)	297 (64.0%)	316 (67.8%)	
Race						0.003
Black	147 (7.9%)	30 (6.4%)	36 (7.7%)	30 (6.5%)	51 (10.9%)	
Hispanic	102 (5.5%)	19 (4.1%)	21 (4.5%)	27 (5.8%)	35 (7.5%)	
White	1,197 (64.2%)	323 (68.9%)	308 (66.2%)	307 (66.2%)	259 (55.6%)	
Others	418 (22.4%)	97 (20.7%)	100 (21.5%)	100 (21.6%)	121 (26.0%)	
Marital status						0.697
Married	720 (38.6%)	185 (39.4%)	172 (37.0%)	182 (39.2%)	181 (38.8%)	
Single	926 (49.7%)	233 (49.7%)	238 (51.2%)	234 (50.4%)	221 (47.4%)	
Unknown	218 (11.7%)	51 (10.9%)	55 (11.8%)	48 (10.3%)	64 (13.7%)	
Insurance type						0.742
Medicare	727 (39.0%)	183 (39.0%)	189 (40.6%)	185 (39.9%)	170 (36.5%)	
Private	544 (29.2%)	135 (28.8%)	126 (27.1%)	142 (30.6%)	141 (30.3%)	
Others	593 (31.8%)	151 (32.2%)	150 (32.3%)	137 (29.5%)	155 (33.3%)	
ICU type						0.148
MICU	977 (52.4%)	245 (52.2%)	252 (54.2%)	245 (52.8%)	235 (50.4%)	
MICU/SICU	279 (15.0%)	77 (16.4%)	77 (16.6%)	68 (14.7%)	57 (12.2%)	
SICU/TSICU	608 (32.6%)	147 (31.3%)	136 (29.2%)	151 (32.5%)	174 (37.3%)	
Infection site						
Blood stream infection	827 (44.4%)	170 (36.2%)	177 (38.1%)	226 (48.7%)	254 (54.5%)	< 0.001
Lung infection	707 (37.9%)	201 (42.9%)	171 (36.8%)	177 (38.1%)	158 (33.9%)	0.040
Abdominal infection	420 (22.5%)	92 (19.6%)	94 (20.2%)	113 (24.4%)	121 (26.0%)	0.052
Severity of illness						
Charlson comorbidity index	6.0 (4.0–8.0)	6.0 (4.0–8.0)	6.0 (4.0–8.0)	6.0 (4.0–8.0)	6.0 (4.0–8.0)	0.940
APS III	63.0 (48.0–79.0)	56.0 (44.0–69.0)	57.0 (45.0–74.0)	63.0 (49.0–79.0)	74.0 (60.0–95.0)	< 0.001
SIRS	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (3.0–4.0)	< 0.001
SAPS II	43.0 (34.0–53.0)	41.0 (33.0–49.0)	41.0 (33.0–49.0)	43.0 (34.0–52.0)	49.0 (38.0–60.0)	< 0.001
OASIS	34.0 (29.0–41.0)	32.0 (27.0–37.0)	34.0 (27.0–39.0)	34.0 (29.0–40.0)	39.0 (32.0–45.0)	< 0.001
Glasgow Coma Scale	15.0 (13.0–15.0)	15.0 (13.0–15.0)	15.0 (13.0–15.0)	14.5 (13.0–15.0)	15.0 (13.0–15.0)	0.145
SOFA	9.0 (7.0–12.0)	8.0 (6.0–11.0)	9.0 (6.0–11.0)	9.0 (7.0–12.0)	11.0 (9.0–15.0)	< 0.001
Liver	1.0 (0.0–3.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	2.0 (0.0–3.0)	2.0 (0.0–3.0)	0.001
Coagulation	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.072
Brain	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.028
Kidney	0.0 (0.0–2.0)	1.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	1.0 (0.0–2.0)	0.025
Circulation	1.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	< 0.001
Respiration	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	< 0.001
MELD score	21.9 (15.9–29.1)	20.6 (14.6–28.0)	20.1 (14.5–28.3)	22.4 (16.4–29.3)	23.4 (18.2–30.8)	< 0.001
CLIF-C OF score	8.0 (7.0–9.0)	8.0 (7.0–9.0)	8.0 (7.0–9.0)	8.0 (7.0–9.0)	8.0 (7.0–10.0)	< 0.001
CLIF-C ACLF score	45.8 (8.5)	44.3 (8.6)	45.3 (7.9)	46.6 (8.4)	46.8 (8.9)	< 0.001
CLIF-C ACLF						0.003
No	1,078 (57.8%)	293 (62.5%)	278 (59.8%)	269 (58.0%)	238 (51.1%)	
Yes	786 (42.2%)	176 (37.5%)	187 (40.2%)	195 (42.0%)	228 (48.9%)	
Laboratory measurements						
Total CO_2 (mEq/L)	23.0 (19.0–26.0)	24.0 (20.0–27.0)	24.0 (21.0–26.0)	23.0 (20.0–26.0)	19.0 (16.0–23.0)	< 0.001
Free calcium (mmol/L)	1.1 (1.0-1.2)	1.1 (1.1–1.2)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	< 0.001
Lactate (mmol/L)	2.5 (1.7-4.0)	1.3 (1.1–1.6)	2.1 (1.8–2.4)	3.1 (2.5–3.7)	6.0 (4.5–8.6)	< 0.001
$PaCO_2$ (mmHg)	39.0 (33.0–45.0)	40.0 (35.0–46.0)	39.0 (34.0–45.0)	39.0 (33.0–44.0)	38.0 (31.0-43.8)	< 0.001

Table 1 (continued)

Variables	Overall (*N* = 1,864)	Quartile 1 (*n* = 469)	Quartile 2 (*n* = 465)	Quartile 3 (*n* = 464)	Quartile 4 (*n* = 466)	*P*
pH	7.4 (7.3–7.4)	7.4 (7.3–7.4)	7.4 (7.3–7.4)	7.4 (7.3–7.4)	7.3 (7.2–7.4)	< 0.001
PaO_2 (mmHg)	83.0 (48.0-156.0)	84.0 (50.0-136.0)	87.0 (47.0-161.0)	73.0 (46.0-142.8)	89.0 (50.0-180.8)	0.111
Alanine aminotransferase (IU/L)	37.0 (21.0-97.3)	31.0 (18.0–66.0)	35.0 (22.0–71.0)	37.0 (21.0–97.0)	52.5 (26.0-243.8)	< 0.001
Asparate aminotransferase (IU/L)	79.0 (43.0-223.0)	62.0 (34.0-127.0)	74.0 (43.0-146.0)	79.0 (44.0-239.5)	136.0 (56.3-560.5)	< 0.001
Total bilirubin (mg/dL)	3.3 (1.5–8.1)	2.3 (1.0-6.5)	2.9 (1.4-8.0)	3.8 (1.8–8.9)	3.9 (2.0-8.6)	< 0.001
Creatinine (mg/dL)	1.4 (0.9–2.4)	1.4 (0.8–2.6)	1.2 (0.8–2.1)	1.3 (0.8–2.4)	1.5 (1.0-2.5)	0.002
Urea nitrogen (mg/dL)	29.0 (17.0–49.0)	32.0 (17.0–56.0)	30.0 (18.0–49.0)	29.0 (17.0–48.0)	26.0 (16.0-42.8)	0.002
Glucose (mg/dL)	129.0 (102.0-179.0)	120.0 (100.0-149.0)	129.0 (103.0-173.0)	132.0 (103.8-177.3)	144.0 (101.3–217.0)	< 0.001
Albumin (g/dL)	2.9 (2.4–3.3)	3.2 (2.8–3.6)	3.0 (2.5–3.3)	2.7 (2.4–3.2)	2.6 (2.2-3.0)	< 0.001
Anion gap (mEq/L)	16.0 (13.0–19.0)	15.0 (12.0–18.0)	14.0 (12.0–17.0)	15.0 (13.0–18.0)	19.0 (15.0–24.0)	< 0.001
Total calcium (mg/dL)	8.2 (7.6–8.9)	8.4 (7.8–8.9)	8.2 (7.6–8.8)	8.2 (7.6–8.8)	8.1 (7.4–8.8)	< 0.001
Chloride (mEq/L)	102.0 (97.0-107.0)	103.0 (98.0-107.0)	103.0 (97.0-107.0)	103.0 (97.0-107.0)	102.0 (96.0-106.0)	0.002
Potassium (mEq/L)	4.2 (3.7–4.8)	4.2 (3.7–4.7)	4.1 (3.7–4.8)	4.2 (3.7–4.8)	4.3 (3.8-5.0)	0.050
Sodium (mEq/L)	137.0 (132.0-140.0)	137.0 (133.0-141.0)	137.0 (132.0-140.0)	137.0 (132.0-141.0)	137.0 (132.0-141.0)	0.140
Red blood cells (m/ul)	3.0 (2.5–3.5)	3.0 (2.5–3.5)	3.0 (2.5–3.5)	2.9 (2.5–3.4)	3.0 (2.5–3.5)	0.520
Red cell distribution width (%)	17.1 (15.4–19.2)	17.1 (15.3–19.0)	16.9 (15.3–19.2)	17.2 (15.6–19.6)	17.1 (15.4–19.1)	0.200
Hemoglobin (g/dL)	9.3 (8.0-10.7)	9.2 (8.0-10.6)	9.4 (8.0-10.8)	9.4 (7.9–10.7)	9.3 (8.1–10.8)	0.773
Hematocrit (%)	28.0 (24.2–32.5)	28.1 (24.3–32.5)	27.9 (24.3–32.3)	27.7 (24.0-32.2)	28.3 (24.2–32.9)	0.723
Platelet count (K/ul)	101.0 (65.0-152.0)	107.0 (68.0-165.0)	99.0 (67.0-146.0)	101.0 (65.8-156.3)	95.5 (59.0-143.8)	0.010
White blood cell count (K/ul)	10.8 (6.8–16.5)	9.7 (6.3–14.6)	10.3 (6.8–15.6)	11.4 (7.9–17.6)	11.7 (6.9–18.6)	< 0.001
Neutrophil count (K/ul)	7.3 (4.0-13.9)	7.2 (4.0-13.5)	6.6 (4.0-13.5)	7.9 (4.0-14.2)	7.9 (4.0-14.8)	0.518
Lymphocyte count (K/ul)	0.7 (0.6–1.3)	0.8 (0.6–1.4)	0.7 (0.6–1.3)	0.8 (0.5–1.1)	0.7 (0.5–1.2)	0.055
Fibrinogen (mg/dL)	166.5 (124.0-260.0)	172.0 (124.0-269.0)	170.0 (124.0-260.0)	166.0 (124.0-254.0)	160.0 (117.3-239.8)	0.049
PT-INR	1.8 (1.5–2.3)	1.6 (1.3–2.1)	1.7 (1.4–2.2)	1.8 (1.5–2.3)	2.0 (1.6–2.5)	< 0.001
aPTT (s)	38.0 (32.2–48.8)	35.9 (30.7–44.6)	36.4 (31.5–46.1)	38.5 (32.8–49.1)	42.2 (34.4–53.4)	< 0.001
Vital signs						
Temperature (°F)	98.2 (97.7–98.8)	98.3 (97.7–98.8)	98.3 (97.7–98.8)	98.2 (97.7–98.8)	98.1 (97.6–98.7)	0.022
Heart rate (bpm)	94.6 (19.9)	89.3 (19.4)	92.4 (18.3)	95.2 (19.4)	101.7 (20.3)	< 0.001
Mean arterial pressure (mmHg)	78.0 (67.0–91.0)	78.0 (67.0–92.0)	78.0 (68.0–90.0)	78.5 (68.0–92.0)	76.5 (66.0-88.8)	0.397
Respiratory rate (bpm)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	< 0.001
SpO_2 (%)	98.0 (95.0-100.0)	98.0 (95.0-100.0)	98.0 (95.0-100.0)	98.0 (95.0-100.0)	99.0 (96.0-100.0)	0.002
Lactate-to-albumin ratio	0.9 (0.6–1.5)	0.4 (0.4–0.5)	0.7 (0.6–0.8)	1.1 (1.0-1.3)	2.3 (1.8–3.2)	< 0.001
Length of stay in the ICU (day)	4.0 (2.2–7.9)	4.0 (2.2–7.9)	3.7 (2.2–7.2)	3.9 (2.1–7.8)	4.2 (2.4–9.1)	0.044
Liver transplantation	52 (2.8%)	18 (3.8%)	16 (3.4%)	11 (2.4%)	7 (1.5%)	0.123
30-day mortality	708 (38.0%)	133 (28.4%)	148 (31.8%)	189 (40.7%)	238 (51.1%)	< 0.001
90-day mortality	863 (46.3%)	174 (37.1%)	185 (39.8%)	232 (50.0%)	272 (58.4%)	< 0.001
180-day mortality	922 (49.5%)	191 (40.7%)	204 (43.9%)	241 (51.9%)	286 (61.4%)	< 0.001

Abbreviations: ACLF, acute-on-chronic liver failure; CLIF-C, European Association for the Study of the Liver—Chronic Liver Failure-Consortium; PT-INR, international normalized ratio (INR) of prothrombin time (PT); ICU, intensive care unit; MICU, medical ICU; SICU, surgical ICU; TSICU, trauma SICU; aPTT, activated partial thromboplastin time; APS III, acute physiology score III; SAPS II, simplified acute physiology score II; SIRS, Systemic inflammatory response syndrome; OASIS, Oxford acute severity of illness score; SOFA, sequential organ failure assessment; MELD, model for end-stage liver disease; OF, organ failure; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, arterial oxygen partial pressure; SpO_2, saturation of pulse oximetry

Statistical analysis: Quantitative data were represented as means (standard deviation, SD) (normally distributed data) or medians (P_{25}-P_{75}) (non-normally distributed data), and were analyzed with One-way analysis of means or Kruskal-Wallis rank sum test. Qualitative data were represented as frequencies (proportions) and analyzed with the Pearson's Chi-squared test

and smoothed curve fitting, we found the nonlinear associations between LAR and all-cause mortality were L-shaped (Fig. 3D and E, and 3 F). We then conducted two-piecewise Cox proportional hazards models to investigate the nonlinear relationship between LAR and all-cause mortality, and found the inflection points of LAR for 30-day, 90-day, and 180-day all-cause mortality were 1.0500, 1.0455, and 1.0476 (all *P* for log-likelihood ratio < 0.01), respectively (Table 3).

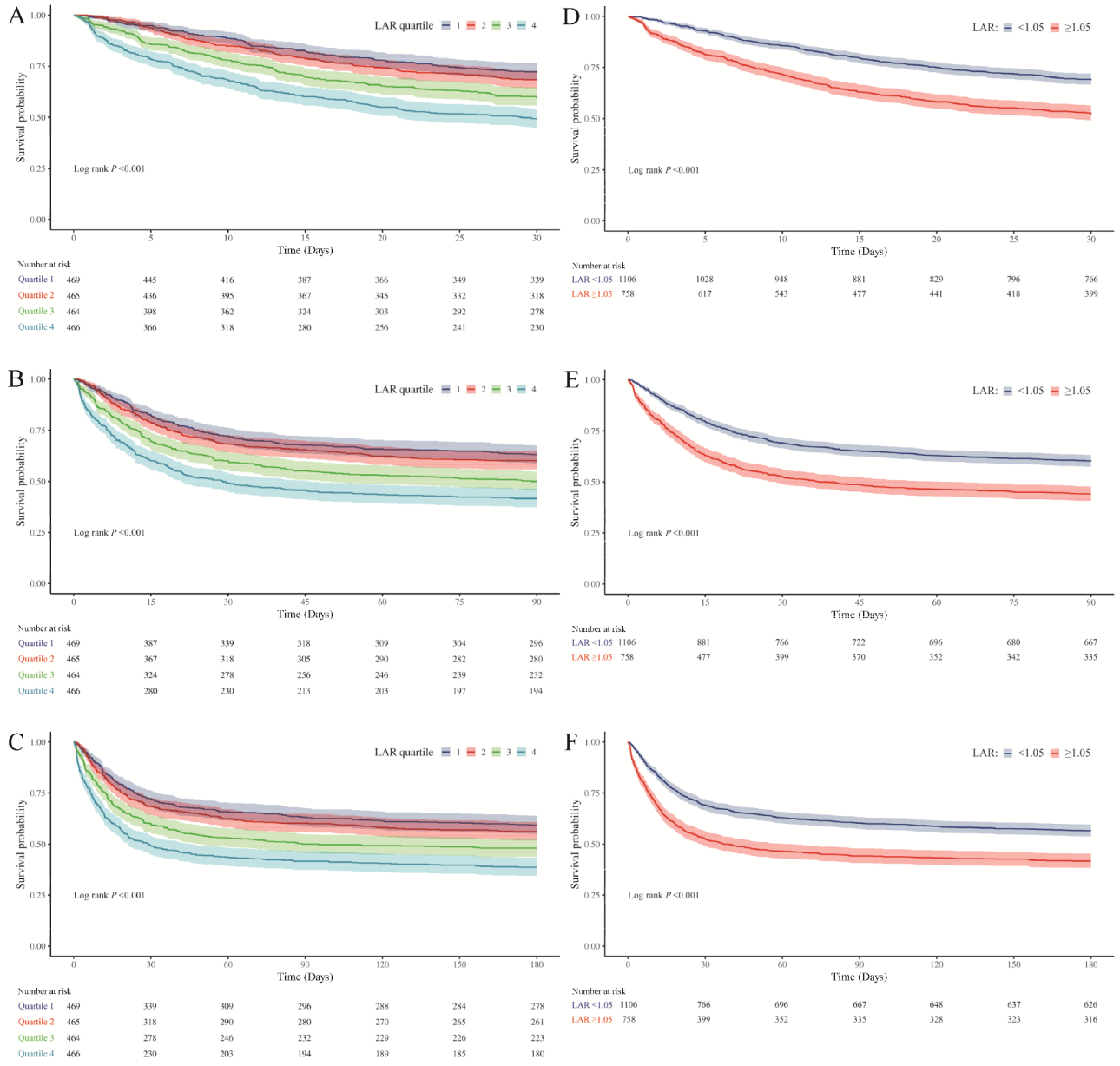

Fig. 2 Survival curves of critically ill cirrhotic patients with sepsis and stratified lactate-to-albumin ratio

When LAR was less than 1.05, each 1-unit increase in LAR was associated with 92%, 83%, and 73% greater aHR of 30-day, 90-day, and 180-day all-cause mortality, respectively (aHR (95% CI): 1.92 (1.38–2.68), 1.83 (1.36–2.47), and 1.73 (1.30–2.31)). When LAR exceeded 1.05, each 1-unit increase in LAR was associated with 11%, 12%, and 13% greater aHR of 30-day, 90-day, and 180-day all-cause mortality, respectively (aHR (95% CI): 1.11 (1.05–1.18), 1.12 (1.07–1.18), and 1.13 (1.07–1.19)).

Stratified analysis of the relationship between LAR and mortality

The Kaplan-Meier survival curves indicated that the survival probability differed significantly between the two groups (LAR < 1.05 and ≥ 1.05) (all log-rank $P < 0.001$; Fig. 2D, E and F). Patients with LAR ≥ 1.05 had lower survival probability during the 30-day, 90-day, and 180-day follow-up. Compared with patients with LAR < 1.05, patients with LAR ≥ 1.05 had higher risks of 30-day, 90-day, and 180-day all-cause mortality (aHR (95% CI): 1.48 (1.27–1.72), 1.44 (1.25–1.66), and 1.38 (1.21–1.57), respectively, all $P < 0.001$) (Table 4). The impact of higher LAR (≥ 1.05) versus lower LAR (< 1.05) on 30-day, 90-day,

Table 2 Relationship between lactate-to-albumin ratio and mortality in critically ill cirrhotic patients with sepsis

	Overall (*N* = 1864)	Quartile 1 (*n* = 469)	Quartile 2 (*n* = 465)	Quartile 3 (*n* = 464)	Quartile 4 (*n* = 466)	*P* for trend
30-day all-cause mortality						
Number of deaths (%)	708 (38.0%)	133 (28.4%)	148 (31.8%)	189 (40.7%)	238 (51.1%)	
Model 1 (HR (95% CI), *P*)	1.28 (1.22–1.33), < 0.001	1.00	1.15 (0.91–1.46), 0.237	1.61 (1.29–2.01), < 0.001	2.28 (1.84–2.81), < 0.001	< 0.001
Model 2 (HR (95% CI), *P*)	1.29 (1.24–1.35), < 0.001	1.00	1.17 (0.93–1.49), 0.179	1.68 (1.34–2.10), < 0.001	2.35 (1.90–2.92), < 0.001	< 0.001
Model 3 (HR (95% CI), *P*)	1.17 (1.11–1.23), < 0.001	1.00	1.15 (0.91–1.46), 0.253	1.45 (1.15–1.81), 0.001	1.76 (1.41–2.20), < 0.001	< 0.001
90-day all-cause mortality						
Number of deaths (%)	863 (46.3%)	174 (37.1%)	185 (39.8%)	232 (50.0%)	272 (58.4%)	
Model 1 (HR (95% CI), *P*)	1.28 (1.22–1.33), < 0.001	1.00	1.11 (0.90–1.36), 0.345	1.53 (1.26–1.87), < 0.001	2.05 (1.70–2.48), < 0.001	< 0.001
Model 2 (HR (95% CI), *P*)	1.28 (1.23–1.33), < 0.001	1.00	1.13 (0.92–1.40), 0.237	1.62 (1.33–1.97), < 0.001	2.14 (1.77–2.60), < 0.001	< 0.001
Model 3 (HR (95% CI), *P*)	1.17 (1.12–1.23), < 0.001	1.00	1.10 (0.89–1.36), 0.366	1.40 (1.15–1.71), 0.001	1.65 (1.35–2.02), < 0.001	< 0.001
180-day all-cause mortality						
Number of deaths (%)	922 (49.5%)	191 (40.7%)	204 (43.9%)	241 (51.9%)	286 (61.4%)	
Model 1 (HR (95% CI), *P*)	1.28 (1.22–1.33), < 0.001	1.00	1.11 (0.91–1.35), 0.293	1.46 (1.21–1.77), < 0.001	1.98 (1.65–2.38), < 0.001	< 0.001
Model 2 (HR (95% CI), *P*)	1.28 (1.23–1.33), < 0.001	1.00	1.15 (0.94–1.40), 0.171	1.56 (1.29–1.89), < 0.001	2.09 (1.74–2.51), < 0.001	< 0.001
Model 3 (HR (95% CI), *P*)	1.17 (1.12–1.23), < 0.001	1.00	1.11 (0.91–1.36), 0.288	1.37 (1.13–1.66), 0.001	1.66 (1.37–2.01), < 0.001	< 0.001

Abbreviations: HR, hazard ratio; CI, confidence interval

The Model 1 was adjusted for none

The Model 2 was partially adjusted for age (years), sex (female vs. male), height (cm), weight (kg), race (Black vs. Hispanic vs. White vs. Others), marital status (Married vs. Single vs. Others), insurance (Medicare vs. Medicaid vs. Private vs. Others), and Charlson Comorbidity Index

The Model 3 was fully adjusted for variables used in Model 2 and ICU type (MICU vs. MICU/SICU vs. SICU/TSICU), infection site (blood stream infection, lung infection, and abdominal infection), disease severity of liver cirrhosis (CLIF-C ACLF score), and disease severity of sepsis (SOFA score)

and 180-day all-cause mortality in critically ill cirrhotic patients with sepsis were similar across a wide range of subgroups stratified by ICU type, age (< 60 vs. ≥60 years), sex, race, insurance, marital status, CCI (1–3 vs. 4–6 vs. ≥7), SOFA score (1–6 vs. 7–12 vs. ≥13), CLIF-C ACLF (yes vs. no), blood stream infection (yes vs. no), lactate (< 2 vs. 2–4 vs. ≥4 mmol/L), and albumin (< 2.5 vs. 2.5-3.0 vs. ≥3.0 g/dL) (all aHR > 1). There was no significant interaction between LAR and stratified variables (all *P* for interaction > 0.05).

Performance of LAR in predicting mortality

The AUCs for LAR in predicting 30-day, 90-day and 180-day all-cause mortality were comparable to those of lactate (all $P > 0.05$) and superior to those of albumin (all $P < 0.001$) (Supplemental file 1: Table S5 and Figure S1).

The AUCs for LAR combined with MELD score ($MELDs_{LAR}$) in predicting 30-day, 90-day and 180-day all-cause mortality exhibited marginal increases compared to the MELD score (Supplemental file 1: Table S6 and Figure S2); the difference in AUC (95% CI) for 30-day overall mortality was statistically significant (0.727 (0.703–0.750) vs. 0.714 (0.690–0.738), $P = 0.029$), but that for 90-day all-cause mortality (0.722 (0.699–0.745) vs. 0.714 (0.690–0.737), $P = 0.114$) and 180-day all-cause mortality (0.705 (0.681–0.728) vs. 0.695 (0.671–0.719), $P = 0.080$) were not statistically significant.

The AUCs for LAR combined with CLIF-C ACLF score ($CLIF\text{-}C\ ACLFs_{LAR}$) in predicting 30-day, 90-day and 180-day all-cause mortality exhibited marginal increases compared to the CLIF-C ACLF score (Supplemental file 1: Table S6 and Figure S2); the differences were all statistically significant (0.701 (0.676–0.725) vs. 0.680 (0.655–0.705), $P = 0.003$; 0.706 (0.683–0.729) vs. 0.688 (0.664–0.712), $P = 0.004$; 0.695 (0.671–0.719) vs. 0.678 (0.654–0.702), $P = 0.010$).

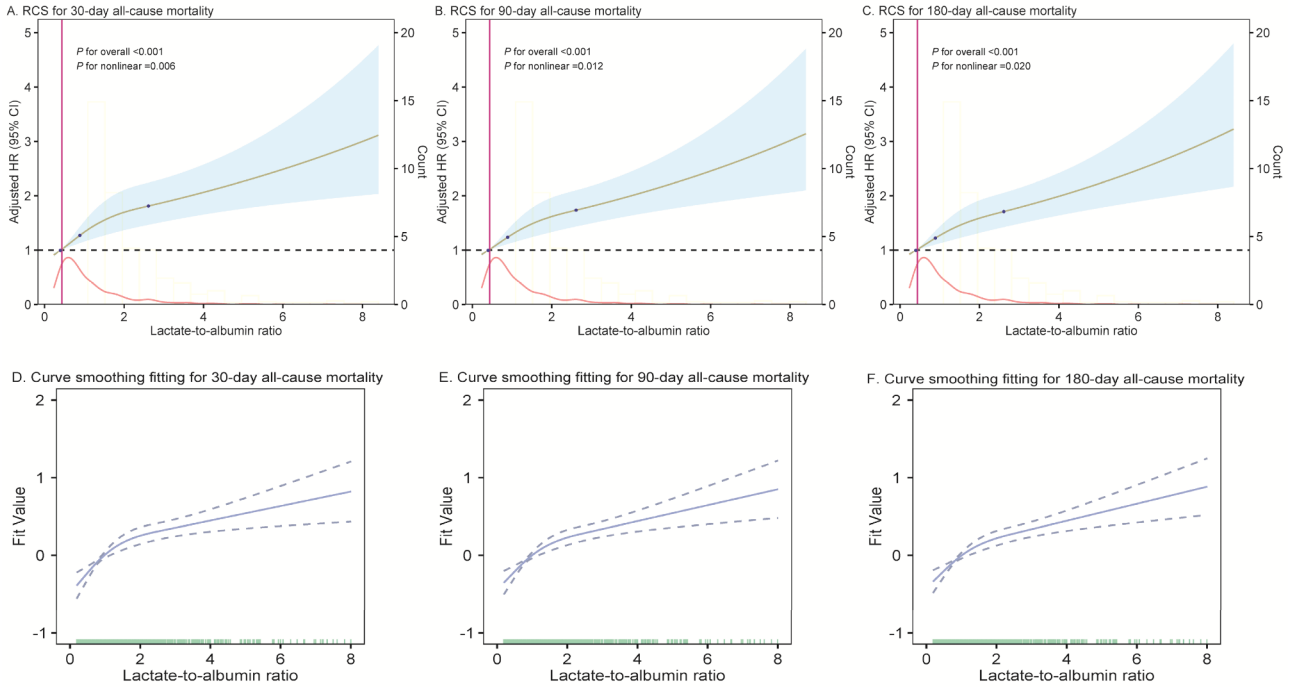

Fig. 3 Relationship between lactate-to-albumin ratio and mortality in critically ill cirrhotic patients with sepsis

Table 3 Threshold effect analysis of lactate-to-albumin ratio on mortality in critically ill cirrhotic patients with sepsis

	Value or adjusted HR (95% CI)[§]	*P*
30-day all-cause mortality		
Fitting by the standard linear model	1.17 (1.11–1.22)	< 0.001
Fitting by the two-piecewise linear model		
Inflection point	1.0500	
Lactate-to-albumin ratio < 1.0500	1.92 (1.38–2.68)	< 0.001
Lactate-to-albumin ratio ≥ 1.0500	1.11 (1.05–1.18)	< 0.001
P for log-likelihood ratio		0.003
90-day all-cause mortality		
Fitting by the standard linear model	1.17 (1.12–1.23)	< 0.001
Fitting by the two-piecewise linear model		
Inflection point	1.0455	
Lactate-to-albumin ratio < 1.0455	1.83 (1.36–2.47)	< 0.001
Lactate-to-albumin ratio ≥ 1.0455	1.12 (1.07–1.18)	< 0.001
P for log-likelihood ratio		0.003
180-day all-cause mortality		
Fitting by the standard linear model	1.17 (1.12–1.23)	< 0.001
Fitting by the two-piecewise linear model		
Inflection point	1.0476	
Lactate-to-albumin ratio < 1.0476	1.73 (1.30–2.31)	< 0.001
Lactate-to-albumin ratio ≥ 1.0476	1.13 (1.07–1.19)	< 0.001
P for log-likelihood ratio		0.007

Abbreviations: HR, hazard ratio; CI, confidence interval

[§], The Cox model is fully adjusted for variables used in Model 3: age (years), sex (female vs. male), height (cm), weight (kg), race (Black vs. Hispanic vs. White vs. Others), marital status (Married vs. Single vs. Others), insurance (Medicare vs. Medicaid vs. Private vs. Others), Charlson Comorbidity Index, ICU type (MICU vs. MICU/SICU vs. SICU/TSICU), infection site (blood stream infection, lung infection, and abdominal infection), disease severity of liver cirrhosis (CLIF-C ACLF score), and disease severity of sepsis (SOFA score)

Table 4 Stratified analysis of lactate-to-albumin ratio (≥ 1.05 vs. <1.05) on mortality in critically ill cirrhotic patients with sepsis

	30-day all-cause mortality			90-day all-cause mortality			180-day all-cause mortality		
	HR (95% CI)[§]	*P*	*P* for interaction	HR (95% CI)[§]	*P*	*P* for interaction	HR (95% CI)[§]	*P*	*P* for interaction
Overall	1.48 (1.27–1.72)	< 0.001		1.44 (1.25–1.66)	< 0.001		1.38 (1.21–1.57)	< 0.001	
ICU type			0.790			0.409			0.401
MICU	1.48 (1.22–1.80)	< 0.001		1.51 (1.26–1.80)	< 0.001		1.41 (1.19–1.66)	< 0.001	
MICU/SICU	1.81 (1.23–2.65)	0.002		1.65 (1.16–2.34)	0.006		1.64 (1.19–2.26)	0.003	
SICU/TSICU	1.37 (0.95–1.97)	0.094		1.25 (0.91–1.73)	0.174		1.23 (0.91–1.66)	0.172	
Age ≥ 60 years			0.469			0.861			0.574
No	1.41 (1.13–1.77)	0.003		1.43 (1.17–1.75)	0.001		1.31 (1.08–1.59)	0.005	
Yes	1.58 (1.27–1.96)	< 0.001		1.48 (1.22–1.80)	< 0.001		1.48 (1.24–1.77)	< 0.001	
Sex			0.379			0.149			0.115
Female	1.40 (1.09–1.80)	0.009		1.31 (1.04–1.65)	0.024		1.21 (0.97–1.51)	0.091	
Male	1.54 (1.26–1.89)	< 0.001		1.55 (1.29–1.85)	< 0.001		1.49 (1.27–1.76)	< 0.001	
Race			0.562			0.562			0.280
Black	1.62 (0.83–3.14)	0.155		1.46 (0.79–2.67)	0.224		1.06 (0.62–1.80)	0.840	
Hispanic	1.83 (0.85–3.95)	0.124		2.04 (1.02–4.11)	0.045		1.81 (0.95–3.45)	0.070	
White	1.39 (1.14–1.70)	0.001		1.39 (1.16–1.67)	< 0.001		1.36 (1.15–1.61)	< 0.001	
Others	1.88 (1.38–2.57)	< 0.001		1.68 (1.27–2.24)	< 0.001		1.67 (1.27–2.20)	< 0.001	
Insurance			0.360			0.330			0.286
Medicare	1.47 (1.14–1.89)	0.003		1.46 (1.16–1.83)	0.001		1.37 (1.11–1.69)	0.003	
Private	1.49 (1.09–2.02)	0.011		1.42 (1.07–1.88)	0.014		1.39 (1.07–1.81)	0.013	
Others	1.83 (1.39–2.40)	< 0.001		1.73 (1.35–2.22)	< 0.001		1.61 (1.28–2.03)	< 0.001	
Marital status			0.156			0.369			0.072
Married	1.44 (1.12–1.85)	0.005		1.36 (1.08–1.72)	0.009		1.38 (1.11–1.71)	0.004	
Single	1.40 (1.11–1.76)	0.005		1.43 (1.16–1.76)	0.001		1.29 (1.07–1.56)	0.009	
Unknown	1.98 (1.33–2.95)	0.001		1.75 (1.22–2.52)	0.002		1.79 (1.26–2.54)	0.001	
Charlson Comorbidity Index			0.589			0.474			0.674
1–3	1.53 (0.96–2.44)	0.073		1.39 (0.90–2.14)	0.136		1.38 (0.93–2.05)	0.109	
4–6	1.53 (1.20–1.94)	0.001		1.51 (1.22–1.87)	< 0.001		1.39 (1.13–1.69)	0.001	
≥7	1.44 (1.14–1.82)	0.002		1.42 (1.15–1.76)	0.001		1.39 (1.14–1.70)	0.001	
SOFA score			0.482			0.335			0.246
1–6	1.93 (1.18–3.15)	0.009		2.01 (1.32–3.05)	0.001		1.97 (1.38–2.81)	< 0.001	
7–12	1.40 (1.13–1.73)	0.002		1.35 (1.12–1.63)	0.002		1.30 (1.09–1.54)	0.004	
≥13	1.51 (1.15–1.98)	0.003		1.51 (1.16–1.95)	0.002		1.45 (1.13–1.88)	0.004	
CLIF-C ACLF			0.839			0.394			0.375
No	1.47 (1.16–1.86)	0.001		1.36 (1.11–1.68)	0.004		1.35 (1.12–1.63)	0.002	
Yes	1.48 (1.20–1.83)	< 0.001		1.52 (1.25–1.84)	< 0.001		1.41 (1.18–1.70)	< 0.001	
Blood stream infection			0.445			0.420			0.134
No	1.48 (1.15–1.90)	0.002		1.43 (1.14–1.80)	0.002		1.33 (1.09–1.63)	0.006	
Yes	1.52 (1.25–1.86)	< 0.001		1.50 (1.25–1.79)	< 0.001		1.46 (1.23–1.73)	< 0.001	
Albumin (g/dL)			0.152			0.225			0.232
<2.5	2.09 (1.49–2.93)	< 0.001		1.95 (1.45–2.61)	< 0.001		1.80 (1.38–2.35)	< 0.001	
2.5-3.0	1.43 (1.05–1.94)	0.024		1.40 (1.06–1.85)	0.017		1.40 (1.09–1.81)	0.008	
≥3.0	1.34 (1.05–1.72)	0.020		1.30 (1.03–1.63)	0.025		1.21 (0.98–1.50)	0.083	
Lactate (mmol/L)			0.767			0.207			0.160
<2	1.31 (0.39–4.39)	0.663		2.47 (0.95–6.38)	0.063		2.71 (1.06–6.92)	0.036	
2–4	1.18 (0.93–1.50)	0.180		1.14 (0.91–1.42)	0.261		1.09 (0.88–1.34)	0.441	
≥4	1.03 (0.14–7.68)	0.977		1.56 (0.21–11.53)	0.664		2.00 (0.27–14.74)	0.497	

Abbreviations: ACLF, acute-on-chronic liver failure; CLIF-C, European Association for the Study of the Liver—Chronic Liver Failure-Consortium; ICU, intensive care unit; MICU, medical ICU; SICU, surgical ICU; TSICU, trauma SICU; SOFA, sequential organ failure assessment; HR, hazard ratio; CI, confidence interval

[§], The Cox model is fully adjusted for variables used in Model 3: age (years), sex (female vs. male), height (cm), weight (kg), race (Black vs. Hispanic vs. White vs. Others), marital status (Married vs. Single vs. Others), insurance (Medicare vs. Medicaid vs. Private vs. Others), Charlson Comorbidity Index, ICU type (MICU vs. MICU/SICU vs. SICU/TSICU), infection site (blood stream infection, lung infection, and abdominal infection), disease severity of liver cirrhosis (CLIF-C ACLF score), and disease severity of sepsis (SOFA score)

Discussion

In this retrospective cohort study based on the MIMIC-IV database (v3.0), we found that higher LAR were significantly associated with higher risks of 30-day, 90-day, and 180-day all-cause mortality in critically ill cirrhotic patients with sepsis. L-shaped nonlinear associations between LAR and all-cause mortality were observed, with an inflection point of 1.05. Compared with patients with LAR < 1.05, patients with LAR ≥ 1.05 had higher risks of 30-day, 90-day, and 180-day all-cause mortality. No potential modifiers were found in the relationship between LAR and all-cause mortality.

LAR is a newly discovered biomarker for evaluating prognosis of critically ill patients and has been studied in some detail in sepsis patients [21–25]. Only three studies investigated the role LAR played in different types of liver diseases [36–38]. The first one retrieved 341 adult critically ill patients with sepsis-associated liver injury (SALI): a total bilirubin level > 2 mg/dL (34.2 μmol/L) with an international normalized ratio of prothrombin time (PT-INR) > 1.5 [39]. It was found that the LAR at admission, SAPS II, SOFA score, and CCI in non-survivors were comparably higher than that in survivors (all $P < 0.05$) [36]. For every 1-unit increase in LAR, the 28-day mortality risk for patients with SALI increased by 21% (HR (95% CI): 1.21 (1.11–1.31), $P < 0.001$) [36]. The second one studied 279 hospitalized cirrhotic patients with CLIF-C ACLF and found that the LAR was an independent predictor for in-hospital mortality (odds ratio (95% CI): 13.20 (3.60–48.30), $P < 0.001$) [37]. The sample size in the last study is relatively smaller. Data from 175 critically ill cirrhotic patients with or without CLIF-C ACLF in ICU was analyzed and it turns out LAR and clinical severity scores (APACHE II, SOFA score, and CLIF-C OF score) in non-survivors were all significantly higher than that in survivors (All $P < 0.001$) [38]. The LAR was one of the independent predictors of ICU mortality, and its predictive accuracy was comparable to APACHE II, SOFA score, and CLIF-C OF score [38]. In our study, we retrieved a large number of critically ill cirrhotic patients with sepsis and found that LAR was positively associated with 30-day, 90-day, and 180-day all-cause mortality (all aHR = 1.17, $P < 0.001$). Interestingly, we found L-shaped nonlinear relationships between LAR and 30-day, 90-day, and 180-day all-cause mortality, with an inflection point of 1.05. Compared with patients with LAR < 1.05, patients with LAR ≥ 1.05 had higher risks of 30-day, 90-day, and 180-day all-cause mortality (aHR (95% CI): 1.48 (1.27–1.72), 1.44 (1.25–1.66), and 1.38 (1.21–1.57), respectively). Taken together, LAR could be used as an independent risk factor for adverse outcomes in critically ill patients with liver diseases, including SALI, critically ill cirrhotic patients with sepsis, and critically ill cirrhotic patients with or without ACLF.

In addition to our study and previous studies on severe liver diseases [36–38], the LAR has also been confirmed to be associated with disease severity and poor short-term prognosis in multiple conditions, including unselected critically ill adults or pediatric patients in the ICU [40–42], unselected critically ill patients with sepsis, with or without associated shock [21–25], and patients with acute pancreatitis [43], traumatic brain injury [44], acute kidney injury [45, 46], coronary heart disease [47–51], or severe burn injury [52]. All of these studies demonstrated that the LAR could effectively serve as an independent risk factor for adverse outcomes in many critically ill conditions.

The lactate level is a reliable parameter for sepsis diagnosis, treatment decisions, and prognosis evaluation [11]. However, the interpretation of serum lactate levels is complicated as it can be influenced by tissue hypoxia, accelerated glycolysis or renal or liver insufficiency. Patients with normal or moderately elevated lactate levels may also face a high risk of death [53]. A multicenter retrospective cohort study found that the AUC of LAR in critically ill sepsis patients was better than that of lactate regardless of lactate level (normal (< 2 mmol/L): 0.68 vs. 0.55, $P < 0.01$; intermediate (2–4 mmol/L): 0.65 vs. 0.50, $P < 0.01$; high (≥ 4 mmol/L): 0.66 vs. 0.62, $P = 0.02$) [25]. In the subgroup with decreased lactate elimination, the AUC value of LAR was also significantly higher than that of lactate (hepatic dysfunction: 0.70 vs. 0.66, $P < 0.01$; renal dysfunction: 0.71 vs. 0.67, $P < 0.01$) [25]. Another large cohort based on the MIMIC-III database found that LAR was positively associated with ICU mortality in unselected critically ill patients [40]. LAR yielded better AUC compared to the lactate level itself, irrelevant to the lactate level (normal (< 2 mmol/L): 0.63 vs. 0.60; intermediate (2–4 mmol/L): 0.58 vs. 0.56; high (≥ 4 mmol/L): 0.67 vs. 0.66) [40]. LAR was also a better prognostic marker for ICU mortality in patients with decreased lactate elimination (hepatic dysfunction: 0.72 vs. 0.70; renal dysfunction 0.70 vs. 0.68) [40]. In our study, we found the AUCs for LAR in predicting 30-day, 90-day and 180-day all-cause mortality were comparable to those of lactate (all $P > 0.05$), and the adjusted and stratified Cox models suggested that lactate (≥ 4 vs. 2–4 vs. <2 mmol/L) was not a potential factor modifying the relationship between LAR (≥ 1.05 vs. <1.05) and 30-day, 90-day, and 180-day all-cause mortality of critically ill cirrhotic patients with sepsis (all P for interaction > 0.05). Therefore, LAR could be used as an independent prognostic marker in critically ill patients with liver diseases at different baseline lactate levels.

Liver transplantation is currently the most effective treatment for end-stage liver diseases, including critically ill cirrhotic patients. But those with recent infection from multi-drug resistant pathogenic micro-organisms

had higher post-liver transplantation mortality (aHR (95% CI): 3.67 (1.63–8.28), $P = 0.002$) [54]. The infection has been considered to be one of contraindications for liver transplantation [55]. Artificial liver support system (ALSS) treatment is another available method in addition to drug therapy building a bridge to liver transplantation [56]. ALSS treatment could effectively remove inflammatory mediators and toxins in patients with end-stage liver diseases and infection [57]. Several studies have shown that ALSS treatment could significantly improve short-term prognosis in cirrhotic patients developed ACLF [58], especially the plasma exchange-centered methods [59–61]. However, even though ALSS has been actively administered in addition to medication, a significant proportion of patients fails to survive [62]. It arouse the need for more refined stratified management. Novel independent prognostic markers, such as LAR, may help to assess patient prognosis more accurately and would guide clinical management. In our study, the AUCs of LAR combined with the MELD score ($MELDs_{LAR}$) were superior to those of the standalone MELD score in predicting 30-day all-cause mortality and were comparable in predicting 90-day and 180-day all-cause mortality. The AUCs of LAR combined with the CLIF-C ACLF score (CLIF-C $ACLFs_{LAR}$) were superior to those of the standalone CLIF-C ACLF score in predicting 30-day, 90-day, and 180-day all-cause mortality.

This study has some limitations. First, this is a retrospective cohort study with a single geographic region of critically ill cirrhotic patients with sepsis. The results from this subset may not be applicable to patients who did not have liver cirrhosis or sepsis. In addition, we could not avoid the variability among investigators during the diagnosis of liver cirrhosis and sepsis as subjects were identified by ICD codes in the MIMIC-IV database. Moreover, we investigated the association between LAR and all-cause mortality by selecting adjusted variables based on clinical significance. There may be unconsidered potential confounding factors. Last but not least, our study only focused on the role of LAR measured for the first time after ICU admission, the value of its dynamic changes needs to be explored in the future.

In conclusion, our findings suggested the LAR was positively and nonlinearly associated with 30-day, 90-day, and 180-day all-cause mortality in critically ill cirrhotic patients with sepsis. More attention should be paid to such patients with higher LAR. A validated model with LAR would help to assess disease severity and predict outcomes in critically ill cirrhotic patients with sepsis and guide clinical management.

Abbreviations

ACLF	Acute-on-chronic liver failure
ALSS	Artificial liver support system
APS III	Acute physiology score III
AUC	Area under the receiver operating characteristic curve
CCI	Charlson comorbidity index
CI	Confidence interval
CLIF-C	European Association for the Study of the Liver—Chronic Liver Failure-Consortium
HR	Hazard ratio
ICU	Intensive care unit
LAR	Lactate-to-albumin ratio
MELD	Model for end-stage liver disease
MIMIC-IV	Medical Information Mart for Intensive Care IV
OASIS	Oxford acute severity of illness score
PT-INR	International normalized ratio of prothrombin time
RCS	Restricted cubic spline
SALI	Sepsis-associated liver injury
SAPS II	Simplified acute physiology score II
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03686-5.

Supplementary Material 1

Acknowledgements
We thank all patients who participated in the MIMIC-IV database for their understanding and recognition of medical research.

Author contributions
MYJ: Full access to all data. MYJ and DLY: Statistical analysis, manuscript drafting, and data interpretation. BL and TH: Study concept and design, as well as the critical revision of manuscript for important intellectual content. All authors have read and approved the final manuscript.

Funding
This work was supported by the National Key Research and Development Program of China (No. 2022YFC2304800) and the 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYGD23030).

Data availability
The original contributions presented in the study are included in the article/supplementary material, and further inquiries can be directed to the corresponding author/s.

Declarations

Ethics approval and consent to participate
MIMIC-IV is the result of a collaboration between Beth Israel Deaconess Medical Center (BIDMC) and Massachusetts Institute of Technology (MIT). Data collected at BIDMC as part of routine clinical care is deidentified, transformed, and made available to researchers who (certification number 64735113) have completed training in human research and signed a data use agreement. The Institutional Review Board at the BIDMC granted a waiver of informed consent and approved the sharing of the research resource.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Received: 24 October 2024 / Accepted: 12 February 2025
Published online: 24 February 2025

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