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Association between lactate-albumin ratio and 28-day mortality in patients with sepsis-associated acute kidney injury: a retrospective cohort study

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The aim of this study was to investigate the correlation between lactate-albumin ratio (LAR) and 28-day mortality in patients with sepsis combined with acute kidney failure (SA-AKI). The study was based on the eICU database and collected data from 1855 patients with SA-AKI. The relationship between LAR and 28-day in-hospital mortality was assessed using multivariate Cox regression models and Kaplan-Meier survival analysis. A generalised summation model was also used to analyse the non-linear relationship between LAR and mortality. The results showed that the 28-day in-hospital mortality rate of the patients was 19.46% (361/1,855), with a significant positive correlation between LAR and mortality (HR: 1.26, 95% CI: 1.18–1.35, $p < 0.001$). The Kaplan-Meier survival curve showed that the highest quartile of LAR (Q4) had the lowest survival rate. Non-linear analysis showed that when the LAR ratio was less than 2.1, mortality increased with each 1-unit increase in the LAR ratio, with an adjusted hazard ratio of 1.48 (95% CI 1.20, 1.84, $p < 0.001$). For patients with SA-AKI, a nonlinear relationship between LAR and 28-day risk of death was observed, with higher LAR associated with higher risk of mortality.

Sepsis represents a significant clinical challenge in the field of intensive care medicine(ICU), particularly when it is complicated by acute kidney failure (AKI)[1];[2]. In such cases, the prognosis for patients is particularly poor[3]. Despite significant advances in critical care medicine in recent years, the mortality rate of patients with sepsis and acute renal failure remains high[4]. Consequently, a more thorough examination of the phenotypes and subphenotypes of patients who exhibit robust survival signals in patients with SA-AKI may enhance us to understand new mechanisms for improving treatment.

Lactic acid is frequently utilized as a crucial indicator for assessing tissue perfusion and metabolic status in clinical settings, persistent hyperlactatemia typically indicates tissue hypoxia and metabolic dysfunction[5]. Albumin serves not only as a vital marker of inflammation and nutritional status but also exerts protective effects on multiple organs, including the scavenging of oxidative free radicals, the promotion of endothelial cell proliferation, and the reduction of apoptosis[6];[7].The lactate-albumin ratio (LAR) has emerged as a significant composite marker extensively investigated in the prognostic evaluation of numerous diseases in recent years[8–10]. A prospective cohort study conducted in an intensive care unit revealed that patients exhibiting elevated levels of LAR were more likely to develop multiple organ dysfunction syndrome (MODS) and demonstrated significantly higher mortality rates[11]. A retrospective cohort study of 341 patients with sepsis associated liver injury based on the Medical Information Mart for Intensive Care IV (v2.2) database examined the association of lactate-albumin ratio (LAR) with 28-day all-cause mortality, The findings of the study indicated that each 1-unit increase in LAR was associated with a 21% increase in the risk of in-hospital sepsis-related mortality, demonstrating a significant positive correlation between the two variables[12]. Nevertheless, comprehensive investigations of LAR in patients with SA-AKI remain insufficient.

We hypothesized that LAR levels in patients with SA-AKI were positively associated with 28-day mortality, and that higher LAR levels were associated with higher mortality. To prove this hypothesis, we performed a

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retrospective multicenter cohort analysis using data from the eICU Collaborative Research Database, which included 208 intensive care units in the United States.

Results

Baseline characteristics

The data from 1,855 patients were subjected to analysis, resulting in a hospital 28-day mortality rate of 19.46% (361/1,855). The median age of the cohort was 65.55 years, and 954 patients (51.43%) were female. The patients were divided into four categories based on the LAR level. Patients in the highest quartile (Q4) exhibited lower BMI, lower GCS scores, higher Apache IV scores, and significantly higher 28-day hospital mortality (30.68% vs. 11.02%, $p < 0.001$) and ICU mortality rates (20.00% vs. 6.04%, $p < 0.001$) compared to those in the lowest quartile (Q1). Significant interquartile differences were observed with respect to gender, ethnicity, and key laboratory parameters, including lactate, albumin, and calcium levels ($p < 0.001$) (Table 1).

Association between LAR and hospital 28-day mortality

To investigate potential correlates of 28-days mortality, we performed univariate Cox regression analyzes (Supplementary Tables 1&2). Three models were used in this study to examine the association between LAR and 28-day in-hospital mortality and intensive care unit mortality. The results showed that the hazard ratio (HR) of continuous LAR to in-hospital mortality was 1.26 (95% confidence interval (CI): 1.18–1.35, $P < 0.001$). The corresponding value for ICU mortality was 1.22 (95% CI: 1.11–1.34, $P < 0.001$). Further analysis of quartiles showed that in model 2, the HR for in-hospital mortality was 2.13 (95% CI: 1.50–3.02, $P < 0.001$) and the HR for ICU mortality was 1.66 (95% CI: 1.00-2.75, $P = 0.05$) in patients in the fourth quartile compared with patients in the first quartile. The results of trend analysis showed a statistically significant positive association between LAR and in-hospital mortality and ICU mortality (trend $P < 0.05$) (Table 2).

Kaplan-Meier survival curves for 28-day mortality

Figure 1 depicts the Kaplan-Meier survival curves for hospital 28-day mortality across the quartiles of the LAR. The results indicate a significant negative correlation between LAR quartile and survival probability, with Q4 exhibiting the lowest survival rate and the highest mortality risk compared to the other quartiles. The log-rank test results demonstrate that the survival differences among the quartiles are statistically significant ($p < 0.0001$). The same results were consistent in terms of ICU 28-day mortality (Supplementary Fig. 1).

Identifcation of nonlinear relationship

Figure 2 illustrates a notable nonlinear correlation between hospital 28-day mortality and LAR. The linear model analysis demonstrates that for each unit increase in LAR, HR for mortality risk is 1.2 (95% CI: 1.1–1.3, $P < 0.001$), indicating a positive correlation between LAR and mortality. A further segmented analysis reveals a significant change at the threshold K. When K is less than 2.1, HR for mortality risk is 1.5 (95% CI: 1.2–1.8, $P < 0.001$), whereas when K is greater than 2.1, HR decreases to 1.1 (95% CI: 0.9–1.2, $P = 0.291$). The likelihood ratio test demonstrates $P < 0.05$, indicating that the nonlinear model is superior to the linear model (Table 3).

Stratified analyses

Stratified analyses showed that age (≤ 60 years, HR: 1.19, $P < 0.001$; >60 years, HR: 1.18, $P < 0.001$), and gender (male, HR: 1.19, $P < 0.001$; female, HR: 1.18, $P = 0.001$) were associated with an increased risk of death. Caucasians (HR: 1.22, $P < 0.001$) and African Americans (HR: 1.25, $P = 0.021$) faced a higher risk, whereas Hispanics (HR: 1.03, $P = 0.744$) had no significant association. In addition, serum potassium levels between 3.5 and 5.5 mmol/L (HR: 1.23, $P < 0.001$) and BUN > 20 mg/dL (HR: 1.24, $P < 0.001$) were associated with increased mortality. In the interaction analyses, no significant interaction was observed for age, sex, and BMI (all P values > 0.05) (Fig. 3). The results of the stratified analyses were consistent with respect to ICU 28-day mortality (Supplementary Fig. 2).

Sensitivity analysis

We employed multiple interpolation techniques to address missing data, and the relationship between LAR and 28-day mortality remained consistent(Supplementary Table 3). The association between LAR and mortality outcomes was further examined at 14 and 30 days of follow-up, yielding comparable results(Supplementary Tables 4&5). An E-value was calculated to evaluate the sensitivity of our findings to potential unmeasured confounding variables. The primary results demonstrated robustness, except in the presence of an unmeasured confounder with a hazard ratio exceeding 3.68. We evaluated and confirmed the proportional hazards assumption of the Cox regression model($p = 0.801$).

Discussion

The findings of this retrospective cohort study indicated that elevated LAR in patients with sepsis combined with acute renal failure was associated with an elevated 28-day risk of mortality in the eICU-CRD database. The primary findings were that there was a non-linear relationship between LAR and the risk of death at 28 days of hospitalisation, with the risk being highest in those with very high LAR. To the best of our knowledge, this is the inaugural study to report the relationship between LAR and 28-day mortality in patients with sepsis combined with acute renal failure.

SA-AKI is a multifaceted clinical syndrome characterized by a complex pathophysiological mechanism involving numerous factors[13,14]. Primarily, acute kidney injury resulting from sepsis is frequently linked to a systemic inflammatory response, which initiates a cascade of immune and inflammatory reactions culminating in microvascular dysfunction and endothelial cell damage within the kidneys[15–17]. Furthermore, sepsis has

Variables	LAR					*P*-value
	Total	Q1(<0.37)	Q2(0.37–0.76)	Q3(0.76–1.67)	Q4(>1.67)	
N	1855	381	401	483	590	
Demographics						
Age (years)	65.55 ± 15.43	64.36 ± 15.71	66.44 ± 14.89	66.66 ± 15.33	64.81 ± 15.64	0.059
Gender						0.025
Male	901 (48.57%)	208 (54.59%)	190 (47.38%)	214 (44.31%)	289 (48.98%)	
Female	954 (51.43%)	173 (45.41%)	211 (52.62%)	269 (55.69%)	301 (51.02%)	
Ethnicity						0.005
Caucasian	1473 (79.41%)	312 (81.89%)	332 (82.79%)	394 (81.57%)	435 (73.73%)	
African American	156 (8.41%)	26 (6.82%)	24 (5.99%)	40 (8.28%)	66 (11.19%)	
Hispanic	101 (5.44%)	23 (6.04%)	24 (5.99%)	19 (3.93%)	35 (5.93%)	
Others	125 (6.74%)	20 (5.25%)	21 (5.24%)	30 (6.21%)	54 (9.15%)	
BMI	29.92 ± 9.19	31.66 ± 9.69	30.05 ± 8.47	29.64 ± 9.20	28.93 ± 9.19	< 0.001
Vital signs						
Temperature	36.54 ± 1.06	36.48 ± 1.00	36.65 ± 1.29	36.65 ± 1.32	36.31 ± 1.64	< 0.001
Respiratory rate (bpm)	29.33((16–38))	25.45(11–35)	28.76 (14–38)	29.17 (16–38)	32.36 (27–40)	< 0.001
Heart rate (/min)	116.31 ± 26.73	104.71 ± 26.48	109.16 ± 29.79	113.38 ± 27.76	120.44 ± 26.67	< 0.001
MAP (mmHg)	75.67(46–100)	77.92(47–114)	75.74 (47–110)	73.12 (46–68)	76.25 (44-115.5)	0.010
Severity of illness						
GCS score						< 0.001
≥ 8	1496 (80.65%)	334 (87.66%)	342 (85.29%)	399 (82.61%)	421 (71.36%)	
<8	359 (19.35%)	47 (12.34%)	59 (14.71%)	84 (17.39%)	169 (28.64%)	
Apache IV score	83.15 ± 27.22	70.07 ± 21.46	76.71 ± 23.64	80.68 ± 23.99	98.08 ± 28.61	< 0.001
Acute Physiology Score III	69.50 ± 26.31	57.49 ± 19.93	63.00 ± 22.64	66.86 ± 22.86	83.90 ± 28.50	< 0.001
Comorbidities						
Metastatic cancer						0.394
No	1798 (97.03%)	373 (97.90%)	390 (97.26%)	469 (97.30%)	566 (96.10%)	
Yes	55 (2.97%)	8 (2.10%)	11 (2.74%)	13 (2.70%)	23 (3.90%)	
COPD						0.062
No	1682 (90.67%)	345 (90.55%)	358 (89.28%)	429 (88.82%)	550 (93.22%)	
Yes	173 (9.33%)	36 (9.45%)	43 (10.72%)	54 (11.18%)	40 (6.78%)	
CHF						0.843
No	1653 (89.11%)	343 (90.03%)	354 (88.28%)	428 (88.61%)	528 (89.49%)	
Yes	202 (10.89%)	38 (9.97%)	47 (11.72%)	55 (11.39%)	62 (10.51%)	
Diabetes						0.076
No	1375 (74.20%)	278 (72.97%)	308 (76.81%)	371 (76.97%)	418 (70.97%)	
Yes	478 (25.80%)	103 (27.03%)	93 (23.19%)	111 (23.03%)	171 (29.03%)	
Pneumonia						0.004
No	1211 (65.28%)	264 (69.29%)	235 (58.60%)	332 (68.74%)	380 (64.41%)	
Yes	644 (34.72%)	117 (30.71%)	166 (41.40%)	151 (31.26%)	210 (35.59%)	
Laboratory data						
Blood urea nitrogen (mg/dL)	49.27(28–63)	50.13 (28–67)	49.17(27–63)	49.76 (29–64)	48.38 (29–61)	0.869
Serum creatinine (mg/dL)	2.68 (1.50–3.20)	2.99 (1.37–3.71)	2.49 (1.37-3)	2.59 (1.5–3.13)	2.67 (1.69–3.12)	0.001
Chloride(mmol/L)	105.76 ± 8.07	105.18 ± 7.69	105.47 ± 8.23	106.01 ± 7.78	106.13 ± 8.42	0.110
Lactate(mmol/L)	2.83 (1.29–3.30)	0.87 (0.7-1)	1.52 (1.3–1.7)	2.28 (1.8–2.6)	5.45 (3.3–6.5)	< 0.001
Albumin(g/dL)	2.45 ± 0.59	2.69 ± 0.50	2.59 ± 0.58	2.38 ± 0.54	2.25 ± 0.60	< 0.001
Calcium(mg/dl)	7.77 ± 0.91	7.87 ± 0.86	7.97 ± 0.87	7.73 ± 0.92	7.59 ± 0.92	< 0.001
Serum potassium (mmol/L)	4.26 ± 0.90	4.28 ± 0.87	4.21 ± 0.84	4.26 ± 0.92	4.28 ± 0.93	0.571
White blood cell (cells x 109/L)	16.20 (9.2–20.4)	14.91 (9.1–16.9)	15.56 (9.3–19.1)	16.69 (9.4-21.33)	17.05 (8.93–22.9)	0.001
RDW (%)	16.10 ± 2.68	16.03 ± 2.58	15.99 ± 2.65	15.90 ± 2.69	16.38 ± 2.73	0.003
Hemoglobin (g/dL)	10.48 ± 2.22	10.05 ± 2.07	10.60 ± 2.22	10.69 ± 2.23	10.52 ± 2.28	< 0.001
Platelets (cells x 109/L)	185.49 ± 115.81	203.35 ± 103.27	191.33 ± 115.51	182.33 ± 108.52	172.66 ± 127.32	< 0.001
Fibrinogen(mg/dL)	431.40 (263–583)	519.04 (316.5–693)	498.2 (316.8-682.7)	427.9 (258.5-578.5)	380.52 (225.5-512.5)	0.003
Hospital 28-day mortality						< 0.001
No	1494 (80.54%)	339 (88.98%)	344 (85.79%)	402 (83.23%)	409 (69.32%)	
Yes	361 (19.46%)	42 (11.02%)	57 (14.21%)	81 (16.77%)	181 (30.68%)	

Continued

Variables	LAR					*P*-value
	Total	Q1(<0.37)	Q2(0.37–0.76)	Q3(0.76–1.67)	Q4(> 1.67)	
ICU 28-day mortality						< 0.001
No	1627 (87.71%)	358 (93.96%)	362 (90.27%)	435 (90.06%)	472 (80.00%)	
Yes	228 (12.29%)	23 (6.04%)	39 (9.73%)	48 (9.94%)	118 (20.00%)	

Table 1. Baseline characteristics of participants. Data are expressed as the mean ± sd, median (interquartile range), or percentage. Among the 1855 patients, the amount of missing values for the covariates were 45 (2.4%) for BMI, 28 (1.5%) for GCS score, 220 (11.8%) forApache IV score and acute physiology score III, 2 (0.1%) for metastatic cancer and diabetes, 9 (0.4%) for calcium, 22 (1.1%) for white blood cell count, 134 (7.2%) for RDW, 20(1.1%) for hemoglobin, 21 (1.1%) for platelets, 221 (11.9%) for fibrinogen. BMI, body mass index; MAP, mean arterial pressure; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; RDW, red cell distribution width.

Outcomes	Crude Model		Model I		Model II	
	HR(95%CI)	*P*-value	HR(95%CI)	*P*-value	HR(95%CI)	*P*-value
LAR(Hospital 28-day mortality)	1.26 (1.18, 1.35)	< 0.0001	1.28 (1.19, 1.37)	< 0.0001	1.26(1.18, 1.35)	< 0.0001
LAR quartile						
Q1	Reference		Reference		Reference	
Q2	1.15 (0.77, 1.72)	0.490	1.12 (0.75, 1.68)	0.570	1.11 (0.74, 1.67)	0.603
Q3	1.23 (0.85, 1.79)	0.272	1.19 (0.82, 1.74)	0.355	1.18 (0.80, 1.72)	0.401
Q4	2.24 (1.60, 3.14)	< 0.001	2.25 (1.60, 3.15)	< 0.001	2.13 (1.50, 3.02)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	
LAR(ICU 28-day mortality)	1.22 (1.12, 1.33)	< 0.0001	1.23 (1.13, 1.34)	< 0.0001	1.22 (1.11, 1.34)	< 0.0001
LAR quartile						
Q1	Reference		Reference		Reference	
Q2	1.25 (0.74, 2.11)	0.399	1.27 (0.75, 2.15)	0.370	1.11 (0.63, 1.95)	0.725
Q3	1.12 (0.68, 1.85)	0.65	1.12 (0.68, 1.85)	0.658	1.02(0.74, 1.63)	0.821
Q4	1.90 (1.21, 2.97)	0.005	1.93 (1.23, 3.02)	0.004	1.66 (1.00, 2.75)	0.050
P for trend	0.001		0.001		0.011	

Table 2. Multivariable Cox regression analysis to assess the association between LAR and 28-days mortality in patients with SA-AKI. The data were presented as HR with 95%CI and p-value; crude model adjusted for: none; model I adjusted for: age and gender; model II adjusted for: age, gender, BMI, ethnicity, GCS score, Apache IV score, acute physiology score II, metastatic cancer, COPD, CHF, diabetes, pneumonia, blood Urea nitrogen, serum creatinine, chloride, lactate, calcium, serum potassium, white blood cell, RDW, hemoglobin, platelets, fibrinogen.

been demonstrated to induce damage and dysfunction in the renal tubular epithelium, closely associated with disruptions in immune mechanisms, inflammatory cascades, and coagulation pathways[18–20]. Empirical evidence indicates that the incidence and mortality rates of SA-AKI was notably elevated among intensive care unit (ICU) patients[4]. A multicentre prospective observational study reported that 62.3% of patients with severe sepsis developed SA-AKI, with severe cases (grades 2 and 3) significantly correlated with increased in-hospital mortality[21]. Additionally, a systematic review and meta-analysis corroborated the high incidence and mortality rates associated with SA-AKI[22].

In patients with SA-AKI, abnormal lactate metabolism is a complex process caused by tissue hypoperfusion, an inflammatory cascade, and mitochondrial dysfunction[23]. Persistent hyperlactacemia reflects persistent tissue hypoxia and metabolic disorders in patients, which can significantly increase the risk of hospitalisation death by aggravating inflammation and damaging mitochondrial function, forming a vicious metabolic cycle[24]. The lactic acid level is not only an important indicator of disease severity, but also a key pathophysiological basis of multiple organ dysfunction[25].

Albumin serves as a crucial indicator of inflammatory processes and systemic nutritional status[26]. Albumin exerts its renoprotective effects through multiple mechanisms. These include the effective scavenging of reactive oxygen species through cysteine residues and methionine, which prevents oxidative damage[27,28] the promotion of glomerular endothelial cell proliferation and the expression of TGF-β, which stimulates the production of type I collagen[29]; and the reduction of apoptosis through the PI3K-Akt signalling pathway[30]. Additionally, albumin can stimulate the DNA synthesis of renal tubular cells through the calcium signalling pathway[31]. Collectively, these mechanisms illustrate the physiological significance of albumin in renal protection and functional maintenance. However, low albumin levels are often associated with poor outcomes in patients with AKI[32,33].

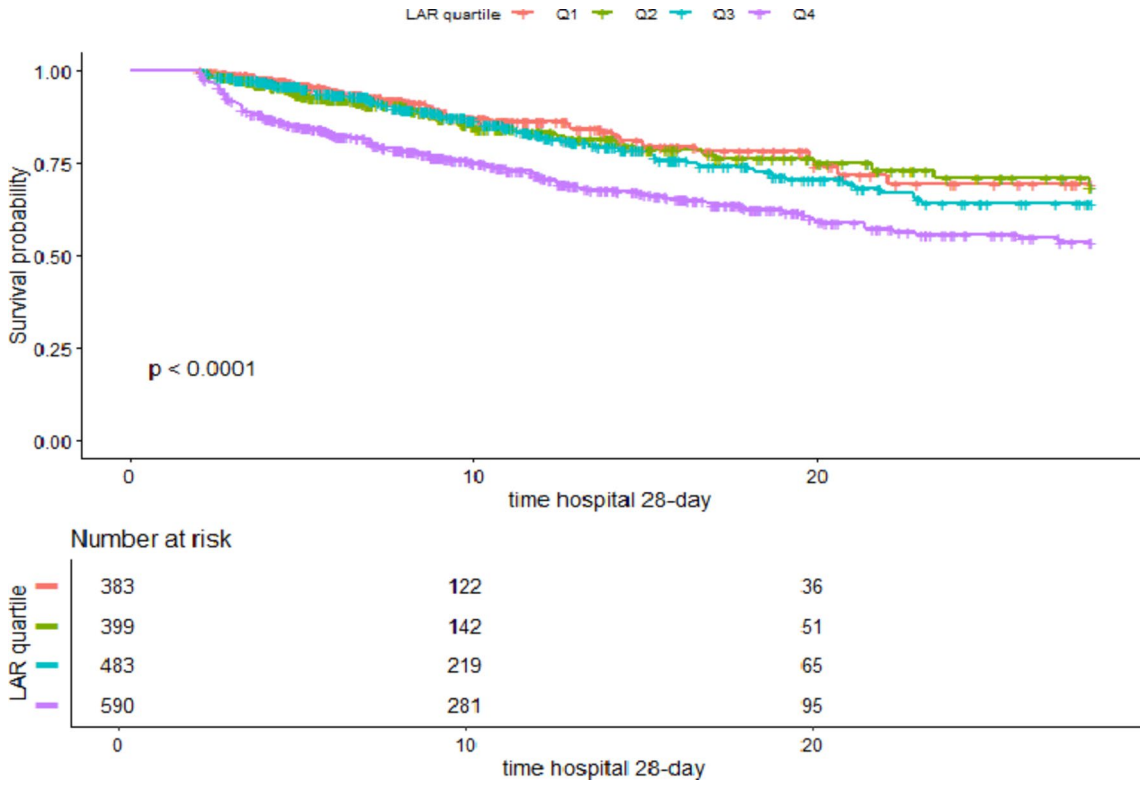

Fig. 1. Kaplan-Meier survival curves for hospital 28-day Mortality by ALR quartiles in patients with SA-AKI.

The LAR, a metric that utilises both lactate and albumin to assess the degree of circulatory metabolism, inflammation, and nutritional status, has demonstrated efficacy in the prognosis assessment of numerous diseases[34,35]. Studies have demonstrated the prognostic value of LAR in patients with severe acute respiratory syndrome (SARS) and nasopharyngeal carcinoma[36,37]. In patients with chronic obstructive pulmonary disease (COPD), the lactate/albumin ratio serves as a crucial marker of early prognosis in critically ill patients[38]. In critically ill patients with septic myocardial injury, elevated LAR levels have been associated with an increased risk of in-hospital mortality, and ALR has demonstrated a direct correlation with all-cause mortality[39]. These findings are partially consistent with our conclusion that ALR exhibits a significant and positive association with 28-day mortality in patients with SA-AKI. Through hierarchical analysis, we have ascertained that the positive correlation remains consistent within each subgroup. Concurrently, a nonlinear relationship was identified between ALR and the prognosis of SA-AKI patients, suggesting that clinicians can positively influence the prognosis of patients by detecting an increase in this indicator early on.

Study advantages and limitations

The present study has certain advantages. Firstly, it was a large-sample multicentre study; secondly, we analysed LAR as both a continuous and categorical variable; thirdly, we applied a two-segmented linear model to construct a threshold-effects analysis of the relationship between ALR and 28-day in-hospital mortality in patients with SA-AKI; and we used stratified analyses to avoid, as far as possible, the occurrence of chance in the statistical analyses and to improve the stability of the results.

The present study is not without its limitations. Firstly, A prevalent issue in observational studies is the presence of unmeasured confounding factors. In the current study, there was an absence of data regarding interventions during the initial stabilization phase; for instance, the administration of albumin could potentially result in reduced LAR levels and improved survival outcomes, representing an unmeasured confounding variable. We assessed the potential impact of such unmeasured confounders using E-value sensitivity analysis, which indicated that a single unmeasured confounder is unlikely to fully account for the observed association. Additional limitations of our study include the presence of missing data for certain variables. Nevertheless, we employed contemporary methodologies to address the missing data, thereby minimizing potential bias. Lactate and albumin data in this study were missing a lot, possibly because most of the patients were in emergency departments, such as hospitals, and their lactate and albumin levels were not timely detected. Therefore, the conclusions of this study cannot be extrapolated to this group of people.

Secondly, the study was conducted with a follow-up period of 28 days. During this time, some patients were not monitored, as the majority were discharged. Based on our observations, most discharged patients were in a state of survival, which likely did not impact our findings. A Cox proportional hazards model regression analysis was also performed at 14 and 30 days of follow-up, yielding results consistent with the core findings at 28 days.

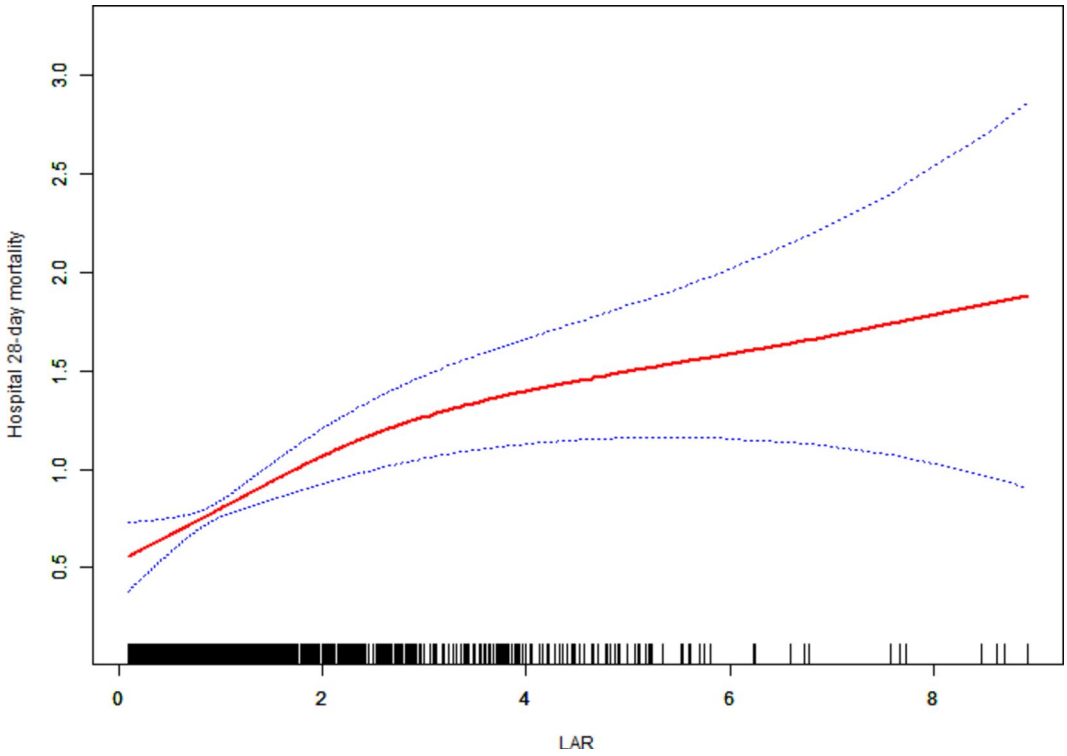

Fig. 2. Associations between LAR and hospital 28-day mortality in patients with SA-AKI. A threshold, nonlinear association between LAR and hospital 28-day mortality was found in a generalized additive model (GAM).The solid red line signifies the smooth curve fit between the variables. The dashed lines denote the 95% confidence interval derived from the aforementioned fit. Adjusted for Age, Gender, BMI, Ethnicity, GCS score, Apache IV score, Acute Physiology Score II, Metastatic cancer, COPD, CHF, Diabetes, Pneumonia, Blood urea nitrogen, Serum creatinine, chloride, Lactate, Calcium, Serum potassium, White blood cell, RDW, Hemoglobin, Platelets, fibrinogen.

Models	28-day mortality HR,95%CI	*P*-value
Model I		
Linear effect	1.19 (1.10, 1.29)	< 0.001
Model II		
Knot (K)	2.1	
Effect 1 (< K)	1.48 (1.20, 1.84)	< 0.001
Effect 2 (> K)	1.07 (0.94, 1.23)	0.291
Difference in effect (2 – 1)	0.72 (0.53, 0.98)	0.036
Likelihood ratio test		0.035

Table 3. Threshold effect analysis of LAR and hospital 28-day mortality in patients with SA-AKI. Data were presented as HR (95% CI) *P*-value; Model I, linear analysis; Model II, non-linear analysis. Adjusted for Age, Gender, BMI, Ethnicity, GCS score, Apache IV score, Acute Physiology Score II, Metastatic cancer, COPD, CHF, Diabetes, Pneumonia, Blood urea nitrogen, Serum creatinine, chloride, Lactate, Calcium, Serum potassium, White blood cell, RDW, Hemoglobin, Platelets, fibrinogen.

However, it is important to note that these findings are based on short-term follow-up and may not be applicable to follow-up periods extending to 60 days or longer.

Finally, the database is derived from studies conducted on U.S. populations, and the absence of external validation may limit the generalizability of the findings to patient populations in other countries or regions. Future research should focus on conducting high-quality prospective studies that incorporate external validation.

Conclusion

The present study utilised data from the eICU-CRD database to identify 1855 patients with SA-AKI. The findings indicated a positive correlation between LAR levels and 28-day mortality, suggesting a potential nonlinear

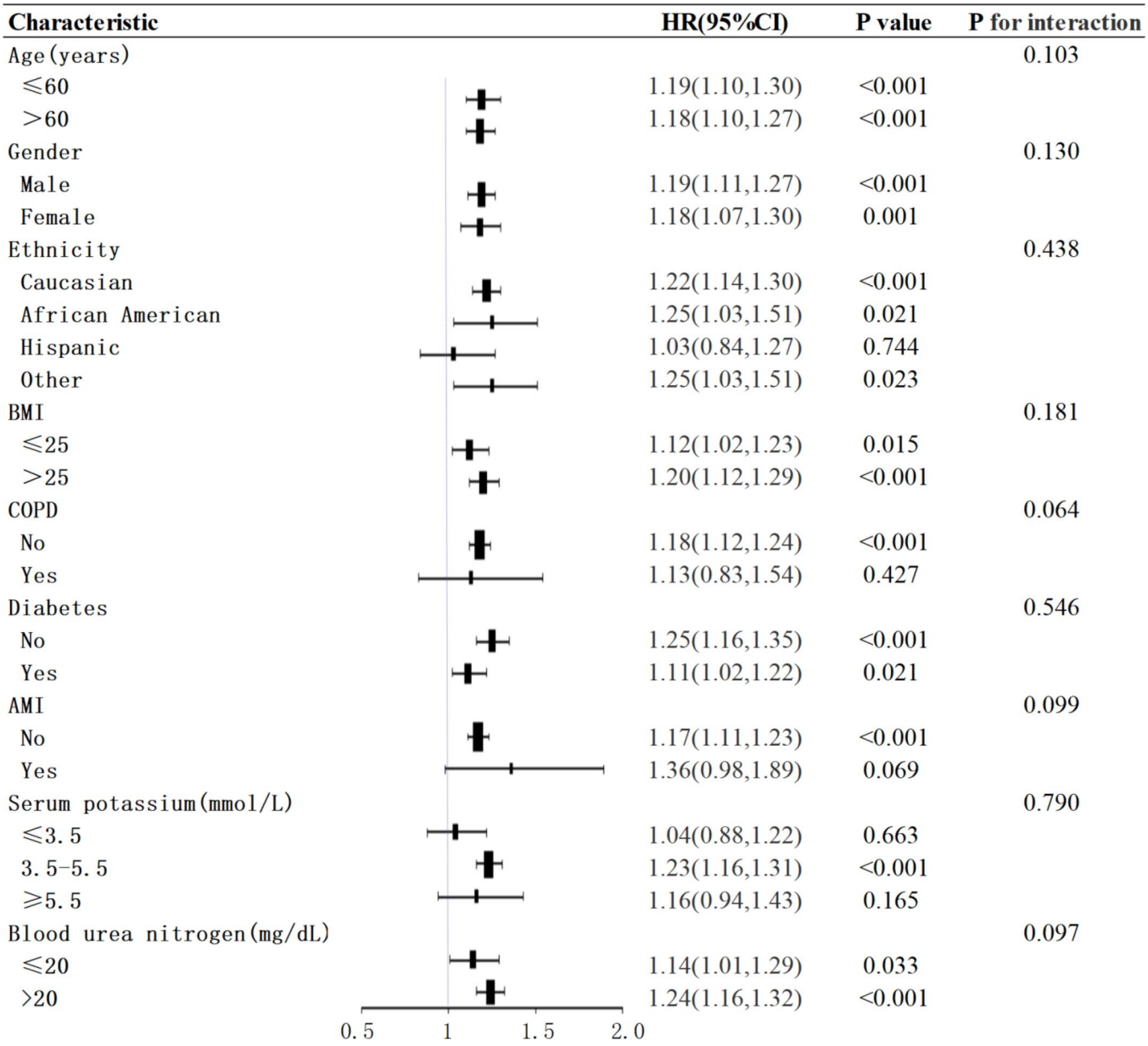

Fig. 3. Stratified analysis of the associations between LAR and hospital 28-days mortality. HR (95% CI) were derived from Cox regression models. Adjustment for age, gender, BMI, ethnicity, GCS score, Apache IV score, Acute Physiology Score II, metastatic cancer, COPD, AMI, diabetes, pneumonia, blood urea nitrogen, serum creatinine, chloride, lactate, calcium, serum potassium, white blood cell, RDW, hemoglobin, platelets, fibrinogen. Age, gender, BMI, ethnicity, COPD, diabetes, AMI, serum potassium, blood urea nitrogen were not adjusted for in each corresponding stratified analyses.

relationship between LAR and hospitalised 28-day mortality. The necessity for further research is highlighted, in particular the need for prospective studies to validate these results.

Methods

Data source

Data for this study were obtained from the eICU Collaborative Research Database (eICU-CRD), a multicentre database containing more than 200,000 ICU admissions from 208 hospitals in the United States during 2014 and 2015[40]. The database provides detailed clinical data from the eICU telemedicine programme, including demographic information, physiological readings, diagnoses (International Classification of Diseases, Ninth Edition (ICD-9) codes), and other clinical data.

This study was conducted in strict adherence to the ethical standards outlined in the Declaration of Helsinki (1964) and its subsequent amendments. After completing the course "Protection of Human Research Participants" (No. 65890571), the use of the database was approved by the Institutional Review Board (IRB) of

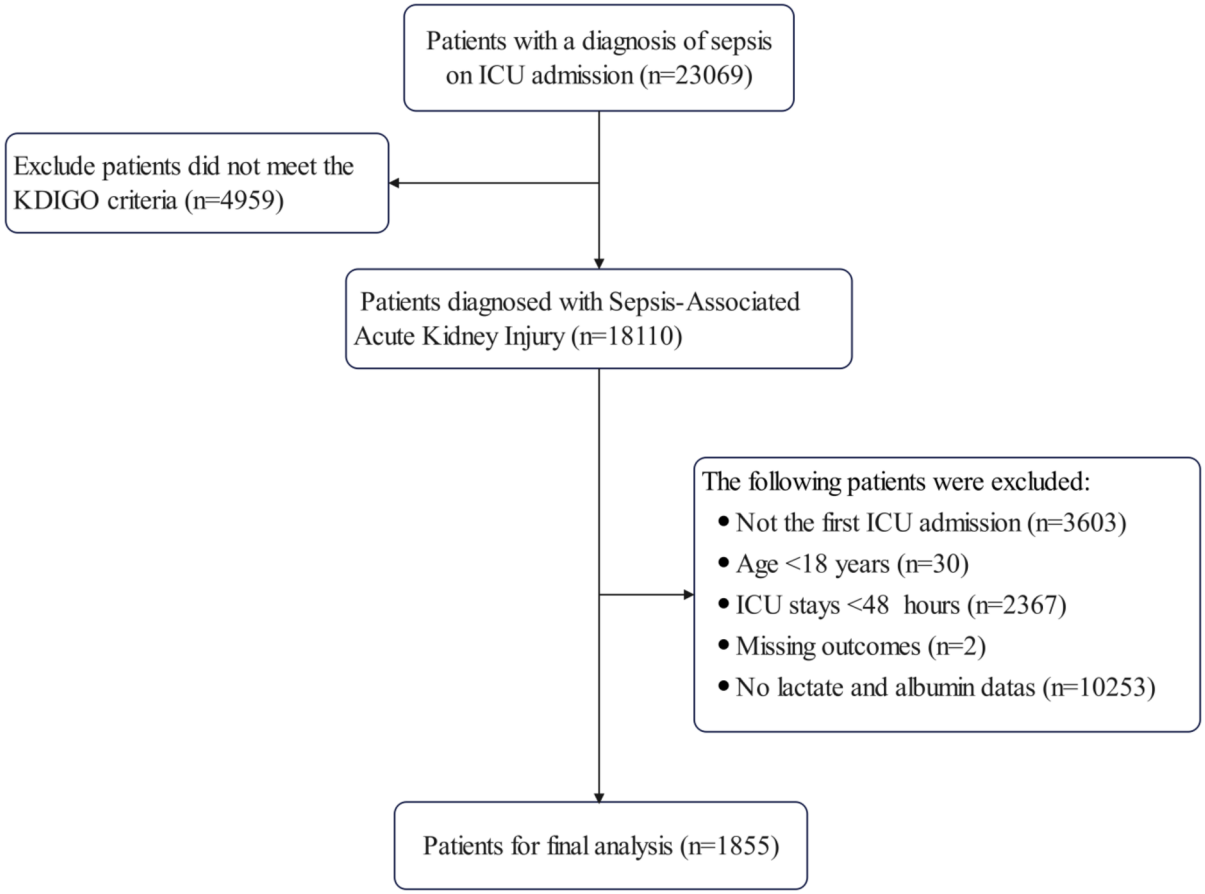

Fig. 4. Flow chart of study population.

Massachusetts Institute of Technology. Because of the retrospective nature of this study and the absence of direct patient intervention, the IRB of Massachusetts Institute of Technology waived the requirement for obtaining written informed consent. The study was compliant with the safe harbor provisions of the Health Insurance Portability and Accountability Act (HIPAA) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Study population

This retrospective observational study included all patients with an initial diagnosis of sepsis based on International Classification of Diseases (ICD) codes from the eICU Collaborative Research Database (ICD code: A41.9)[41]. Inclusion criteria for participant selection were as follows: (1) Patients diagnosed with AKI and aged 18years or older, meeting the diagnostic criteria according to the Kidney Disease: Improving Global Outcomes (KDIGO) clinic practice guideline[42]. (2) Patients who were admitted to ICU for the first time.Exclusion criteria were as follows: (1) Patients admitted to the intensive care unit for less than 48 h; (2) Patients with missing treatment outcomes; (3) Patients with incomplete lactate and albumin data.Te study fowchart was presented in Fig. 4.

Variables

Study covariates included demographic data, vital signs, severity scores, comorbidities, haematological indicators and outcomes. The extracted data were as follows age, gender, body mass index, race, body temperature, heart rate, respiratory rate, mean arterial pressure (MAP), GCS score, Apache IV score, Acute Physiology Score II, metastatic cancer, chronic obstructive pulmonary disease, chronic Heart Failure, Diabetes Mellitus, Pneumonia, Blood Urea Nitrogen, Serum Creatinine, Chloride, Lactate, Calcium, Serum Potassium, Leukocytes, RDW, Haemoglobin, Platelets, Fibrinogen, 28 day mortality in ICU, and 28 day mortality in hospital. If multiple vital sign measurements or laboratory tests were performed during the patient's stay in the ICU, only the initial data within 24 h of admission were extracted for subsequent analyses. If covariate values were missing, they were expressed as dummy variables.

Outcomes

The primary outcome of the study was all-cause hospital 28-day mortality in patients with SA-AKI, which was represented by survival status at hospital discharge. ICU 28-day mortality, defined as survival status at the time of ICU discharge, was considered a secondary outcome measure.

Statistical analysis

Continuous variables that followed a normal distribution were expressed as the mean ± standard deviation (SD), and those that were not normally distributed were expressed as the median (quartile 1-quartile 3). Categorical variables were expressed as the frequency (percentage). Continuous variables were compared across quartiles of the lactate/albumin ratio using one-way ANOVA or Kruskal–Wallis test based on distributional assumptions, while categorical variables were analyzed using chi-square tests. We used the proportional risk hypothesis of Cox regression.

The hazard ratio (HR) and 95% confidence interval (CI) between LAR and primary endpoints were estimated using Cox proportional hazard models, with adjustments made for multiple models. Model I adjusted for: age and gender; Model II adjusted for: age, gender, BMI, ethnicity, GCS score, Apache IV score, Acute Physiology Score II, metastatic cancer, COPD, CHF, diabetes, pneumonia, blood urea nitrogen, serum creatinine, chloride, lactate, calcium, serum potassium, white blood cell, RDW, hemoglobin, platelets, fibrinogen. The incidence of primary outcome events between groups according to different levels of LAR was assessed using Kaplan-Meier survival analysis, and differences between groups were evaluated using log-rank tests. These confounding variables were selected based on a review of analogous studies and their demonstrated association with the outcomes of interest or their capacity to alter effect estimates by more than 10%[43], with consideration given to clinical significance. The relationship between LAR and hospital 28-day mortality was compared using generalised additive models: Model I (linear model) and Model II (non-linear model). A log-likelihood ratio test was used to identify the superior model and the threshold effect of LAR in Model II was analysed.We stratified according to variables such as age, sex, BMI and comorbidities and analysed the risk of death at each level using Cox proportional risk models.

We conducted a series of sensitivity analyses to evaluate the robustness of the primary outcome. Initially, we addressed missing data through multiple imputation, applied when the missing data for a variable exceeded 1%[44]. Subsequently, we developed outcome measures with 14-day and 30-day follow-ups to assess the stability of core outcomes across different time points. Finally, we calculated E-values to investigate the potential for unmeasured confounding between LAR and 28-day mortality[45].

The statistical analyses were conducted using EmpowerStats (www.empowerstats.com, X&Y Solutions, Inc. Boston, MA) and R software version 3.6.1 (http://www.r-project.org). A two-sided p-value of less than 0.05 was considered to be statistically significant.

Data availability

All data in this research were obtained from the eICU database. These data can be found below: https://eicu-crd.mit.edu/.

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H.T. wrote the manuscript. T.H., M.Q. prepared figures and tables. H.T., T.H., M.X. made critical revisions.

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Declarations

Competing interests
The authors declare no competing interests.

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