scientific reports

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Association between advanced lung cancer inflammation index and all-cause mortality in critically ill patients with sepsis: analysis of the MIMIC-IV database

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This study aimed to explore the association between the advanced lung cancer inflammation (ALI) index and the risk of mortality in critically ill patients with sepsis. This retrospective study included 6489 critically ill patients with sepsis from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database. The participants were grouped into four groups according to the ALI index quartiles. The outcome was in-hospital mortality and intensive care unit (ICU) mortality. Cox proportional hazards regression analysis and restricted cubic spline regression were used to evaluate the association between the ALI index and clinical outcomes in critically ill patients with sepsis. A total of 6489 patients (59.1% male) were included in the study. The in-hospital and ICU mortality were 25.4% and 19.0%, respectively. Multivariate Cox proportional hazards analysis showed that the ALI index was independently associated with all-cause mortality. After confounders adjusting, ALI index had a significant association with hospital mortality (adjusted hazards ratio, 0.990; 95% confidence interval, 0.985–0.996; $P < 0.001$) and ICU mortality (adjusted hazards ratio, 0.991; 95% confidence interval, 0.985–0.997; $P = 0.004$). Restricted cubic splines revealed a non-linear association between ALI and all-cause mortality in sepsis patients. Our study indicates that the ALI index has a significant association with hospital and ICU all-cause mortality in critically ill sepsis patients. However, further confirmation of these findings necessitates larger prospective studies.

Keywords Advanced lung cancer inflammation index, All-cause mortality, Sepsis, MIMIC-IV database

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection[1]. It remains a significant contributor to morbidity and mortality in intensive care unit (ICU), with short-term mortality rates reaching up to 50%, depending on the severity of the illness[2].

Traditional prognostic scores such as Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) primarily focus on organ dysfunction severity but lack a comprehensive evaluation of nutritional and inflammatory status, which were both pivotal in sepsis progression[3,4]. As key indicators for assessing nutritional and inflammatory status, multiple studies have confirmed that an elevated neutrophil-to-lymphocyte ratio (NLR), reduced serum albumin levels, and low body mass index (BMI) are all significantly associated with poor prognosis in sepsis patients[5–7]. However, single indicator is insufficient to fully reveal the mechanisms of synergistic imbalance between inflammatory responses and nutritional status, as well as the intrinsic relationship between such imbalances and mortality in sepsis.

The advanced lung cancer inflammation index (ALI) is a comprehensive index developed in recent years to assess the nutritional and inflammatory status of patients, encompassing parameters such as albumin, BMI, and NLR[8,9]. All of these parameters are derived from routine laboratory tests and anthropometric measurements, making them highly compatible with standardized electronic health records (EHRs) fields such as body weight, complete blood count, and biochemical indicators[10]. This composition makes ALI well suited to structured

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datasets and suggests its potential for automated, real-time monitoring to enable early detection of nutrition and inflammation imbalances.

This tripartite metric uniquely bridges nutritional reserves (albumin/BMI) and systemic inflammation (NLR), makes ALI index an effective prognostic tool for cancer patients[11–13]. In addition, studies have found ALI index to be associated with prognosis in a variety of inflammatory diseases, such as coronary artery disease, hypertension, and diabetes[14–17]. Notably, lower ALI scores at ICU admission in critically ill heart failure patients independently predict higher in-hospital and 90-day mortality risk, further validating the index's potential utility in critical care management[14].

However, the relationship between ALI index and prognosis of sepsis is currently not well understood. Therefore, the aim of this study was to assess the role of the ALI index in predicting all-cause mortality in critically ill patients with sepsis by analyzing the Medical Information Mart for Intensive Care IV (MIMIC-IV).

Materials and methods

Study population

We conducted a retrospective observational study using data from the publicly available MIMIC-IV3.1 database, covering January 1, 2008, to December 31, 2019[18]. The study protocol was approved by the Institutional Review Boards of the Massachusetts Institute of Technology (Cambridge, MA) and the Beth Israel Deaconess Medical Center (Boston, MA). The author Lei Zhang completed the required Collaborative Institutional Training Initiative (CITI) program and was granted access to the database (Record ID: 64101469). A waiver of informed consent was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center (Boston, MA), given the retrospective nature of the study and the use of fully de-identified data. The study was conducted in accordance with the principles of the Declaration of Helsinki.

We included adult patients meeting Sepsis-3 criteria, which are defined as suspected or confirmed infection plus a Sequential Organ Failure Assessment (SOFA) score ≥ 2 within 24 h of ICU admission[19]. The exclusion criteria were: (1) patients aged less than 18 years at the time of first admission; (2) length of stay in ICU was less than 48 h; (3) patients with multiple admissions to the ICU for sepsis, for whom only from the first admission data were extracted; (4) missing BMI, Albumin, neutrophil, and lymphocyte counts within 24 h of admission. The flowchart of this study is presented in Fig. 1.

Variable extraction

The software PostgreSQL (version 16.1.0) and Navicat Premium (version 17.1.9) were used to extract information with a running Structured Query Language (SQL). We extracted data from the MIMIC-IV3.1 database for the first 24 h of ICU admission, including patient demographics (age, gender, BMI, race), vital signs (temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiration rate, and pulse oximeter oxygen saturation (SpO_2)), and admission severity metrics (Sequential Organ Failure Assessment (SOFA), Acute Physiology Score III (APS III), Simplified Acute Physiological Score II (SAPS II), Oxford Acute Severity of Illness Score (OASIS) and Glasgow Coma Scale (GCS)). Other relevant data, including laboratory test results, clinical outcomes, and comorbidities were obtained. All laboratory parameters extracted from the MIMIC-IV3.1 database were measured at the first time after ICU admission. Follow-up began on the admission date and ended on the date of death. ALI index upon admission was calculated using the following formula: ALI index = BMI $\times$ Alb / NLR, where BMI is weight in kilograms divided by height in meters squared, Alb is serum albumin in grams per deciliter, and NLR is the ratio of absolute neutrophil count to absolute lymphocyte count.

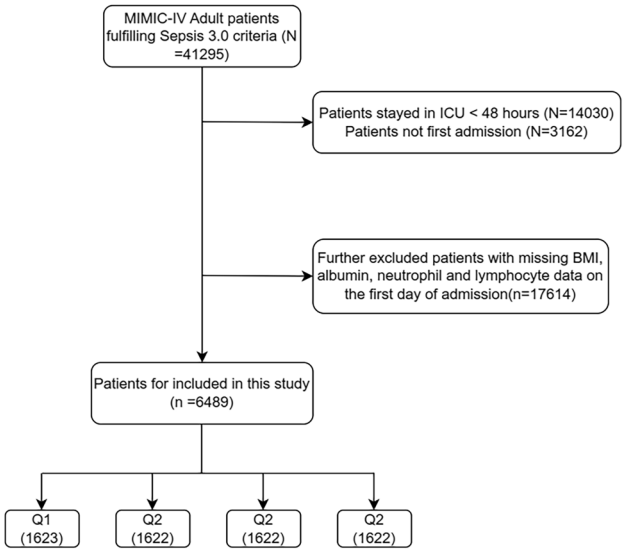

Fig. 1. Inclusion/exclusion criteria. MIMIC: Medical Information Mart for Intensive Care.

To minimize bias, variables were excluded if they had more than 20% missing values. Variables with missing data less than 20% were processed by multiple imputation using a random forest algorithm (trained by other non-missing variables) by the "mice" package of R software (Additional file 1: Table S1).

Clinical outcomes

The primary endpoint was all-cause in-hospital mortality, and the second endpoint was ICU mortality. Patient mortality information for discharged patients was accessed from the US Social Security Death Index.

Statistical analysis

The ALI index was divided into four groups according to quartiles. Categorical variables were evaluated using Fisher's exact or chi-square tests and were presented as counts (percentages). For continuous variables, the Wilcoxon rank-sum test, Student's t-test, or one-way analysis of variance were employed. Kaplan-Meier survival analysis was employed to assess the incidence of endpoints across groups stratified by different ALI index levels, with differences evaluated via log-rank tests. Cox proportional hazards models were used to calculate the hazards ratio (HR) and 95% confidence interval (CI) for the association between the ALI index and endpoints, and also adjusted for some models. And clinically relevant and prognosis-associated variables were also enrolled in the multivariate model: model 1: unadjusted; model 2: adjusted for age, gender, race; model 3 adjusted for age, gender, race, atrial fibrillation, diabetes, heart failure, hypertension, myocardial infarction, renal failure, sofa, Platelets, white blood cell (WBC) count, alkaline phosphatase (Alp), prothrombin time (Ptt), aspartate aminotransferase (Ast), international normalized ratio (Inr), prothrombin time (Pt), Hemoglobin, Sodium, alanine aminotransferase (Alt).

Further, we also analyzed the nonlinear association between baseline ALI indexand hospital all-cause mortality and ICU mortality using a restricted cubic spline analysis. Receiver operating characteristic (ROC) curves were constructed to determine the cutoff value of the ALI index. The ALI index was entered into the models as continuous variable or ordinal variables (the first quartile of the ALI index was set as a reference group). The P values for trends were calculated using the quartile levels. Subgroup analyses were performed to explore potential differences across various subgroups based on age (< 65 and ≥ 65 years), gender, BMI (< 30 and ≥ 30 kg/m2), diabetes, hypertension, atrial fibrillation, heart failure, myocardial infarction and renal failure, to evaluate the consistency of the prognostic value of the ALI index for primary outcomes. The interactions between ALI index and variables used for stratification were tested using likelihood ratio tests. Data processing and analysis were carried out via R version 4.4.2, with statistical significance set at $P < 0.05$ for two-tailed tests.

Results

Baseline characteristics

A total of 6489 patients were included in the final data analysis. The median age of the included patients was 65.14 (IQR: 53.92–76.21) years, and 3837 (59.1%) were men. In-hospital, ICU, 30-day, and 90-day mortality rates were 25.4%, 19.0%, 28.0% and 37.0%, respectively. Patients were stratified into four groups based on the quartiles of ALI index as follows: Q1 (ALI < 4.6; $n = 1623$), Q2 (4.6–8.8; $n = 1622$), Q3 (8.8–16.3; $n = 1622$) and Q4 (ALI ≥ 16.3; $n = 1622$). The baseline characteristics of these patients are shown in Table 1. Compared with higher quartiles, Q1 patients had lower BMI, temperature, SBP, DBP, SpO_2, hematocrit, lymphocyte, albumin, bicarbonate, chloride, sodium, basophil, eosinophil, calcium, and hemoglobin. They also had higher age, SOFA, APS III, SAPS II, OASIS, heart rate, respiration rate, WBC, neutrophil, anion gap, creatinine, total bilirubin, ALP, INR, PT, Blood Urea Nitrogen (BUN), and in-hospital, ICU, 30-day, and 90-day mortality, and higher prevalence of atrial fibrillation and renal failure. In the non-survivor group (Table 2), patients were older, had higher severity scores, greater prevalence of atrial fibrillation, heart failure, myocardial infarction, and renal failure, and higher WBC, monocyte, neutrophil, anion gap, creatinine, potassium, total bilirubin, ALT, ALP, PTT, AST, INR, PT, calcium, and BUN. The median ALI index was significantly lower in non-survivors than survivors (7.33 vs. 9.39; $P < 0.001$).

Primary outcomes

The Kaplan-Meier survival curves for the primary outcomes, stratified by ALI index quartiles, are presented in Fig. 2. Significant differences were observerd at 30-day and 90-day (log-rank P all < 0.001). We evaluated the the diagnostic efficacy of the ALI index using the ROC analysis. However, the area under the curve (AUC) of ALI index was not good enough (in hospital death AUC:0.571, $P < 0.001$; ICU death AUC: 0.560, $P < 0.001$). The cutoff value of ALI index was 7.78 and 7.18 for hospital death and ICU death, respectively.

Multivariate Cox proportional hazards analysis showed that the ALI index was independently associated with lower in-hospital mortality (HR, 0.990; 95% CI, 0.985–0.996; $P < 0.001$), and ICU mortality (HR, 0.991; 95% CI, 0.985–0.997; $P = 0.004$). These results were further confirmed in the fully adjusted Model 3, specifically, the HR for in-hospital mortality in the highest ALI index quartile was 0.711 (95% CI, 0.615–0.822; $P < 0.001$), and for ICU mortality, it was 0.730 (95% CI, 0.615–0.867; $P < 0.001$), both compared with the lowest quartile. Compared with the Q1 group, the Q2, Q3 and Q4 groups exhibited significantly lower risks of in-hospital and ICU mortality, with all trend p-values below 0.05 (Table 3; Fig. 3a and b). Furthermore, the results of the restricted cubic spline analysis indicated a non-linear relationship between the ALI index and both hospital mortality and ICU mortality in sepsis patients (P for non-linearity = 0.012 and P for non-linearity = 0.025, respectively), and low levels of ALI index were associated with an increased risk of hospital mortality and ICU mortality in this population (Fig. 3c and d).

Variable	Overall(*N* = 6489)	Q1(*N* = 1623)	Q2(*N* = 1622)	Q3(*N* = 1622)	Q4(*N* = 1622)	*p*
Age (years)	65.14 [53.92, 76.21]	67.97 [56.16, 78.68]	65.03 [53.53, 75.71]	63.68 [53.62, 75.17]	64.13 [52.74, 75.11]	< 0.001
Height (cm)	170.00 [163.00, 178.00]	170.00 [163.00, 178.00]	170.00 [163.00, 178.00]	170.00 [163.00, 178.00]	170.00 [163.00, 178.00]	0.368
Weight (kg)	80.00 [66.70, 96.90]	72.30 [61.35, 87.72]	78.00 [65.33, 93.57]	81.85 [68.70, 98.90]	86.85 [72.80, 105.47]	< 0.001
BMI	27.62 [23.67, 32.90]	25.41 [21.75, 29.88]	27.04 [23.37, 31.89]	28.47 [24.57, 33.70]	29.99 [25.69, 35.68]	< 0.001
Men, n (%)	3837 (59.1)	968 (59.6)	963 (59.4)	939 (57.9)	967 (59.6)	0.704
Race, n (%)						< 0.001
White	3896 (60.0)	1030 (63.5)	987 (60.9)	968 (59.7)	911 (56.2)	
Black	680 (10.5)	135 (8.3)	137 (8.4)	175 (10.8)	233 (14.4)	
Asian	197 (3.0)	61 (3.8)	40 (2.5)	46 (2.8)	50 (3.1)	
Hispanic	225 (3.5)	53 (3.3)	53 (3.3)	57 (3.5)	62 (3.8)	
Others	1491 (23.0)	344 (21.2)	405 (25.0)	376 (23.2)	366 (22.6)	
SOFA	4.00 [2.00, 5.00]	4.00 [3.00, 5.00]	4.00 [2.00, 5.00]	4.00 [2.00, 5.00]	3.00 [2.00, 5.00]	< 0.001
APS III	56.00 [43.00, 73.00]	61.00 [48.00, 79.00]	56.00 [44.00, 73.00]	54.00 [42.00, 70.00]	50.50 [38.00, 67.00]	< 0.001
SAPS II	43.00 [34.00, 53.00]	47.00 [37.00, 57.00]	43.00 [34.00, 53.00]	42.00 [32.00, 51.00]	40.00 [31.00, 50.00]	< 0.001
OASIS	37.00 [32.00, 43.00]	39.00 [33.00, 45.00]	37.00 [32.00, 43.00]	37.00 [31.00, 42.00]	36.00 [31.00, 42.00]	< 0.001
GCS	15.00 [13.00, 15.00]	15.00 [13.00, 15.00]	15.00 [13.00, 15.00]	15.00 [13.00, 15.00]	15.00 [14.00, 15.00]	0.449
Temperature(°C)	36.91 [36.60, 37.31]	36.84 [36.56, 37.24]	36.92 [36.62, 37.32]	36.94 [36.62, 37.32]	36.93 [36.62, 37.35]	< 0.001
SBP, mmHg	110.66[103.00,121.05]	108.52[101.57,118.10]	110.56[103.08,120.38]	111.21[103.39,122.71]	112.71[104.27,122.89]	< 0.001
DBP, mmHg	61.03 [55.12, 67.52]	60.03 [54.93, 66.20]	60.67 [54.47, 67.40]	61.56 [55.61, 68.28]	61.83 [55.78, 68.16]	< 0.001
Heart rate	88.19 [76.54, 101.44]	91.58 [79.20, 104.75]	88.24 [76.88, 102.27]	87.13 [76.51, 100.35]	85.65 [74.13, 98.37]	< 0.001
Respiration rate	20.17 [17.56, 23.52]	20.79 [17.92, 24.26]	20.48 [17.72, 23.80]	20.02 [17.50, 23.28]	19.64 [17.14, 22.67]	< 0.001
Spo2, %	97.33 [95.71, 98.75]	97.11 [95.50, 98.66]	97.47 [95.80, 98.81]	97.29 [95.64, 98.77]	97.42 [95.89, 98.73]	< 0.001
Glucose, mg/dL	164.00[128.00,228.00]	164.00[128.00,228.00]	165.00[130.25,225.00]	166.00[129.25,234.00]	160.00[125.00,227.75]	0.155
Commorbidities						
Atrial fibrillation,	2078 (32.0)	590 (36.4)	502 (30.9)	504 (31.1)	482 (29.7)	< 0.001
Diabetes	973 (15.0)	207 (12.8)	233 (14.4)	242 (14.9)	291 (17.9)	0.001
Heart failure	2228 (34.3)	574 (35.4)	559 (34.5)	575 (35.5)	520 (32.1)	0.145
Hypertension	2199 (33.9)	490 (30.2)	528 (32.6)	571 (35.2)	610 (37.6)	< 0.001
Myocardial infarction	854 (13.2)	206 (12.7)	207 (12.8)	219 (13.5)	222 (13.7)	0.778
Renal failure	3747 (57.7)	1031 (63.5)	948 (58.4)	924 (57.0)	844 (52.0)	< 0.001
Laboratory tests						
Hematocrit, %	34.70 [30.00, 40.00]	33.40 [28.95, 38.45]	34.30 [30.00, 39.60]	35.10 [30.30, 40.20]	36.20 [31.20, 41.30]	< 0.001
Platelets, K/uL	210.00[144.00,293.00]	211.00[140.50,315.00]	213.00[149.00,293.75]	208.00[144.00,291.00]	210.00[143.25,279.00]	0.082
WBC, K/uL	14.90 [10.40, 20.40]	18.80 [13.70, 26.20]	15.90 [11.43, 20.80]	13.70 [9.80, 18.80]	11.90 [8.43, 16.28]	< 0.001
Lymphocyte, K/uL	1.04 [0.64, 1.61]	0.55 [0.35, 0.84]	0.92 [0.65, 1.29]	1.21 [0.87, 1.70]	1.73 [1.18, 2.45]	< 0.001
Monocyte, K/uL	0.66 [0.39, 1.06]	0.65 [0.37, 1.09]	0.71 [0.42, 1.13]	0.66 [0.39, 1.03]	0.63 [0.40, 0.99]	0.001
Neutrophil, K/uL	10.80 [6.99, 15.80]	15.23 [10.83, 21.51]	12.06 [8.30, 16.49]	9.68 [6.70, 13.93]	7.16 [4.87, 10.52]	< 0.001
Albumin, g/dL	3.20 [2.70, 3.60]	2.80 [2.40, 3.30]	3.10 [2.60, 3.60]	3.30 [2.80, 3.70]	3.50 [3.00, 3.90]	< 0.001
Aniongap, mEq/L	17.00 [14.00, 21.00]	18.00 [15.00, 21.00]	17.00 [14.00, 21.00]	17.00 [14.00, 21.00]	17.00 [14.00, 20.00]	< 0.001
Bicarbonate, mEq/L	23.00 [20.00, 26.00]	23.00 [20.00, 26.00]	23.00 [20.00, 26.00]	24.00 [21.00, 26.00]	24.00 [21.00, 27.00]	< 0.001
Chloride, mEq/L	106.00[101.00,110.00]	105.00[100.00,110.00]	106.00[101.00,110.00]	106.00[101.00,110.00]	106.00[102.00,110.00]	0.031
Creatinine, mg/dL	1.40 [0.90, 2.50]	1.60 [1.00, 2.90]	1.50 [1.00, 2.60]	1.40 [0.92, 2.30]	1.30 [0.90, 2.10]	< 0.001
Sodium, mEq/L	140.00[137.00,143.00]	139.00[136.00,143.00]	140.00[137.00,143.00]	140.00[137.00,144.00]	141.00[138.00,144.00]	< 0.001
Potassium, mEq/L	4.60 [4.20, 5.30]	4.60 [4.20, 5.20]	4.60 [4.20, 5.30]	4.60 [4.10, 5.20]	4.60 [4.20, 5.30]	0.087
Basophil, %	0.03 [0.01, 0.05]	0.02 [0.00, 0.04]	0.02 [0.01, 0.05]	0.03 [0.01, 0.05]	0.03 [0.01, 0.05]	< 0.001
Eosinophil, %	0.03 [0.00, 0.11]	0.01 [0.00, 0.05]	0.02 [0.00, 0.08]	0.04 [0.01, 0.12]	0.07 [0.02, 0.16]	< 0.001
Total bilirubin, mg/dL	0.80 [0.40, 1.70]	0.80 [0.50, 1.90]	0.80 [0.50, 1.90]	0.80 [0.40, 1.60]	0.70 [0.40, 1.40]	< 0.001
Alt, U/L	32.00 [18.00, 79.00]	33.00 [19.00, 88.00]	33.00 [18.00, 82.00]	33.00 [19.00, 79.00]	30.00 [18.00, 71.00]	0.149
Alp, U/L	95.00 [68.00, 142.00]	111.00 [77.00, 172.00]	96.00 [68.00, 145.00]	90.00 [65.00, 130.00]	88.00 [63.00, 127.75]	< 0.001
Ptt	35.30 [29.40, 52.00]	36.10 [30.00, 52.55]	35.15 [29.30, 51.30]	35.10 [29.20, 52.38]	34.65 [29.30, 51.58]	0.177
Ast, U/L	54.00 [28.00, 138.00]	54.00 [29.00, 145.00]	57.00 [29.00, 140.00]	55.00 [29.00, 147.75]	50.00 [27.00, 121.00]	0.007
Inr	1.40 [1.20, 1.90]	1.50 [1.30, 2.00]	1.40 [1.20, 1.90]	1.40 [1.20, 1.90]	1.40 [1.20, 1.80]	< 0.001
Pt	15.50 [13.30, 20.70]	16.40 [13.90, 21.70]	15.60 [13.40, 21.10]	15.40 [13.20, 20.40]	14.90 [13.03, 19.60]	< 0.001
Calcium, mg/dL	8.50 [8.00, 9.00]	8.30 [7.80, 8.80]	8.50 [8.00, 9.00]	8.60 [8.10, 9.10]	8.70 [8.20, 9.10]	< 0.001
Bun, mg/dL	30.00 [18.00, 49.00]	35.00 [21.00, 57.00]	31.00 [19.00, 51.00]	28.00 [18.00, 46.00]	25.00 [16.00, 42.00]	< 0.001
Hemoglobin, g/dL	11.20 [9.60, 13.10]	10.70 [9.30, 12.50]	11.10 [9.60, 13.00]	11.40 [9.70, 13.20]	11.80 [10.10, 13.50]	< 0.001
Continued						

Variable	Overall(*N* = 6489)	Q1(*N* = 1623)	Q2(*N* = 1622)	Q3(*N* = 1622)	Q4(*N* = 1622)	*p*
ALI	8.84 [4.60, 16.28]	2.82 [1.91, 3.70]	6.56 [5.54, 7.60]	11.72 [10.24, 13.74]	24.44 [19.58, 32.33]	< 0.001
LOS Hospital, day	12.76 [7.49, 21.60]	12.95 [7.73, 21.93]	12.82 [7.82, 21.26]	12.57 [7.33, 21.32]	12.66 [7.09, 21.59]	0.284
LOS ICU, day	6.30 [3.70, 11.64]	6.27 [3.76, 11.20]	6.52 [3.78, 11.58]	6.14 [3.64, 11.83]	6.18 [3.58, 11.90]	0.779
Mortality, n (%)						
30-day	1880 (29.0)	610 (37.6)	469 (28.9)	436 (26.9)	365 (22.5)	< 0.001
90-day	2400 (37.0)	794 (48.9)	591 (36.4)	544 (33.5)	471 (29.0)	< 0.001
In-hospital	1646 (25.4)	532 (32.8)	409 (25.2)	388 (23.9)	317 (19.5)	< 0.001
In-ICU	1236 (19.0)	382 (23.5)	317 (19.5)	300 (18.5)	237 (14.6)	< 0.001

Table 1. Characteristics and outcomes of participants categorized by ALI index. Abbreviation: ALI index, advanced lung cancer inflammation index; BMI, body mass index; SOFA, sequential organ failure assessment; APSIII, acute physiology score III; SAPSII, simplifed acute physiological score II; OASIS, oxford acute severity of illness score; GCS, glasgow coma scale; WBC, white blood cell; SBP, systolic blood pressure; DBP, diastolic blood pressure; Spo2, pulse oximeter oxygen Saturation; Alt, alanine aminotransferase; Alp, alkaline phosphatase; Ptt, partial thromboplastin time; Ast, aspartate aminotransferase; Inr, international normalized ratio; Pt, prothrombin time; Bun, blood urea nitrogen.

Subgroup analysis

To further evaluate the association between ALI and mortality, we performed stratified analyses for in-hospital and ICU deaths by age, gender, BMI, diabetes, hypertension, atrial fibrillation, heart failure, myocardial infarction, and renal failure (Figs. 4 and 5). Subgroup analysis showed that the association between the ALI index and risk of in-hospital mortality was consistent across subgroups stratified by age, gender, BMI, diabetes, atrial fibrillation, heart failure, myocardial infarction (P for interaction > 0.05). In contrast, two significant interactions were observed in subgroup defined by hypertension and renal failure (P for interaction = 0.001 and 0.003, respectively; Fig. 4). For ICU mortality stratified analyses, no significant interactions were identified between the ALI index and age, gender, BMI, diabetes, atrial fibrillation, heart failure (P for interaction > 0.05; Fig. 5). However, hypertension, renal failure and myocardial infarction showed significant interaction (P for interaction < 0.05; Fig. 5). The results of the stratifed analysis consistently demonstrated a consistent association of ALI index values across most sub-populations.

Discussion

In the present study, we used the open-source MIMIC-IV3.1 database to evaluate the ability of the ALI index to predict short-term outcomes among critically ill patients with sepsis. The results of this study indicated that a lower ALI index was significantly associations with all-cause ICU and hospital mortality in critically ill patients with sepsis. Even after adjusting for confounding risk factors, the ALI index was still strongly associated with all-cause ICU and hospital mortality. Building on its established use in critically ill heart failure patients, our findings extend the ALI index's applicability to sepsis critical illness, demonstrating consistent prognostic value across diverse acute care populations.Sepsis is a life-threatening medical condition that occurs when the host mounts an uncontrolled or abnormal immune response to overwhelming infection[20]. In sepsis, there is a series of pro-inflammatory and anti-inflammatory reactions that lead to complications such as fever, cardiovascular shock, and systemic organ failure in patients[21]. The involvement of inflammatory mediators, neurotransmitters, and gene regulators drives the development of local inflammatory responses[22]. Multiple studies have shown that interleukin-6 (IL-6), C-reactive protein (CRP), and NLR are closely associated with prognosis in sepsis patients[23,24]. On one hand, low albumin levels are associated with increased risk of sepsis and mortality[25]. On the other hand, BMI serves as an independent predictor of in-hospital death in sepsis patients, with those having higher BMI exhibiting lower mortality[26]. These findings suggest that both inflammatory and nutritional status should be taken into account when comprehensively assessing the prognosis of sepsis patients.

The ALI index is calculated by combining serum albumin, BMI and the inflammatory parameter NLR, and has been proven to predict prognosis in various cancers[27–30]. Unlike previous indices that include only NLR and albumin, ALI also incorporates BMI to assess nutritional status. A recent study showed that the ALI index was associated with long-term all-cause mortality in gastric cancer patients, serving as a comprehensive indicator of nutrition status and inflammation[31]. Another study demonstrated that the ALI index was superior to the prognostic nutritional index, NLR, and systemic immunoinflammatory index in predicting and differentiating sarcopenia[32].

From an ICU management perspective, the ALI index provides a physiologically informed measure of the nutrition–inflammation interplay. Unlike manually recorded organ dysfunction scores such as SOFA or APACHE II, the ALI index leverages automated data extraction from EHRs to dynamically calculate risk scores, positioning it as a promising tool for real-time risk stratification in sepsis patients[33]. Clinically validated ALI cut-points enable classification of sepsis patients into distinct risk tiers, each aligned with tailored intervention protocols[34]. For example, patients with low ALI scores should promptly receive intensified therapy, including NLR-guided immune modulation, early correction of hypoalbuminemia, and BMI-adjusted high-calorie, high-protein enteral nutrition, to address severe nutrition–inflammation imbalance[35–37]. When integrated into ICU

Variable	Overall(*N* = 6489)	Survivor(*N* = 4843)	Non-survivor(*N* = 1646)	*p*
Age (years)	65.14 [53.92, 76.21]	64.04 [52.85, 75.22]	68.12 [57.87, 78.86]	< 0.001
Height (cm)	170.00 [163.00, 178.00]	170.00 [163.00, 178.00]	169.50 [163.00, 178.00]	0.018
Weight (kg)	80.00 [66.70, 96.90]	80.00 [66.88, 97.00]	79.40 [66.10, 96.50]	0.327
BMI	27.70 [23.77, 33.02]	27.70 [23.77, 32.85]	27.74 [23.76, 33.46]	0.823
Men, n (%)	3837 (59.1)	2857 (59.0)	980 (59.5)	0.719
Race, n (%)				< 0.001
White	3896 (60.0)	2993 (61.8)	903 (54.9)	
Black	680 (10.5)	519 (10.7)	161 (9.8)	
Asian	197 (3.0)	145 (3.0)	52 (3.2)	
Hispanic	225 (3.5)	172 (3.6)	53 (3.2)	
Others	1491 (23.0)	1014 (20.9)	477 (29.0)	
SOFA	4.00 [2.00, 5.00]	3.00 [2.00, 5.00]	4.00 [3.00, 6.00]	< 0.001
APS III	56.00 [43.00, 73.00]	52.00 [40.00, 68.00]	67.00 [52.00, 86.00]	< 0.001
SAPS II	43.00 [34.00, 53.00]	40.00 [32.00, 50.00]	50.00 [40.00, 61.00]	< 0.001
OASIS	37.00 [32.00, 43.00]	36.00 [31.00, 42.00]	40.00 [34.00, 46.00]	< 0.001
GCS	15.00 [13.00, 15.00]	15.00 [13.50, 15.00]	15.00 [13.00, 15.00]	0.081
Temperature(°C)	36.91 [36.60, 37.31]	36.94 [36.64, 37.36]	36.80 [36.46, 37.16]	< 0.001
SBP, mmHg	110.66 [103.00, 121.05]	111.09 [103.38, 121.41]	109.49 [102.30, 119.65]	< 0.001
DBP, mmHg	61.03 [55.12, 67.52]	61.33 [55.43, 67.65]	59.98 [54.12, 66.93]	< 0.001
Heart rate	88.19 [76.54, 101.44]	87.54 [76.30, 100.43]	90.58 [77.72, 103.99]	< 0.001
Respiration rate	20.17 [17.56, 23.52]	19.89 [17.31, 23.10]	21.32 [18.30, 24.51]	< 0.001
Spo2, %	97.33 [95.71, 98.75]	97.42 [95.85, 98.77]	97.04 [95.19, 98.68]	< 0.001
Glucose, mg/dL	164.00 [128.00, 228.00]	161.00 [127.00, 223.00]	174.00 [133.00, 242.75]	< 0.001
Commorbidities				
Atrial fibrillation	2078 (32.0)	1423 (29.4)	655 (39.8)	< 0.001
Diabetes	973 (15.0)	742 (15.3)	231 (14.0)	0.221
Heart failure	2228 (34.3)	1624 (33.5)	604 (36.7)	0.021
Hypertension	2199 (33.9)	1690 (34.9)	509 (30.9)	0.004
Myocardial infarction	854 (13.2)	606 (12.5)	248 (15.1)	0.009
Renal failure	3747 (57.7)	2565 (53.0)	1182 (71.8)	< 0.001
Laboratory tests				
Hematocrit, %	34.70 [30.00, 40.00]	34.90 [30.30, 40.10]	34.30 [29.20, 39.70]	0.004
Platelets, K/uL	210.00 [144.00, 293.00]	214.00 [148.00, 296.00]	197.50 [128.00, 280.00]	< 0.001
WBC, K/uL	14.90 [10.40, 20.40]	14.60 [10.30, 20.00]	15.90 [10.90, 21.60]	< 0.001
Lymphocyte, K/uL	1.04 [0.64, 1.61]	1.07 [0.66, 1.63]	0.94 [0.57, 1.53]	< 0.001
Monocyte, K/uL	0.66 [0.39, 1.06]	0.65 [0.39, 1.04]	0.68 [0.41, 1.12]	0.021
Neutrophil, K/uL	10.80 [6.99, 15.80]	10.55 [6.85, 15.51]	11.52 [7.48, 16.54]	< 0.001
Albumin, g/dL	3.20 [2.70, 3.60]	3.20 [2.70, 3.70]	3.00 [2.50, 3.60]	< 0.001
Aniongap, mEq/L	17.00 [14.00, 21.00]	17.00 [14.00, 21.00]	19.00 [15.00, 23.00]	< 0.001
Bicarbonate, mEq/L	23.00 [20.00, 26.00]	24.00 [21.00, 27.00]	23.00 [20.00, 26.00]	< 0.001
Chloride, mEq/L	106.00 [101.00, 110.00]	106.00 [102.00, 110.00]	105.00 [100.00, 110.00]	< 0.001
Creatinine, mg/dL	1.40 [0.90, 2.50]	1.30 [0.90, 2.30]	1.75 [1.10, 2.98]	< 0.001
Sodium, mEq/L	140.00 [137.00, 143.00]	140.00 [137.00, 143.00]	140.00 [136.00, 144.00]	0.27
Potassium, mEq/L	4.60 [4.20, 5.30]	4.60 [4.10, 5.20]	4.70 [4.30, 5.50]	< 0.001
Basophil, %	0.03 [0.01, 0.05]	0.03 [0.01, 0.05]	0.02 [0.00, 0.05]	< 0.001
Eosinophil, %	0.03 [0.00, 0.11]	0.03 [0.00, 0.11]	0.02 [0.00, 0.09]	< 0.001
Total bilirubin, mg/dL	0.80 [0.40, 1.70]	0.70 [0.40, 1.60]	0.90 [0.50, 2.38]	< 0.001
Alt, U/L	32.00 [18.00, 79.00]	31.00 [18.00, 72.00]	37.50 [20.00, 111.00]	< 0.001
Alp, U/L	95.00 [68.00, 142.00]	91.00 [66.00, 137.00]	107.00 [75.00, 161.75]	< 0.001
Ptt	35.30 [29.40, 52.00]	34.10 [29.10, 48.10]	39.50 [31.00, 63.10]	< 0.001
Ast, U/L	54.00 [28.00, 138.00]	50.00 [27.00, 120.00]	71.00 [34.00, 228.00]	< 0.001
Inr	1.40 [1.20, 1.90]	1.40 [1.20, 1.80]	1.60 [1.30, 2.30]	< 0.001
Continued				

Variable	Overall($N=6489$)	Survivor($N=4843$)	Non-survivor($N=1646$)	p
Pt	15.50 [13.30, 20.70]	15.20 [13.20, 19.60]	17.10 [13.90, 25.20]	< 0.001
Calcium, mg/dL	8.50 [8.00, 9.00]	8.50 [8.00, 9.00]	8.60 [8.10, 9.10]	0.04
Bun, mg/dL	30.00 [18.00, 49.00]	28.00 [17.00, 46.00]	36.00 [22.00, 56.00]	< 0.001
Hemoglobin, g/dL	11.20 [9.60, 13.10]	11.30 [9.70, 13.10]	11.00 [9.40, 12.80]	< 0.001
ALI	8.84 [4.60, 16.28]	9.39 [4.95, 17.19]	7.33 [3.71, 13.77]	< 0.001

Table 2. Baseline characteristics of the survivors and non-survivors groups. Abbreviation: ALI index, advanced lung cancer inflammation index; BMI, body mass index; SOFA, sequential organ failure assessment; APSIII, acute physiology score III; SAPSII, simplifed acute physiological score II; OASIS, oxford acute severity of illness score; GCS, glasgow coma scale; WBC, white blood cell; SBP, systolic blood pressure; DBP, diastolic blood pressure; Spo2, pulse oximeter oxygen Saturation; Alt, alanine aminotransferase; Alp, alkaline phosphatase; Ptt, partial thromboplastin time; Ast, aspartate aminotransferase; Inr, international normalized ratio; Pt, prothrombin time; Bun, blood urea nitrogen.

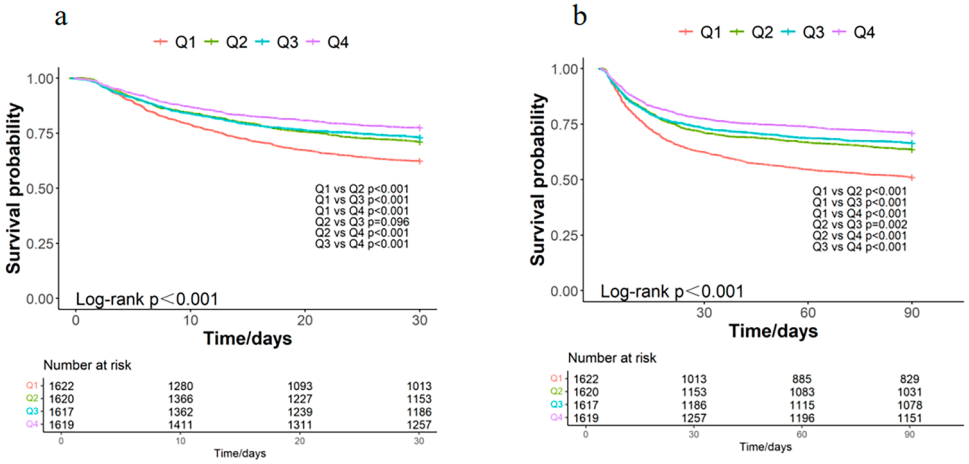

Fig. 2. Kaplan–Meier survival analysis curves for all-cause mortality according to groups at 30 days (**a**), and 90 days (**b**).

Categories	Model1		Model2		Model3	
	HR(95% CI)	P	HR(95% CI)	P	HR(95% CI)	P
Hospital mortality						
ALI as continuous	0.985 (0.980–0.990)	< 0.001	0.987(0.981–0.992)	< 0.001	0.990(0.985–0.996)	< 0.001
Q1($N=1687$)						
Q2($N=1687$)	0.770 (0.677–0.876)	< 0.001	0.790 (0.695–0.899)	< 0.001	0.830(90.728–0.946)	0.005
Q3($N=1686$)	0.757(0.664–0.862)	< 0.001	0.786(0.689–0.896)	< 0.001	0.845(0.738–0.968)	0.015
Q4($N=1687$)	0.607 (0.528–0.698)	< 0.001	0.633(0.551–0.728)	< 0.001	0.711(0.615–0.822)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	
ICU mortality						
ALI as continuous	0.984 (0.978–0.989)	< 0.001	0.985 (0.979–0.991)	< 0.001	0.991(0.985–0.997)	0.004
Q1($N=1687$)						
Q2($N=1687$)	0.800 (0.690–0.929)	0.003	0.806 (0.694–0.935)	0.005	0.866(0.744–1.008)	0.063
Q3($N=1686$)	0.777(0.668–0.904)	0.001	0.787(0.676–0.916)	0.002	0.874(0.747–1.022)	0.092
Q4($N=1687$)	0.591 (0.503–0.695)	< 0.001	0.609(90.517–0.717)	< 0.001	0.730(0.615–0.867)	< 0.001
P for trend	< 0.001		< 0.001		0.001	

Table 3. Cox proportional hazard ratios (HR) for all-cause mortality. Model 1 was unadjusted. Model 2 was adjusted for sex, age, and race. Model 3 was adjusted for the variables in model 2 and further adjusted for atrial fibrillation, diabetes, heart failure, hypertension, myocardial infarction, renal failure, Sofa, Platelets, WBC, Alp, Ptt, Ast, Inr, Pt, Hemoglobin, Sodium, Alt.

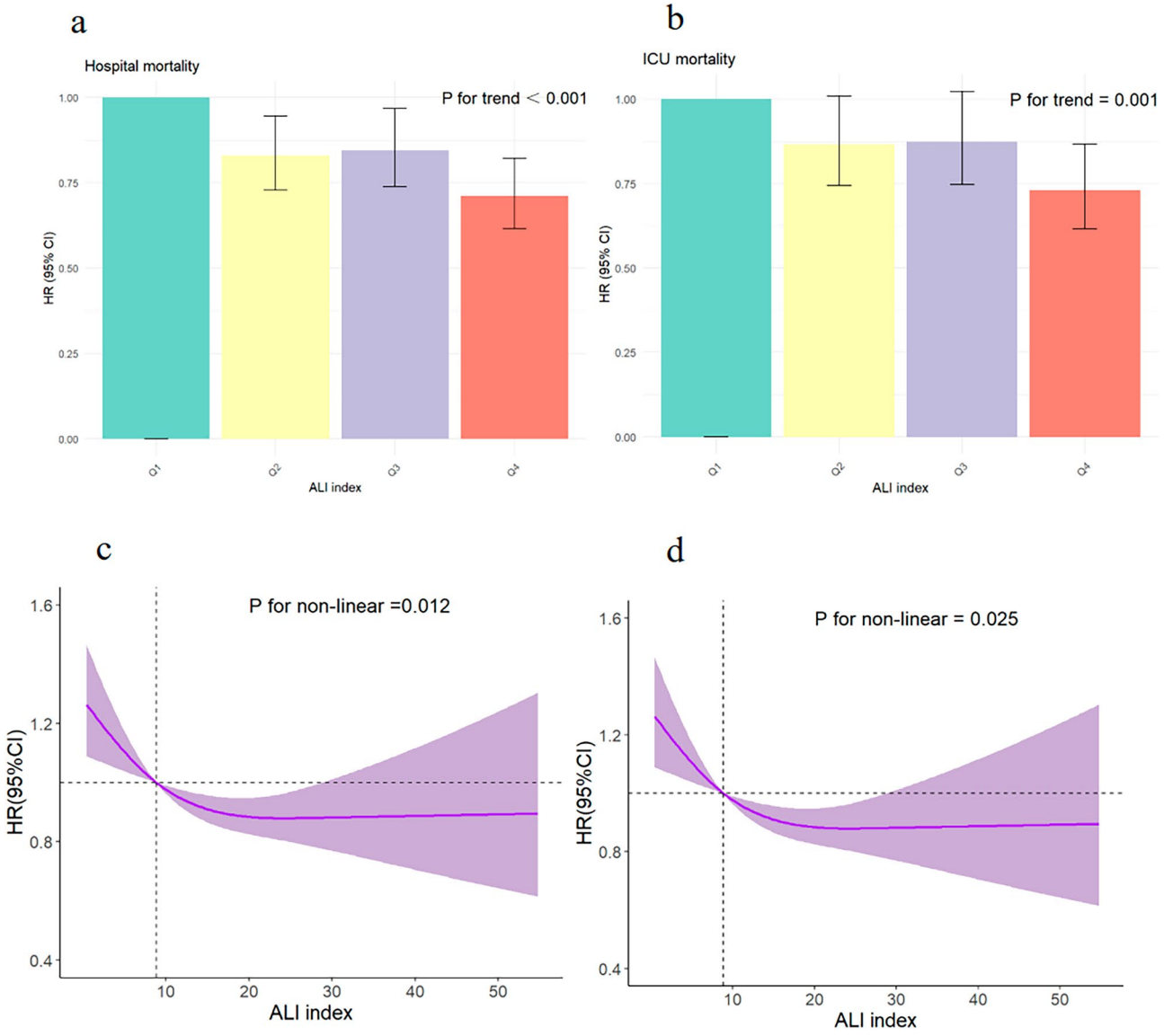

Fig. 3. The relationship for the levels of ALI index with in-hospital mortality and ICU mortality. (**a**, **b**) Hazards ratios (95% CIs) for in-hospital and in-ICU mortality according to ALI index quartiles after adjusting for sex, age, race, atrial fibrillation, diabetes, heart failure, hypertension, myocardial infarction, renal failure, Sofa, Platelets, WBC, Alp, Ptt, Ast, Inr, Pt, Hemoglobin, Sodium, Alt. Error bars indicate 95% CIs. The first quartile is the reference. (**c**) Restricted cubic spline for hospital mortality. (**d**) Restricted cubic spline for ICU mortality. HR, hazards ratio; CI, confidence interval; ICU, intensive care unit; ALI, advanced lung cancer inflammation.

workflows, the ALI index functions not only as a prognostic marker but also as a decision-support tool bridging pathophysiological mechanisms with precision-guided early interventions.

Our results suggested that a higher ALI index was associated with a lower risk of hospital and ICU death. Several elements might underlie this complex relationship. Firstly, the prognosis of sepsis is closely tied to the severity of inflammatory responses. Previous studies had indicated that the NLR represented the inflammatory immune response, and a high neutrophil count was a sign of non-specific inflammation, while a low lymphocyte count suggested a relative deficiency in immune regulation[38]. Furthermore, a correlation between elevated NLR and poorer prognoses in sepsis patients was found in prior studies[5]. The findings in Table 1 revealed that spanning from group Q1 to Q4, there was a significant decrease in neutrophils and a significant increase in lymphocytes, with a corresponding decrease in NLR, paralleled by a substantial decline in the risk of all-cause mortality. Therefore, we proposed a consistent trend: a decrease in NLR correlated with a concurrent reduction in mortality risk in sepsis patients. Secondly, serum albumin was a frequently utilized marker for assessing nutritional status. Prior studies indicated a negative correlation between albumin levels and the incidence of sepsis[39]. Owing to its anti-inflammatory effects, albumin served an essential role in sepsis therapy. Sepsis patients with higher albumin levels had a better prognosis compared to those with lower levels. This evidence suggested that albumin levels were closely related to the occurrence of sepsis, the progression of complications, and prognosis. In this study,

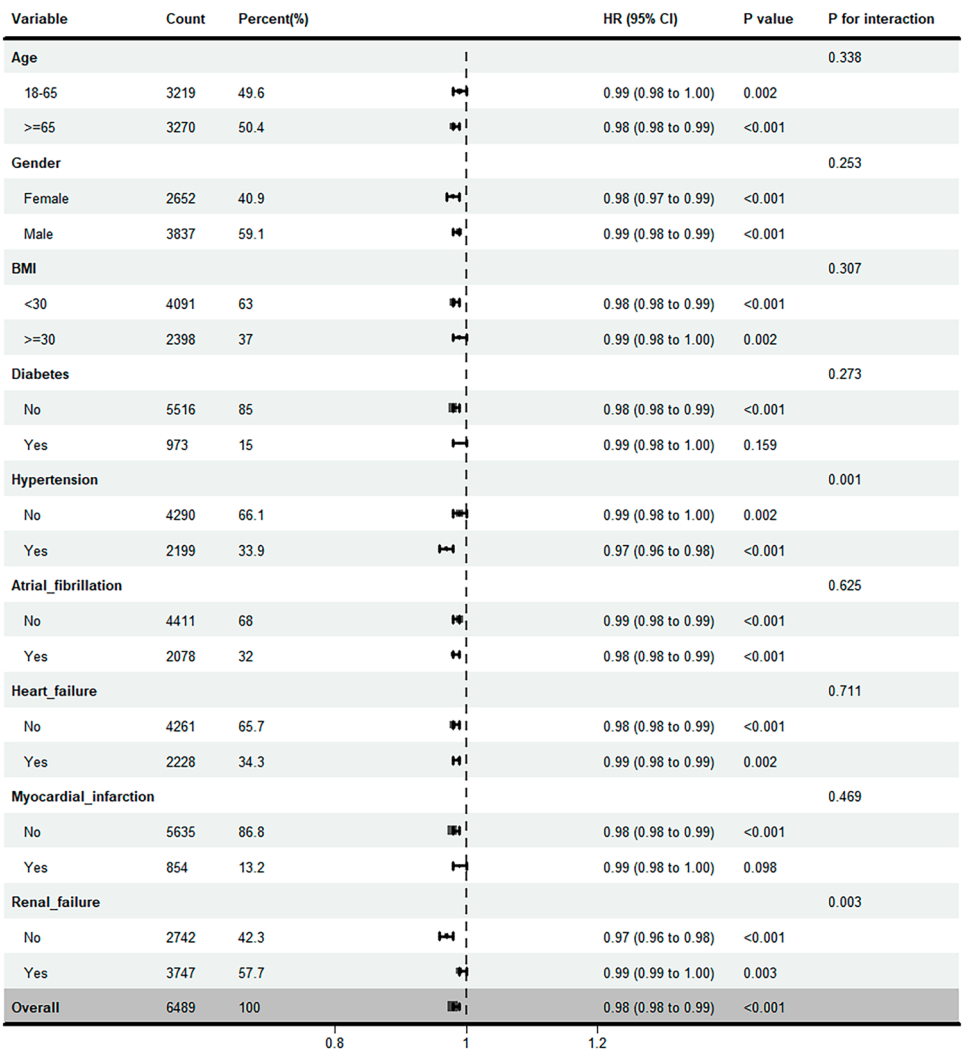

Fig. 4. Subgroup analyses for the association of ALI index with in-hospital mortality. HR, hazards ratio; CI, confidence interval.

we noticed that from group Q1 to Q4, albumin levels gradually increased, and all-cause mortality significantly decreased. Therefore, we believed that the elevated albumin levels mainly contributed to consistent decrease in the risk of all-cause mortality for sepsis patients. Finally, we examined the impact of BMI on the mortality of sepsis patients. Obesity was often a high-risk factor for a variety of diseases. However, the relationship between BMI and the prognosis of sepsis patients was controversial[40]. Previous studies had shown that sepsis patients with higher BMI had a lower mortality rate, a paradox that might be explained by the obesity paradox[41]. In other words, obesity was associated with a lower mortality rate in sepsis. The underlying mechanism might be that patients with higher BMI had stronger anti-inflammatory capabilities[42]. This study indicated that as BMI levels increased from Q1 to Q4, the risk of all-cause mortality among patients with sepsis significantly decreased.

Our study further analyzed the risk stratification of various subgroups. The results suggested that the predictive value of the ALI index for hospital mortality and ICU mortality was consistent among sepsis patients, regardless of age, gender, obesity, atrial fibrillation, and heart failure. However, we did not observe a significant association between ALI and in-hospital mortality among patients with baseline diabetes or myocardial infarction possibly because these comorbidities independently confer a poorer prognosis[43,44]. Additionally, the current study revealed that the predictive value of the ALI index significantly differs between sepsis patients with and without atrial fibrillation and between those with and without renal failure. This was because sepsis patients with renal failure had a higher mortality rate, and hypertension could reduce the mortality rate[45,46]. Finally, we confirmed a significant linear relationship between the ALI index and in-hospital mortality, supporting that the ALI index could be a reliable tool for detecting high mortality risk in sepsis patients.

Notably, although a similar study was recently published after our submission[47], our research presents several important distinctions. We employed the updated MIMIC-IV3.1 database with a larger sample size, incorporated survival analysis for 90-day mortality, conducted comprehensive in-hospital all-cause mortality analysis, and performed more granular subgroup stratifications. Together, these features enhance the robustness and clinical applicability of our findings regarding the prognostic value of the ALI index in critically ill sepsis patients.

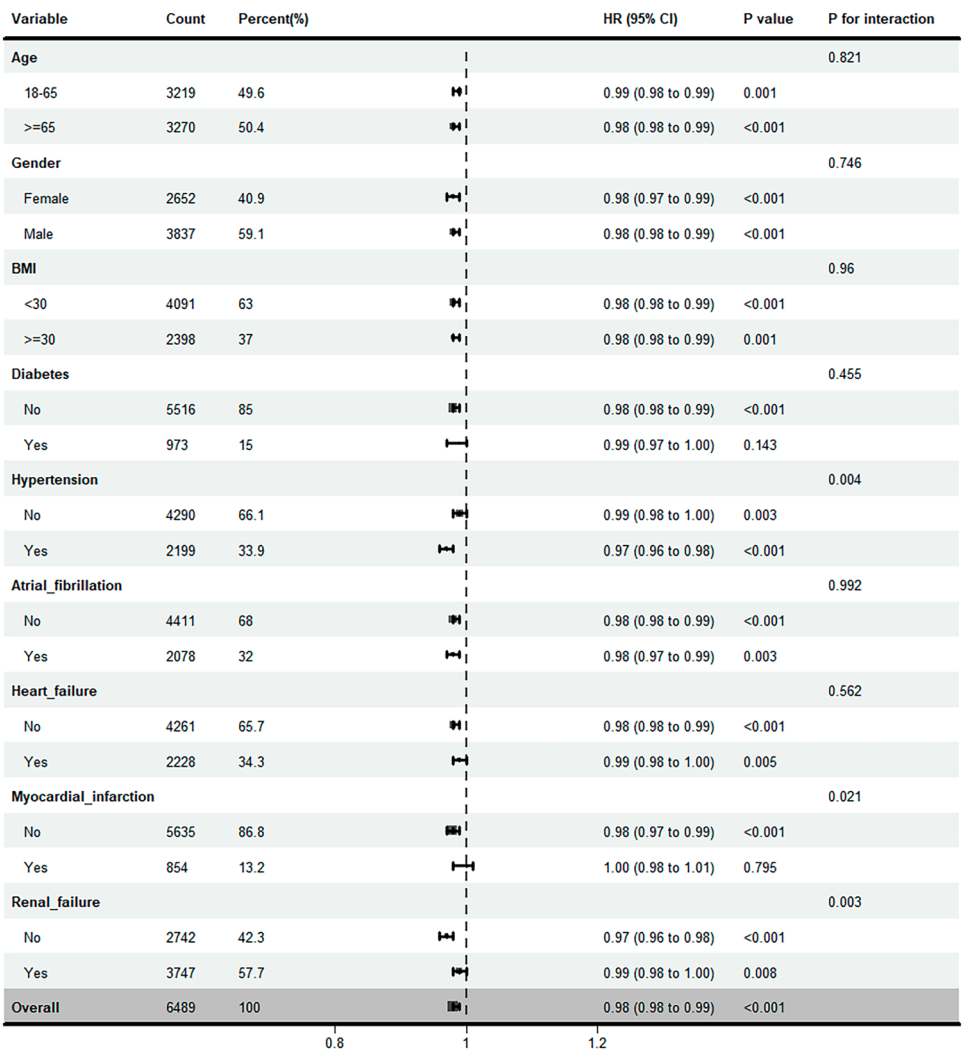

Fig. 5. Subgroup analyses for the association of ALI index with ICU mortality. HR, hazards ratio; CI, confidence interval.

This study has several strengths. Firstly, our analysis based on a large public database with nationally representativeness, verified that the ALI index was an important independent risk factor in critically ill patients with sepsis in a US cohort. Secondly, we considered a multitude of confounding factors and utilized multivariable-adjusted Cox analysis, stratified analysis, and interaction analysis. Lastly, the ALI index is an easily calculable and derivable comprehensive index, offering high convenience and practicality for clinical use.

This study also has some limitations. First, as this was an observational research, it cannot definitively establish a causal link between the ALI index and the mortality associated with sepsis patients. Second, we collected data from the first-time measurements, and did not dynamically monitor the data during the follow-up period. To address these limitations, we plan to leverage hospital EHR data to expand the sample size, clarify the causality, employ additional statistical methods to minimize bias, and perform external validation in independent cohorts or diverse populations.

Conclusions

In conclusion, our results extended the utility of the ALI index to critically ill patients with sepsis and demonstrated that the ALI index could be used as a potential index for risk stratification of in-hospital and ICU mortality among these patients. Therefore, enhancing risk assessment and directing subsequent interventions. However, additional prospective studies are required to validate these findings.

Data availability

The data utilized in this study were sourced from the MIMIC-IV database. For more information about the database, please visit: https://mimic.physionet.org/. The datasets extracted and analyzed during this study can be made available by the corresponding author upon reasonable request.

Received: 6 January 2025; Accepted: 23 June 2025
Published online: 01 July 2025

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Author contributions

Lei Zhang designed the study. Lei Zhang extracted, collected and analyzed data. Minye Li, Jianfei Liu prepared tables and figures. Zhanwei Zhao, Lijun Zhou reviewed the results, interpreted data, and wrote the manuscript. All authors have made an intellectual contribution to the manuscript and approved the submission.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-08713-9.

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