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Research article

Association between albumin-bilirubin score and in-hospital mortality in patients with sepsis: Evidence from two large databases

Erya Gou [a,1], Qilin Yang [a,1], Jieru Chen [a], Tianyu Kong [a], Zhiwei Tang [a], Qirui Wen [a], Wenxing Huang [a], Guangqian Yang [b], Wenling Li [a], Deliang Wen [a], Zhenhui Zhang [a,c,*]

[a] Department of Critical Care, The Second Affiliated Hospital of Guangzhou Medical University, No. 250 Changgang East Road, Haizhu District, Guangzhou, China
[b] Information Center, The Second Affiliated Hospital of Guangzhou Medical University, No. 250 Changgang East Road, Haizhu District, Guangzhou, China
[c] State Key Laboratory of Respiratory Disease, Clinical Laboratory Medicine Department, China

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ABSTRACT

Background: The Albumin-Bilirubin (ALBI) score, recommended for assessing the prognosis of hepatocellular carcinoma patients, has garnered attention. The efficacy of ALBI score in forecasting the risk of death in sepsis patients remains limited. We designed two cohort studies to assess the association between ALBI score and in-hospital mortality in patients with sepsis.
Methods: A retrospective analysis was conducted utilizing data from the Second Affiliated Hospital of Guangzhou Medical University and the Medical Information Mart for Intensive Care IV(MIMIC-IV). Patients diagnosed with sepsis were included in the analysis. The primary outcome was the in-hospital mortality. Multivariate Cox regression analysis was conducted to assess the independent association between the ALBI score and mortality, with adjustment for potential confounders. Subgroup analysis was conducted to assess the robustness of the findings.
Results: The Guangzhou Sepsis Cohort (GZSC) of the Second Affiliated Hospital of Guangzhou Medical University comprised 2969 participants, while the MIMIC-IV database included 8841 participants. The ALBI score were categorized into < -2.60, $-2.60 \sim -1.39$, and > -1.39. After adjusting for confounders, a linear relationship was observed between ALBI score and mortality. Patients with a high ALBI grade were associated with higher in-hospital mortality in both the GZSC (HR: 1.52, 95%CI: 1.24–1.87, $p < 0.001$) and the MIMIC-IV database (HR: 1.57, 95%CI: 1.46–1.70, $p < 0.001$).
Conclusions: A high ALBI score is associated with higher in-hospital mortality among sepsis patients in ICU.

* Corresponding author. Department of Critical Care, The Second Affiliated Hospital of Guangzhou Medical University, No. 250 Changgang East Road, Haizhu District, Guangzhou, China.
E-mail addresses: gouerya623@163.com (E. Gou), yangqilin@gzhmu.edu.cn (Q. Yang), chenjieru77@163.com (J. Chen), ktyfancy@126.com (T. Kong), tzwicu@126.com (Z. Tang), wen.qirui@163.com (Q. Wen), huangwenxingicu@163.com (W. Huang), 2009682038@gzhmu.edu.cn (G. Yang), 18130906778@163.com (W. Li), deliangw@163.com (D. Wen), zhzhhicu@126.com (Z. Zhang).
[1] Contributed equally.

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1. Introduction

Sepsis, a critical condition in intensive care units (ICUs), arises from an infection that leads to an overactive immune reaction and can lead to the failure of multiple organs [1,2]. It is a widespread and perilous health issue, impacting more than 30 million individuals globally each year and causing nearly 6 million fatalities [3]. Despite medical progress, the survival rate for sepsis remains poor [4,5]. Early identification of patients at high risk and with unfavorable outcomes is essential for providing prompt and suitable medical care [6].

During sepsis, the liver has essential roles, including immune defense and metabolic adaptation to inflammation, as well as nutrient metabolism [7]. Liver failure in sepsis is a significant complication that exacerbates the condition's severity and is associated with poor outcomes [8,9]. It is valuable to access liver function in sepsis patients.

The Albumin-Bilirubin (ALBI) score was recommended to evaluate prognosis of hepatocellular carcinoma patients by Johnson et al. [10]. The ALBI score is a simple index used to evaluate liver function because of including only serum albumin and bilirubin levels. It is also applied to predict the mortality of patients with liver injury [11–13]. However, the efficacy of ALBI score in forecasting the risk of death in critically ill sepsis patients remains to be determined. This study is aimed to investigate the association between ALBI score and in-hospital mortality in patients with sepsis.

2. Methods

2.1. Data sources and setting

A real-world cohort study was initiated, leveraging data from two distinct sources: the Medical Information database of the Intensive Care Unit (ICU) at Guangzhou Medical University's Second Affiliated Hospital, and the Medical Information Mart for Intensive Care (MIMIC-IV). The Guangzhou database encompasses a wealth of information on ICU patients treated from 2017 to 2021 [14]. Guangzhou Medical University's Second Affiliated Hospital functions as a tertiary teaching hospital. This database contains patients with various infection, injury, cancer, etc. Through screening of clinical data by the SOFA score greater than 2 points as a result of a pathological host reaction to infection, We only include sepsis patient's database named GZSC(Guangzhou Sepsis Cohort). The MIMIC-IV database, to which we have secured access, is an extensive repository of more than 70000 clinical individuals in ICU patients from the Beth Israel Deaconess Medical Center, spanning the years 2008–2019 [15,16]. A certificate number 1154503 has been issued to Erya Gou for the utilization of the MIMIC database.

2.2. Study population

Eligibility for inclusion in our study was extended to all individuals from both the Guangzhou Sepsis Cohort (GZSC) and the MIMIC-IV database. We focused on adult patients, aged 18 years and older, who met the sepsis-3 diagnosis criteria. This diagnosis was based on the Sequential Organ Failure Assessment (SOFA) score greater than 2 points as a result of a pathological host reaction to infection [1]. The exclusion criteria is (1) Individuals with ICU stays shorter than 24 h; (2) Lacking data of bilirubin or albumin levels.

2.3. Exposure

The ALBI score was calculated using the following equation: ALBI = [log10bilirubin (μmol/L) × 0.66 − 0.085 × albumin (g/L)] [10]. Patients with sepsis were categorized into three groups based on their ALBI scores: < -2.60, -2.60 to -1.39, and > -1.39 [17].

2.4. Covariates

Data from the database were comprehensively extracted for this study, encompassing a range of demographic details such as age and gender. Additionally, laboratory results from tests performed within the first 24 h following ICU admission were included, like white blood cell counts and serum creatinine levels. The study also accounted for various clinical interventions initiated on the initial ICU day, such as mechanical ventilation and continuous renal replacement therapy (CRRT). Furthermore, the Sequential Organ Failure Assessment (SOFA) scores were documented to assess organ dysfunction.

3. Outcomes

3.1. The primary outcome was in-hospital mortality

3.1.1. Statistical analysis

Continuous variables exhibiting normal distribution were reported as the mean accompanied by the standard deviation (SD). Conversely, those with a skewed distribution were depicted through the median along with the interquartile range (IQR). Categorical data were represented in terms of frequencies and their respective percentages. To ascertain the normalcy of continuous variables, either the Student's t-test or the Wilcoxon rank-sum test was employed, depending on the distribution. For the analysis of categorical variables, the Pearson's chi-squared test was the primary method, with Fisher's exact test used when appropriate.

Curve fitting techniques were employed to explore the correlation between the ALBI score and the likelihood of in-hospital mortality. The relationship was further assessed using multivariable Cox regression models, which were utilized to determine the ALBI score's independent effect on mortality and to compute the corresponding hazard ratios (HR) along with their 95 % confidence intervals (CI). Kaplan–Meier methodology was applied to create survival curves, which were subsequently analyzed using the log-rank test to identify significant differences. To address potential survival bias, subgroup analyses were conducted, categorizing the data based on pertinent covariates.

All analyses were conducted using R version 4.2.2, available from The R Foundation (http://www.R-project.org), and Free Statistics software, version 1.9 (Beijing, China, http://www.clinicalscientists.cn/freestatistics). A two-tailed p-value threshold of <0.05 was applied to determine statistical significance [18].

3.2. Sensitivity analysis

Receiver operator characteristic (ROC) curve was used to evaluate the predictive value. Gender, age(categorized as 65 years) and sepsis-associated liver injury (SALI) were included in the subgroup analysis. SALI was defined by total bilirubin (TBIL) $>$ 2 mg/dL and the occurrence of an international normalized ratio (INR) $>$ 1.5 in the presence of sepsis [7,19].

4. Results

4.1. Population and baseline characteristics

Following the application of inclusion and exclusion criteria, our study enrolled a total of 2969 patients from the Guangzhou Sepsis Cohort (GZSC) and 8841 patients from the MIMIC-IV database, as illustrated in Fig. 1. The detailed baseline characteristics of these patients are presented in Table 1. Patients with higher ALBI grades, as opposed to those with grade 1, were typically older, predominantly male, and exhibited elevated Mean Arterial Pressure (MAP), Blood Urea Nitrogen (BUN), bilirubin levels, and SOFA scores. Additionally, there was a higher incidence of vasoactive medication use and continuous renal replacement therapy (CRRT) among the higher-grade patients, contrasted with lower serum total calcium and albumin levels. Discrepancies in other characteristics between the two databases were observed, including variations in respiratory rate, white blood cell count, and length of ICU stay.

4.2. Primary outcome

The mortality rates of patients within the cohort were 22.1 % (657/2969) in GZSC and 20.5 % (1725/8841) in MIMIC-IV, respectively. Meanwhile, in the GZSC database, the mortality rates of patients in ALBI group 1, 2 and 3 were 17.5 % (24/2969), 19.5 % (367/2969), 28.1 % (266/2969), respectively(Table 2).

4.3. Relationship between ALBI and in-hospital mortality in patients with sepsis in ICU

The curve fitting analysis showed a linear trend between the ALBI score and in-hospital mortality both two databases(eFig. 1A and B). The Kaplan-Meier curve showed a higher mortality rate in patients of grade 3 (ALBI -2.60～ −1.39) ($p < 0.0001$, in GZSC (Fig. 2A)) ($p < 0.0001$, in MIMIC-IV (Fig. 2B)).

The results of multivariate COX regression model are shown in Table 3. In the adjusted model, each point increase in ALBI was associated with a 52 % or 57 % increase in mortality risk(GZSC: HR:1.52,95%CI:1.24–1.87, $p < 0.001$ vs. MIMIC-IV: HR:1.57, 95% CI:1.46–1.70, $p < 0.001$). Patients with high ALBI level had a significantly higher risk of in-hospital mortality (HR: 2.00, 95 % CI:1.08–3.71, $p = 0.027$), compared to those with low ALBI levels. Similar results were also found in MIMIC IV database(HR: 2.00, 95% CI:1.68–2.39, $p < 0.001$).

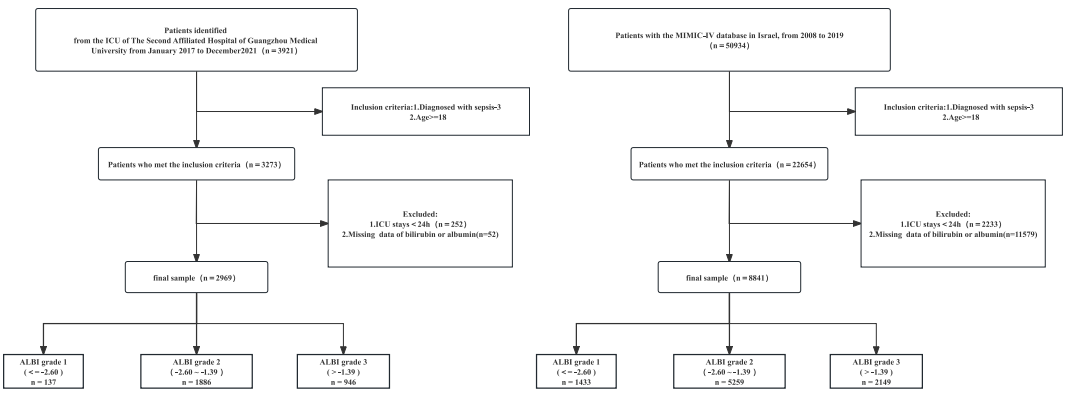

Fig. 1. The flow chart of the study.

Table 1
Baseline characteristics of the study participants.

Variables	GZSC					MIMIC-IV				
	Total (n = 2969)	ALBI ≤ −2.60 (n = 137)	−2.60 <ALBI ≤ −1.39 (n = 1886)	ALBI > -1.39 (n = 946)	P value	Total (n = 8841)	ALBI ≤ −2.60 (n = 1433)	−2.60 <ALBI ≤ −1.39 (n = 5259)	ALBI > -1.39 (n = 2149)	P value
Demographics										
Sex, n (%)					0.455					0.071
Male	1884 (63.5)	93 (67.9)	1200 (63.6)	591 (62.5)		5053 (57.2)	855 (59.7)	2962 (56.3)	1236 (57.5)	
Female	1085 (36.5)	44 (32.1)	686 (36.4)	355 (37.5)		3788 (42.8)	578 (40.3)	2297 (43.7)	913 (42.5)	
Age (years)	66.6 ± 16.7	60.8 ± 17.9	66.8 ± 17.0	67.0 ± 15.9	<0.001	63.4 ± 16.8	61.6 ± 17.6	64.8 ± 16.7	60.9 ± 16.0	<0.001
Vital signs										
MAP(mmHg)	88.1 ± 27.0	102.0 ± 24.2	90.3 ± 28.1	81.6 ± 23.5	<0.001	77.0 ± 10.8	81.1 ± 11.3	77.1 ± 10.8	74.0 ± 9.6	<0.001
Heart rate(bpm)	102.1 ± 27.4	103.3 ± 27.4	99.9 ± 28.0	106.3 ± 25.7	<0.001	89.3 ± 17.4	85.0 ± 16.0	88.6 ± 17.3	93.6 ± 17.7	<0.001
Respiratory rate (bpm)	23.1 ± 8.1	23.8 ± 8.2	23.1 ± 8.4	23.0 ± 7.6	0.723	20.3 ± 4.3	19.5 ± 3.7	20.5 ± 4.2	20.6 ± 4.7	<0.001
Temperature(°C)	36.9 ± 0.9	37.0 ± 0.9	36.9 ± 0.9	36.8 ± 1.0	0.063	36.9 ± 0.7	37.0 ± 0.6	36.9 ± 0.7	36.8 ± 0.7	<0.001
SPO2(%)	92.7 ± 50.6	97.6 ± 35.9	90.2 ± 52.1	96.9 ± 50.6	0.605	96.8 ± 2.3	97.2 ± 1.9	96.8 ± 2.2	96.7 ± 2.7	<0.001
Laboratory findings										
White blood cell(× 10^9)	11.7 (7.5, 17.1)	12.0 (8.7, 16.2)	11.7 (7.8, 17.0)	11.5 (6.3, 17.7)	0.433	14.1 (9.6, 19.8)	13.7 (10.2, 18.1)	13.8 (9.5, 19.5)	14.9 (9.6, 21.7)	<0.001
Creatinine (mg/dL)	1.3(0.9, 2.6)	1.1 (0.8, 2.3)	1.3 (0.9, 2.8)	1.3 (0.9, 2.5)	0.175	1.3 (0.9, 2.2)	1.2 (0.9, 1.8)	1.3 (0.9, 2.2)	1.4 (0.9, 2.4)	<0.001
BUN (mg/dL)	25.7 (16.3,46.6)	19.7(13.4,36.6)	25.4(16.3,46.3)	27.7(17.1,48.3)	<0.001	27.0 (17.0, 45.0)	22.0 (15.0, 34.0)	28.0 (17.0, 46.0)	30.0 (18.0, 50.0)	<0.001
Potassium (mmol/L)	3.9 ± 1.6	4.0 ± 0.9	3.9 ± 1.4	3.9 ± 2.0	0.882	4.7 ± 1.0	4.8 ± 1.1	4.7 ± 1.0	4.7 ± 0.9	<0.001
Sodium (mmol/L)	139.2 ± 8.8	140.4 ± 7.3	139.5 ± 8.7	138.4 ± 9.1	0.002	140.2 ± 6.0	141.3 ± 5.4	140.4 ± 6.0	138.9 ± 6.1	<0.001
Chlorine (mmol/L)	104.4 ± 9.3	102.7 ± 9.5	103.9 ± 9.2	105.5 ± 9.4	<0.001	106.3 ± 7.2	106.3 ± 6.7	106.3 ± 7.2	106.3 ± 7.6	0.997
Calcium (mmol/L)	2.0 ± 0.2	2.2 ± 0.2	2.1 ± 0.2	1.9 ± 0.2	<0.001	2.1 ± 0.2	2.3 ± 0.2	2.1 ± 0.2	2.0 ± 0.3	<0.001
Bilirubin,mg/dl	0.5 (0.3, 1.0)	0.4 (0.3, 0.8)	0.5(0.3, 1.0)	0.6(0.4, 1.0)	<0.001	0.8 (0.5, 2.0)	0.5 (0.3, 0.7)	0.7 (0.4, 1.4)	2.6 (1.1, 6.3)	<0.001
Albumin,g/dl	28.5 ± 6.5	40.7 ± 2.9	31.1 ± 3.9	21.7 ± 4.3	<0.001	3.2 ± 0.7	4.2 ± 0.4	3.2 ± 0.4	2.4 ± 0.4	<0.001
Scoring system										
SOFA score	9.0 (7.0, 12.0)	9.0 (7.0, 10.0)	9.0 (7.0, 11.0)	10.0 (8.0, 13.0)	<0.001	3.0 (2.0, 5.0)	3.0 (2.0, 4.0)	3.0 (2.0, 5.0)	4.0 (3.0, 6.0)	<0.001
In-hospital management										
CRRT	550 (18.5)	22 (16.1)	334 (17.7)	194 (20.5)	0.146	609 (7.2)	75 (5.5)	327 (6.5)	207 (10.2)	<0.001
Mechanical ventilation	2016 (67.9)	87 (63.5)	1239 (65.7)	690 (72.9)	<0.001	4904 (58.4)	814 (59.9)	2832 (56.5)	1258 (61.9)	<0.001

MAP, mean arterial pressure; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy.

Table 2
Primary outcome of total patients.

Variables	GZSC					MIMIC-IV				
	Total (n = 2969)	ALBI ≤ −2.60 (n = 137)	−2.60 <ALBI ≤ −1.39 (n = 1886)	ALBI > -1.39 (n = 946)	P value	Total (n = 8841)	ALBI ≤ −2.60 (n = 1433)	−2.60 <ALBI ≤ −1.39 (n = 5259)	ALBI > -1.39 (n = 2149)	P value
Los ICU (days)	14.4 (8.0, 25.0)	15.6 (8.5, 27.8)	15.0 (8.2, 25.8)	13.5 (7.1, 22.2)	<0.001	6.1 ± 6.8	6.2 ± 7.3	5.9 ± 6.6	6.4 ± 7.0	0.004
In-hospital mortality,n,%	657 (22.1)	24 (17.5)	367 (19.5)	266 (28.1)	<0.001	1725 (20.5)	195 (14.4)	925 (18.4)	605 (29.8)	<0.001

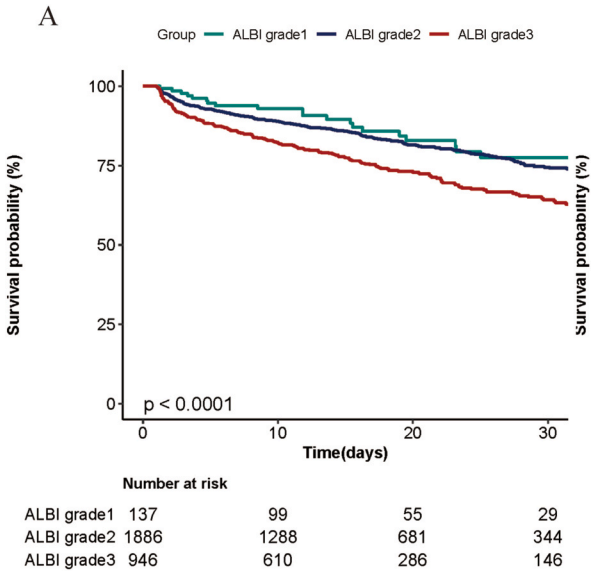

Fig. 2A. K-M analysis of in patients with sepsis of GZSC.

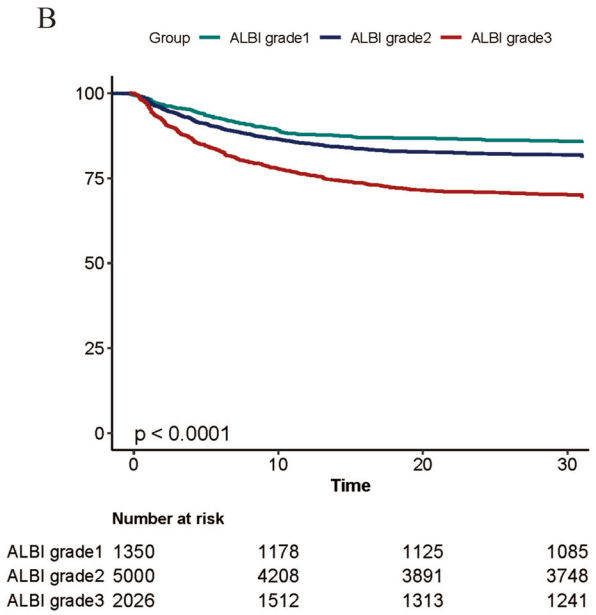

Fig. 2B. K-M analysis of in patients with sepsis of MIMIC-IV.

4.4. Sensitivity analysis

The area under the curves for ALBI was 0.570 in the GZSC database and 0.598 in the MIMIC-IV database (eFig. 2A and B). Meanwhile we incorporated the SOFA score for comparative analysis. Subgroup analysis showed that patients with high ALBI had a significantly higher risk of in-hospital mortality in GZSC and MIMIC-IV, compared to low ALBI, except patients with SAIL(Fig. 3A and B). In patients with SAIL, the risk of in-hospital mortality is not statistically significant regardless of the ALBI score's height.

5. Discussion

In this cohort study, we reported that the ALBI grade was a predictor of patients with sepsis. Our findings revealed that among high ALBI grade was associated with higher in-hospital mortality in both the GZSC(HR:1.52,95%CI:1.24–1.87, $p < 0.001$) and the MIMIC-IV database(HR:1.57, 95%CI:1.46–1.70, $p < 0.001$). The results remained stable in subgroup analysis.

Table 3
Association between ALBI score and in-hospital motality in multiple regression model.

	GZSC				MIMIC-IV			
	Crude Model		Adjusted Model		Crude Model		Adjusted Model	
	HR (95 % CI)	**P value**	**HR (95 % CI)**	**P value**	**HR (95 % CI)**	**P value**	**HR (95 % CI)**	**P value**
Continuous variable								
ALBI	1.42 (1.26–1.60)	<0.001	1.52 (1.24–1.87)	<0.001	1.63 (1.52–1.74)	<0.001	1.57 (1.46–1.70)	<0.001
Categorical variables								
ALBI ≤ −2.60	Ref		Ref		Ref		Ref	
−2.60 <ALBI ≤ −1.39	1.11 (0.77–1.58)	0.581	1.25 (0.7–2.22)	0.457	1.32 (1.13–1.54)	<0.001	1.16 (0.98–1.36)	0.080
ALBI > -1.39	1.81 (1.26–2.6)	0.001	2.00 (1.08–3.71)	0.027	2.32 (1.98–2.73)	<0.001	2.00 (1.68–2.39)	<0.001
Trend for test		<0.001		<0.001		<0.001		<0.001

Adjusted Model: adjusted for Age, Gender, Heart rate, Respiratory rate, SPO2, Temperature,WBC, Potassium, Sodium, Chlorine, Calcium, Creatinine, BUN, CRRT, Mechanical ventilation.

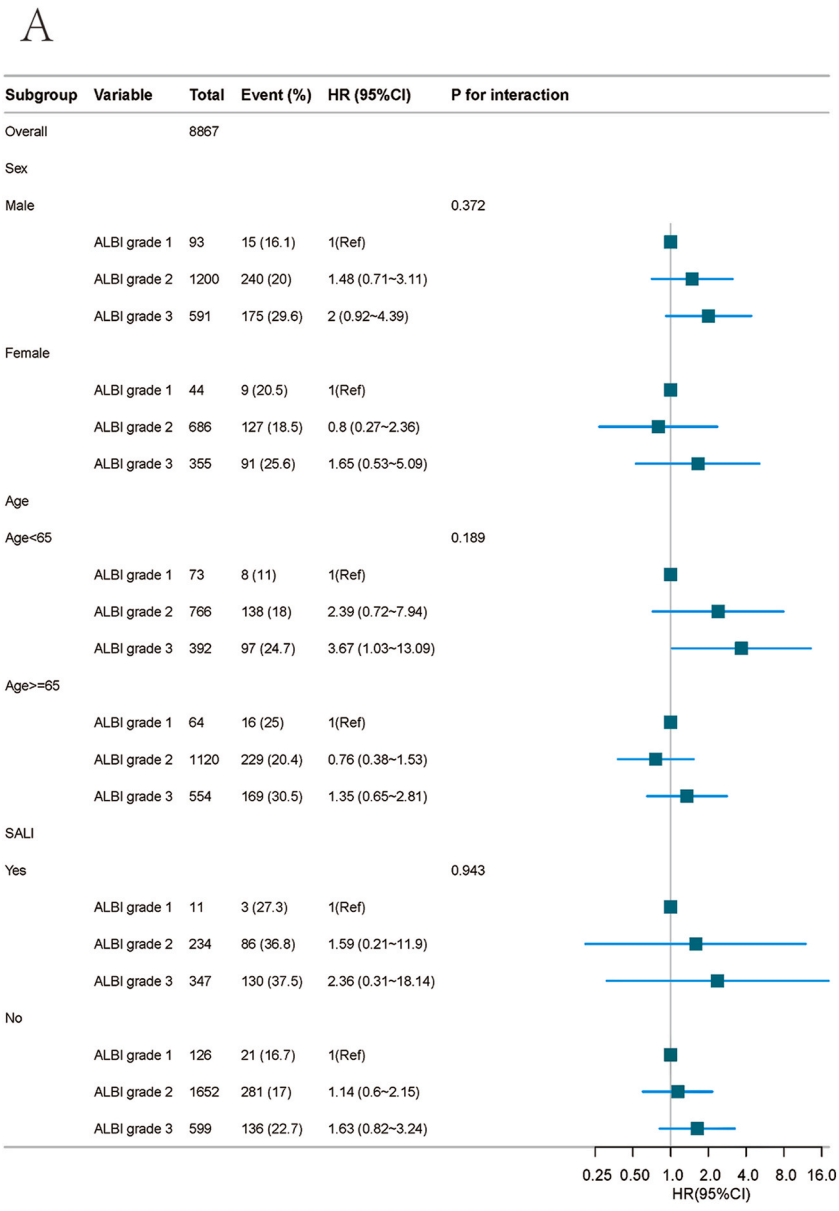

Fig. 3A. Stratified analyses of the association between ALBI grade and in-hospital mortality status according to sex, age and SAIL in GZSC.

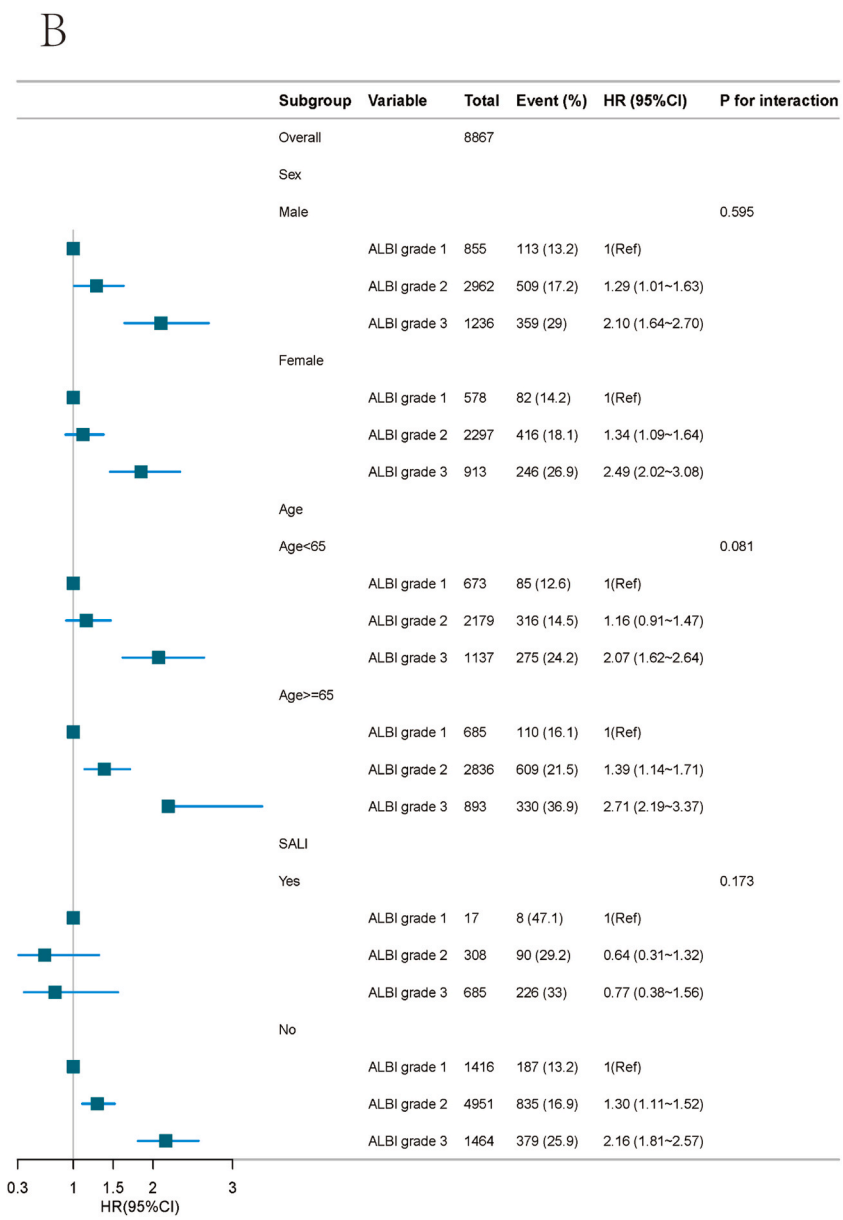

Fig. 3B. Stratified analyses of the association between ALBI grade and in-hospital mortality status according to sex, age and SAIL in MIMIC-IV.

The ALBI score, which includes serum bilirubin and albumin levels, was developed as a new model to assess liver function and predict the survival of patients with liver disease [10]. The ALBI score originated for HCC patients to estimate the extent of liver dysfunction. Meanwhile, it has also been widely used in patients without HCC [20–22]. A meta-analysis indicates a strong association between elevated preoperative ALBI scores and the risk of postoperative liver failure and mortality following hepatectomy [13]. In our study, we use ALBI score to assess liver function and prognosis of patients with sepsis. We found that a high ALBI grade was associated with higher in-hospital mortality in these patients.

Besides its application in predicting liver diseases [11–13], the ALBI score has been used to predict survival in patients with heart failure [23,24]. Su Han et al.($n = 9749$) conducted the in-hospital mortality rate for heart failure patients(HF) escalated by 8.2 % per 0.1-point rise in the ALBI score (OR 1.082; 95 % CI:1.052–1.114; $p < 0.001$) [24]. Similaly, Luo et al.($n = 3381$) reached the same conclusions in HF patients. Compared with the low ALBI group, the odds ratio (OR) for the short-term all-cause mortality of high group was 2.41 (95 % CI: 1.85–3.15, $P < 0.001$) [23]. In our study, we extented the use of ALBI in patients with sepsis. It was found that it could evaluate the prognosis of patients with sepsis.

Liver failure is a common complications of sepsis [7]. Therefore, we included SALI as a variable in subgroup analyses. In patients with SAIL, risk of in-hospital mortality is not statistically significant no matter ALBI score height. The reason maybe the sample size of

SALI in the ALBI grade 1, the reference group was small(n = 11 and n = 17). Rendering the results in this part were biased(Fig. 3A and B).

Interestingly, the relationship between ALBI and mortality was also observed in non-SALI patients(HR: 2.16; 95 % CI:1.81–2.57; Fig. 3B). This means that in patients without sepsis-related liver injury, a higher ALBI score is associated with an increased risk of death. The specific mechanisms need further exploration.

Our study suggests that early assessment of the ALBI score can identify patients with a high risk of death, even patients without SAIL. Further research is needed to determine whether early liver-protective therapy in patients with high sepsis severity scores can improve their prognosis.

This study also has some limitations. Firstly, all laboratory data represent initial values at ICU admission. Causal relationship between ALBI and in-hospital mortality is unknown. Marginal structural models, a new class of causal models that allowed for improved adjustment of confounding affected by previous treatment [25]. We plan to research this relationship in the context of causal inference used marginal structural models in the future. Secondly, the baseline characteristics varied significantly across the three database groups. To address these disparities, we utilized a multivariable Cox proportional hazards regression model, enhancing the reliability of our results. While we acknowledge that some estimation bias may remain, our methodological approach aims to minimize its impact. Finally, bilirubin and albumin levels, recorded within the first 24 h of ICU admission, were available for only about 50 % of the patients in the MIMIC-IV database. However, the results of GZSC is similar to those of the MIMIC IV database. In conclusion, despite these limitations, our study provides valuable evidence on the association between ALBI and in-hospital mortality in sepsis patients. The large sample size, long follow-up period, and adjustment for confounding factors contribute to the strength of our findings. Further research is warranted to confirm and expand upon our results.

6. Conclusion

A high ALBI score is associated with higher in-hospital mortality among sepsis patients in ICU. These findings have significant implications for risk stratification and management of sepsis patients.

Ethics approval and consent to participate

The Clinical Research and Applied Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University approved the ethical review of this study(2023-hg-ks-22). The MIMIC-IV database has already received approval from the institutional review boards at Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. Our research adhered to local legislation and institutional guidelines. Furthermore, the need for written informed consent was waived by the same ethics committee, given that the database does not contain protected health information.

Consent for publication

All authors have reviewed and approved the manuscript for publication.

Availability of data and materials

Datasets can be obtained by contacting the corresponding author upon a reasonable request.

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CRediT authorship contribution statement

Erya Gou: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Qilin Yang:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Data curation. **Jieru Chen:** Methodology, Investigation, Formal analysis. **Tianyu Kong:** Supervision, Software, Investigation. **Zhiwei Tang:** Visualization, Validation, Software, Data curation. **Qirui Wen:** Formal analysis, Data curation, Conceptualization. **Wenxing Huang:** Project administration, Methodology, Investigation. **Guangqian Yang:** Investigation, Data curation. **Wenling Li:** Formal analysis, Data curation. **Deliang Wen:** Supervision, Software, Resources, Investigation. **Zhenhui Zhang:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34697.

Abbreviations

ALBI: Albumin-Bilirubin
MIMIC-IV: Medical Information Mart for Intensive Care-IV
GZSC: Guangzhou Sepsis Cohort
ICU: Iintensive Care Unit
SOFA score: sequential organ failure assessment score
CRRT: continuous renal replacement therapy
SD: standard deviation
IQR: interquartile range
HR: hazard ratios
CI: confidence intervals
ROC: Receiver operator characteristic
MAP: mean arterial pressure
WBC: white blood cell
PaO_2: partial pressure of oxygen in arterial blood
BUN: blood urea nitrogen
Los ICU days: days of ICU stay
SALI: sepsis-associated liver injury

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