Total SOFA and SOFA Kidney are Associated with Short Term and Long term Outcoming of Sepsis-Associated Liver Injury

He Miao
The First Hospital of China Medical University: The First Affiliated Hospital of China Medical University
Hong Liang
China Medical University
Yuteng Ma
The First Hospital of China Medical University: The First Affiliated Hospital of China Medical University
Cong Tian
Philips research China
Yanan Ma
China Medical University
Xiaochun Ma
The First Hospital of China Medical University: The First Affiliated Hospital of China Medical University
Renyu Ding (renyuding@126.com)
The First Hospital of China Medical University https://orcid.org/0000-0001-7751-821X

Research

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Abstract

Background: Liver injury is considered as a common complication of sepsis. However, there are still few studies on short-term and long-term prognostic factors of sepsis-associated liver injury (SALI). The objective of our study is to conduct a large sample data cohort study to explore the risk factors for short-term and long-term prognosis of SALI.

Methods: Data from a public, US-based, critical-care database (Medical Information Mart for Intensive Care-III [MIMIC-III]) was used. Septic patients who met the definition of acute liver injury were enrolled. Variables extracted from MIMIC-III were used to evaluate patient demographics, clinical characteristics on Day 1 of intensive care unit admission, and clinical outcomes. The Logistic regression models were used to calculate risk ratio (RR) and 95% confidence intervals (CIs) after adjusting for potential factors.

Results: Among the 14687 participants in our study, there were 3140 (21.38%) with SALI. SALI was significantly positively associated with ICU mortality (RR, 1.54; 95% CI, 1.32, 1.79), 28-day mortality (RR, 1.27; 95% CI, 1.11, 1.45) and 1-year mortality (RR, 1.19; 95% CI, 1.06, 1.34) after adjusting confounding factors. Stratified by SOFA, there was a positive association between SALI and ICU mortality (RR, 2.15; 95% CI, 1.64, 2.80), 28-day mortality (RR, 1.60; 95% CI, 1.28, 1.99), 1-year mortality (RR, 1.24; 95% CI, 1.04, 1.48) after adjusting confounding factors among people with sofa score ≤ 5. Similar results were also obtained between SALI and ICU mortality (RR,1.40; 95% CI, 1.17, 1.67), 28-day mortality (RR, 1.17; 95% CI, 0.99, 1.38), 1-year mortality (RR, 1.19; 95% CI, 1.02, 1.38) after adjusting confounding factors among people with sofa score> 5. Compared with SOFA renal> 1, SALI had a stronger positive correlation with ICU mortality (RR, 1.36; 95% CI, 1.01, 1.84), 28-day mortality (RR, 1.19; 95% CI, 0.91, 1.56), 1-year mortality (RR, 1.11; 95% CI, 0.88, 1.41) after adjusted confounding factors among people with SOFA renal ≤ 1.

Conclusions: SALI was an independent risk factor for ICU mortality, 28-day mortality and 1-year mortality. And there is a close association between liver and kidney in sepsis, but the mechanism is still unclear and requires further study.

Background

Sepsis is an organ dysfunction syndrome resulting from dysregulated host response to infection and can develop into severe sepsis and septic shock. It is high morbidity and mortality[1, 2]. Sepsis can cause life-threatening multiple organ dysfunction, including the liver, kidneys, lungs, gastrointestinal tract, and circulation[2]. Traditionally, liver injury has been considered as a late manifestation of sepsis-induced multiple organ dysfunction syndrome. Recently, it has been shown that liver injury is an early event in sepsis[3–5].

Studies have shown that liver injury was considered as an independent risk factor of poor prognosis in sepsis and was a powerful independent predictor of ICU mortality[6–8]. Based on a few small-sample studies, the incidence of SALI is estimated to be in the range of 30–34.7% and the mortality of SALI is

estimated to be in the range of 30–60%[3,9–13]. Kobashi, H et al[3] demonstrated that the poor prognosis ratio(the proportion of the patients who died or whose condition had worsened or was unchanged)of SALI was 50.6% in a retrospective cohort study. Dou, J et al[11] demonstrated that hospital mortality of pediatric patients with SALI was 23.81%. Y. R. KANG et al[9] demonstrated that ICU mortality in septic shock patients with hepatic dysfunction was 36% and in-hospital mortality was 48% in a retrospective observational study. It is therefore essential to find factors associated with high mortality in sepsis-associated liver injury.

At present, there are few studies on the factors associated with short-term and long-term prognosis of liver injury in sepsis. SOFA score has been demonstrated to be an effective predictor of ICU mortality in sepsis[14, 15]. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) was released in 2016. The consensus definition included the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score[2]. The SOFA score consists of six different subscores: respiratory, cardiovascular, liver, coagulation, renal, and neurological[14, 16]. It reflects the number of dysfunctional organs as well as the degree of damage[17, 18].Therefore the SOFA score is commonly used to predict ICU mortality in critically ill patients, especially those with sepsis[19, 20]. Gupta, T et al demonstrated that elevated hepatic SOFA scores were most predictive of in-hospital death[21]. In addition, serum T-BIL level lactate level, lactate clearance rate, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and decreased C3 and C4 were all independent risk factors for the prognosis of liver injury [22–25]. However, there is still a lack of cohort studies with large samples, and there are few studies on the long-term prognosis of SALI[26]. There are also fewer studies exploring the interaction between organs in sepsis.

Thus, the purpose of our research is to investigate the association between SALI and ICU mortality, 28-day mortality, 1-year mortality in the cohort study. Also, we further evaluated the relationship between SALI and mortality with short term and long term stratified by SOFA component.

Materials And Methods

Database

A public US-based critical-care database (Medical Information Mart for Intensive Care-III [MIMIC-III]) was employed for this study. MIMIC-III consists of de-identified health-related data associated with 49,785 distinct hospital admissions for 38,597 adult patients in multiple intensive care units (ICU) of Beth Israel Deaconess Medical Center (BIDMC) between 2001 and 2012[27]. This study undertook an analysis of the third-party database, which is anonymized and publicly available with preexisting institutional review board (IRB) approval.

Participants

Adult patients (> 18 years) who satisfied the third Sepsis definition (Sepsis 3.0: sepsis as a condition with life-threatening organ dysfunction caused by a dysregulated host response to infection) at ICU admission were included (Fig. 1)[2]. We screened patients with documented or suspected infection, plus an acute change in the total SOFA score of ≥ 2 points at ICU admission[2]. Infection was diagnosed by the International Classification of Diseases (Nine version, ICD-9) diagnostic code in the MIMIC-III that was implemented by Angus et al.[28]. Patients with preexisting liver diseases, as identified by Quan et al.[29]or biliary disease were excluded based on the ICD-9 diagnostic code.

In the absence of standardized diagnostic criteria for SALI, septic patients who met the definition of acute liver injury were eligible for study inclusion. Acute liver injury was defined as a state wherein the patient's blood reports met at least one of these four conditions: (i) ALT ≥ 80 U/L; (ii) AST ≥ 80 U/L; (iii) T-Bil ≥ 3.0 mg/dL; and (iv) serum direct bilirubin (D-Bil) ≥ 0.6 mg/L. In patients with multiple ICU admissions for acute liver injury, only the first session was included for analysis.

In the MIMIC-III cohort, 18,328 adult admissions satisfied the criteria of Sepsis 3.0 at ICU admission. After excluding patients with preexisting liver and biliary diseases, 14,687 patients remained, of whom 3,140 (21%) were diagnosed with SALI (Fig. 1).

Data collection

The following variables were extracted from the MIMIC-III database to evaluate the patient demographics and clinical characteristics: age, sex, SOFA score, Acute Physiology and Chronic Health Evaluation (APACHE) III score, mechanical ventilation, renal replacement (RRT), vasopressor use in the first 24 h of ICU admission, and other comorbidities including solid tumor, diabetes. The APACHE III and SOFA scores were calculated within the first 24 h following ICU admission by using the code of the MIMIC-III repository[30]. Other variables, including platelet count (PLT), partial thromboplastin time (PTT), Urine output, lactate measured more than once in the first 24 h of ICU admission were expressed as mean values.

statistical Analysis

The normal variables were expressed as the mean ± SD and the nonnormal variables were median (IQR). T-test and Nonparametric tests were used to detect differences among groups. Also, categorical variables were shown as percentages (%). Also, RR and 95% confidence intervals (CIs) were calculated by the binary logistic regression model. In the multivariate logistic regression models, the associations between SALI and ICU morality, 28-day morality, 1-year morality were identified after adjusting for age (years), gender (female, male), SOFA score, APACHEIII score, urine output (mL), mechanical ventilation (no, yes), RRT (no, yes), vasopressor use (no, yes), solid tumor (no, yes), diabetes (no, yes), alcohol abuse (no, yes), lactate (mmol/L), PLT (K/μL), PTT (s). After adjusting for potential factors, we also performed subgroup analyses stratified by SOFA renal (≤ 1, > 1), SOFA respiration (≤ 2, > 2), SOFA coagulation (0, > 0), SOFA cardiovascular (≤ 1, > 1) and SOFA cns (0, > 0).

Then, we did an interaction test by comparing the model with product terms between stratified covariates. All statistical tests were two-sided and performed using the IBM SPSS Statistics 21.0 software (IBM, Asia Analytics Shanghai).

Results

Among the 14687 participants in our study, there were 11547 people without SALI (78.62%) and 3140 (21.38%) with SALI. Compared with non-SALI, people with SALI were younger. Compared with males, females were more likely to have SALI. People with SALI were higher sore of sofa than people without SALI. (Table 1). Age was related with ICU mortality (RR, 1.02; 95% CI, 1.02, 1.03), 28-day mortality (RR, 1.03; 95% CI, 1.03, 1.04) and 1-year mortality (RR, 1.04; 95% CI, 1.03, 1.04). SALI had significantly positive association with ICU mortality (RR, 1.33; 95% CI, 1.30, 1.35), 28-day mortality (RR, 1.23; 95% CI, 1.22, 1.25) and 1-year mortality (RR, 1.16; 95% CI, 1.14, 1.17) (Table 2). As shown in Table 3, after adjusting for age, gender, SOFA score, APACHEIII score, urine output, mechanical ventilation, RRT, vasopressor use, solid tumor, diabetes, alcohol abuse, lactate, PLT, PTT, SALI was significantly positively associated with ICU mortality (RR, 1.54; 95% CI, 1.32, 1.79), 28-day mortality (RR, 1.27; 95% CI, 1.11, 1.45) and 1-year mortality (RR, 1.19; 95% CI, 1.06, 1.34) (Table 3). Stratified by SOFA, there was a positive association between SALI and ICU mortality (RR, 2.15; 95% CI, 1.64, 2.80), 28-day mortality (RR, 1.60; 95% CI, 1.28, 1.99), 1-year mortality (RR, 1.24; 95% CI, 1.04, 1.48) after adjusting confounding factors among people with sofa score ≤ 5. Similar results were also obtained between SALI and ICU mortality (RR,1.40; 95% CI, 1.17, 1.67), 28-day mortality (RR, 1.17; 95% CI, 0.99, 1.38), 1-year mortality (RR, 1.19; 95% CI, 1.02, 1.38) after adjusting confounding among people with sofa score > 5. Also, there was an interaction between total SOFA and SALI (Table 4). Compared with SOFA renal > 1, SALI had a stronger positive correlation with ICU mortality (RR, 1.36; 95% CI, 1.01, 1.84), 28-day mortality (RR, 1.19; 95% CI, 0.91, 1.56), 1-year mortality (RR, 1.11; 95% CI, 0.88, 1.41) after adjusted confounding factors among people with SOFA renal ≤ 1. Also, SOFA renal was interacted with SALI (Tables 5–7).

Table 1
Demographic and clinical characteristics of study cohort in MIMIC-III

Characteristic	Liver Function Group		*P*
	Non-SALI group	SALI group	
N (%)	11547 (78.62)	3140 (21.38)	
Age (years)	69.76 ± 15.58	65.20 ± 16.81	**< 0.001**
Gender			**< 0.001**
Female	5715 (49.49)	1838 (58.54)	
Male	5832 (50.51)	1302 (41.46)	
SOFA score	4.72 ± 2.47	6.77 ± 3.52	**< 0.001**
Respiration	1.93 ± 1.29	2.18 ± 1.42	**< 0.001**
Renal	1.17 ± 1.31	1.29 ± 1.32	**< 0.001**
Cardiovascular	1.42 ± 1.13	1.93 ± 1.43	**< 0.001**
Cns	0.80 ± 1.08	0.69 ± 1.13	**< 0.001**
Coagulation	0.38 ± 0.72	0.78 ± 1.06	**< 0.001**
Liver	0.14 ± 0.40	0.96 ± 1.10	**< 0.001**
APACHEIII score	48.28 ± 18.35	57.81 ± 23.23	**< 0.001**
Urine output (mL)	1488.00 (882.75-2312.75)	1450.00 (798.50–2390.00)	**0.044**
Mechanical Ventilation			**< 0.001**
No	6507 (56.35)	1322 (42.10)	
Yes	5040 (43.65)	1818 (57.90)	
RRT			0.566
No	10831 (93.80)	2954 (94.08)	
Yes	716 (6.20)	186 (5.92)	
Vasopressor use			**< 0.001**
No	8033 (69.57)	1611 (51.31)	
Yes	3514 (30.43)	1529 (48.69)	
Values were median (IQR) or mean ± SD or n (%).			
The values of polytomous variables may not sum to 100% due to rounding.			
Abbreviations: RRT: renal replacement; PLT: platelet count; PTT: partial thromboplastin time.			

Characteristic	Liver Function Group		*P*
	Non-SALI group	SALI group	
Solid tumor			0.729
No	11120 (96.30)	3028 (96.43)	
Yes	427 (3.70)	112 (3.57)	
Diabetes			**< 0.001**
No	7784 (67.41)	2305 (73.41)	
Yes	3763 (32.59)	835 (26.59)	
Alcohol abuse			**< 0.001**
No	11178 (96.80)	2967 (94.49)	
Yes	369 (3.20)	173 (5.51)	
Lactate (mmol/L)	1.70 (1.20–2.38)	2.27 (1.50–3.64)	**< 0.001**
PLT (K/μL)	224.83 (163.00-306.00)	187.00 (124.00-267.58)	**< 0.001**
PTT (s)	31.20 (26.95–38.70)	34.05 (28.55–46.60)	**< 0.001**
Values were median (IQR) or mean ± SD or n (%).			
The values of polytomous variables may not sum to 100% due to rounding.			
Abbreviations: RRT: renal replacement; PLT: platelet count; PTT: partial thromboplastin time.			

Table 2
Univariate analysis between characteristics of participants and mortality

Characteristics	Statistics	ICU Mortality, RR (95% CI)	28-day Mortality, RR (95% CI)	1-year Mortality, RR (95% CI)
Age (years)	68.79 ± 15.96	**1.02 (1.02, 1.03)**	**1.03 (1.03, 1.04)**	**1.04 (1.03, 1.04)**
Gender				
Female	7553 (51.43)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Male	7134 (48.57)	1.004 (0.91, 1.11)	1.01 (0.93, 1.10)	0.94 (0.88, 1.01)
SOFA score	5.16 ± 2.85	**1.33 (1.30, 1.35)**	**1.23 (1.22, 1.25)**	**1.16 (1.14, 1.17)**
Respiration	1.99 ± 1.33	**1.25 (1.19, 1.32)**	**1.14 (1.09, 1.19)**	**1.05 (1.01, 1.09)**
Cardiovascular	1.53 ± 1.22	**1.59 (1.53, 1.65)**	**1.34 (1.30, 1.39)**	**1.19 (1.16, 1.23)**
Renal	1.19 ± 1.31	**1.43 (1.38, 1.48)**	**1.34 (1.30, 1.38)**	**1.31 (1.27, 1.34)**
Cns	0.78 ± 1.09	**1.13 (1.08, 1.18)**	**1.25 (1.20, 1.29)**	**1.17 (1.14, 1.21)**
Coagulation	0.46 ± 0.82	**1.40 (1.33, 1.47)**	**1.29 (1.24, 1.35)**	**1.21 (1.16, 1.26)**
Liver	0.40 ± 0.81	**1.24 (1.15, 1.33)**	**1.19 (1.12, 1.26)**	**1.12 (1.06, 1.18)**
APACHEIII score	50.32 ± 19.88	**1.05 (1.04, 1.05)**	**1.04 (1.04, 1.04)**	**1.03 (1.03, 1.03)**
Urine output (mL)	1480.00 (861.00, 2330.00)	**0.999 (0.999, 0.999)**	**0.999 (0.999, 0.999)**	**0.999 (0.999, 0.999)**
Mechanical Ventilation				
No	7829 (53.31)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Yes	6858 (46.69)	**2.53 (2.28, 2.82)**	**1.36 (1.25, 1.48)**	1.05 (0.99, 1.13)
RRT				

Values were median (IQR) or mean ± SD or n (%).

The values of polytomous variables may not sum to 100% due to rounding.

Abbreviations: RRT: renal replacement; PLT: platelet count; PTT: partial thromboplastin time; RR: relative risk.

Characteristics	Statistics	ICU Mortality, RR (95% CI)	28-day Mortality, RR (95% CI)	1-year Mortality, RR (95% CI)
No	13785 (93.86)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Yes	902 (6.14)	**1.36 (1.12, 1.64)**	**1.21 (1.03, 1.43)**	**1.67 (1.46, 1.91)**
Vasopressor use				
No	9644 (65.66)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Yes	5043 (34.34)	**2.64 (2.38, 2.92)**	**1.66 (1.52, 1.80)**	**1.23 (1.15, 1.32)**
Solid tumor				
No	14148 (96.33)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Yes	539 (3.67)	**1.44 (1.13, 1.82)**	**1.86 (1.54, 2.24)**	**2.49 (2.09, 2.97)**
Diabetes				
No	10089 (68.69)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Yes	4598 (31.31)	**0.86 (0.77, 0.96)**	**0.87 (0.80, 0.96)**	0.99 (0.92, 1.06)
Alcohol abuse				
No	14145 (96.31)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Yes	542 (3.69)	**0.58 (0.41, 0.80)**	**0.43 (0.32, 0.58)**	**0.35 (0.28, 0.43)**
Lactate (mmol/L)	1.80 (1.30, 2.61)	**1.40 (1.36, 1.44)**	**1.32 (1.28, 1.35)**	**1.20 (1.17, 1.23)**
PLT (K/μL)	217.00 (154.00, 298.00)	**0.999 (0.999, 0.9996)**	0.999 (0.999, 1.0001)	1.0001 (0.999, 1.0003)
PTT (s)	31.80 (27.20, 40.20)	**1.02 (1.01, 1.02)**	**1.01 (1.01, 1.01)**	**1.01 (1.01, 1.01)**

Values were median (IQR) or mean ± SD or n (%).

The values of polytomous variables may not sum to 100% due to rounding.

Abbreviations: RRT: renal replacement; PLT: platelet count; PTT: partial thromboplastin time; RR: relative risk.

Table 3
Relationship between liver function and mortality in different models

Exposure	Non-SALI	SALI, RR (95% CI)
ICU Mortality		
Model I[a]	1.0 (Reference)	**3.35 (3.00, 3.74)**
Model II[b]	1.0 (Reference)	**1.54 (1.32, 1.79)**
28-day Mortality		
Model I[a]	1.0 (Reference)	**2.20 (2.00, 2.42)**
Model II[b]	1.0 (Reference)	**1.27 (1.11, 1.45)**
1-year Mortality		
Model I[a]	1.0 (Reference)	**1.70 (1.57, 1.85)**
Model II[b]	1.0 (Reference)	**1.19 (1.06, 1.34)**

[a]Adjust for Age(years).

[b]Adjust for Age (years), Gender (Female, Male), SOFA score, APACHEIII score, Urine output (mL), Mechanical Ventilation (No, Yes), RRT (No, Yes), Vasopressor use (No, Yes), Solid tumor (No, Yes), Diabetes (No, Yes), Alcohol abuse (No, Yes), Lactate (mmol/L), PLT (K/μL), PTT (s).

Table 4
Stratified analyses of between liver function and ICU mortality by sofa score

Exposure	SOFA score ≤ 5		SOFA score > 5		*P* for interaction
	Non-SALI	SALI, RR (95% CI)	Non-SALI	SALI, RR (95% CI)	
ICU Mortality					**< 0.001**
Model I[a]	1.0 (Reference)	**2.97 (2.45–3.61)**	1.0 (Reference)	**2.32 (2.02–2.66)**	
Model II[b]	1.0 (Reference)	**2.15 (1.64, 2.80)**	1.0 (Reference)	**1.40 (1.17, 1.67)**	
28-day Mortality					**< 0.001**
Model I[a]	1.0 (Reference)	**1.75 (1.49–2.06)**	1.0 (Reference)	**1.75 (1.54–1.99)**	
Model II[b]	1.0 (Reference)	**1.60 (1.28, 1.99)**	1.0 (Reference)	1.17 (0.99, 1.38)	
1-year Mortality					**0.010**
Model I[a]	1.0 (Reference)	**1.42 (1.25–1.61)**	1.0 (Reference)	**1.48 (1.32–1.67)**	
Model II[b]	1.0 (Reference)	**1.24 (1.04, 1.48)**	1.0 (Reference)	**1.19 (1.02, 1.38)**	

[a]Adjust for Age(years).

[b]Adjust for Age (years), Gender (Female, Male), SOFA score, APACHEIII score, Urine output (mL), Mechanical Ventilation (No, Yes), RRT (No, Yes), Vasopressor use (No, Yes), Solid tumor (No, Yes), Diabetes (No, Yes), Alcohol abuse (No, Yes), Lactate (mmol/L), PLT (K/μL), PTT (s). Of note, the variables examined in this table were not adjusted.

Table 5
Stratified analyses of between liver function and ICU mortality by sofa components

Exposure	Non-SALI	SALI, RR (95% CI)	*P* for interaction
Renal			**0.041**
≤ 1 (N = 10008)	1.0 (Reference)	**1.36 (1.01, 1.84)**	
> 1 (N = 4672)	1.0 (Reference)	1.01 (0.71, 1.41)	
Respiration			**0.039**
≤ 2 (N = 4235)	1.0 (Reference)	1.39 (0.98, 1.97)	
> 2 (N = 3183)	1.0 (Reference)	1.03 (0.77, 1.38)	
Coagulation			0.527
0 (N = 10193)	1.0 (Reference)	**1.49 (1.12, 1.98)**	
> 0 (N = 4420)	1.0 (Reference)	0.82 (0.57, 1.18)	
Cardiovascular			**0.011**
≤ 1 (N = 10845)	1.0 (Reference)	**1.65 (1.17, 2.33)**	
> 1 (N = 3729)	1.0 (Reference)	0.89 (0.66, 1.20)	
Cns			0.350
0 (N = 8072)	1.0 (Reference)	1.16 (0.88, 1.52)	
> 0 (N = 6468)	1.0 (Reference)	1.14 (0.77, 1.70)	

*Adjust for Age (years), Gender (Female, Male), Respiration, Renal, Cardiovascular, Cns, Coagulation, Liver, APACHEIII score, Urine output (mL), Mechanical Ventilation (No, Yes), RRT (No, Yes), Vasopressor use (No, Yes), Solid tumor (No, Yes), Diabetes (No, Yes), Alcohol abuse (No, Yes), Lactate (mmol/L), PLT (K/μL), PTT (s). Of note, the variables examined in this table were not adjusted.

Table 6
Stratified analyses of between liver function and 28-day mortality by sofa components

Exposure	Non-SALI	SALI, RR (95% CI)	*P* for interaction
Renal			**< 0.001**
≤ 1 (N = 10008)	1.0 (Reference)	1.19 (0.91, 1.56)	
> 1 (N = 4672)	1.0 (Reference)	0.91 (0.65, 1.26)	
Respiration			0.234
≤ 2 (N = 4235)	1.0 (Reference)	1.12 (0.82, 1.53)	
> 2 (N = 3183)	1.0 (Reference)	1.003 (0.76, 1.32)	
Coagulation			0.214
0 (N = 10193)	1.0 (Reference)	1.23 (0.94, 1.60)	
> 0 (N = 4420)	1.0 (Reference)	0.84 (0.60, 1.18)	
Cardiovascular			0.379
≤ 1 (N = 10845)	1.0 (Reference)	**1.46 (1.08, 1.99)**	
> 1 (N = 3729)	1.0 (Reference)	0.78 (0.59, 1.04)	
Cns			**0.013**
0 (N = 8072)	1.0 (Reference)	1.11 (0.86, 1.43)	
> 0 (N = 6468)	1.0 (Reference)	0.94 (0.65, 1.35)	

*Adjust for Age (years), Gender (Female, Male), Respiration, Renal, Cardiovascular, Cns, Coagulation, Liver, APACHEIII score, Urine output (mL), Mechanical Ventilation (No, Yes), RRT (No, Yes), Vasopressor use (No, Yes), Solid tumor (No, Yes), Diabetes (No, Yes), Alcohol abuse (No, Yes), Lactate (mmol/L), PLT (K/μL), PTT (s). Of note, the variables examined in this table were not adjusted.

Table 7
Stratified analyses of between liver function and 1-year mortality by sofa components

Exposure	Non-SALI	SALI, RR (95% CI)	*P* for interaction
Renal			**0.008**
≤ 1 (N = 10008)	1.0 (Reference)	1.11 (0.88, 1.41)	
> 1 (N = 4672)	1.0 (Reference)	0.76 (0.55, 1.04)	
Respiration			0.083
≤ 2 (N = 4235)	1.0 (Reference)	1.04 (0.79, 1.37)	
> 2 (N = 3183)	1.0 (Reference)	0.89 (0.69, 1.16)	
Coagulation			0.087
0 (N = 10193)	1.0 (Reference)	1.02 (0.81, 1.29)	
> 0 (N = 4420)	1.0 (Reference)	0.89 (0.65, 1.23)	
Cardiovascular			0.107
≤ 1 (N = 10845)	1.0 (Reference)	1.29 (0.99, 1.69)	
> 1 (N = 3729)	1.0 (Reference)	0.70 (0.53, 0.92)	
Cns			0.297
0 (N = 8072)	1.0 (Reference)	0.95 (0.75, 1.19)	
> 0 (N = 6468)	1.0 (Reference)	1.01 (0.72, 1.40)	
*Adjust for Age (years), Gender (Female, Male), Respiration, Renal, Cardiovascular, Cns, Coagulation, Liver, APACHEIII score, Urine output (mL), Mechanical Ventilation (No, Yes), RRT (No, Yes), Vasopressor use (No, Yes), Solid tumor (No, Yes), Diabetes (No, Yes), Alcohol abuse (No, Yes), Lactate (mmol/L), PLT (K/μL), PTT (s). Of note, the variables examined in this table were not adjusted.			
Abbreviations: ICU, intensive care unit; SALI, sepsis-associated liver injury.			

Discussion

We found that SALI was an independent risk factor for ICU mortality, 28-day mortality and 1-year mortality. Also, stratified by SOFA (5 points), there was a positive association between SALI and ICU mortality, 28-day mortality, 1-year mortality. Interestingly, compared with SOFA renal > 1, SALI had a stronger positive correlation with ICU mortality, 28-day mortality, 1-year mortality among people with SOFA renal ≤ 1.

Liver injury is a risk factor for the prognosis of sepsis and an important predictor of poor prognosis in septic patients[3, 8, 13, 31, 32]. This study showed that ICU mortality in patients with SALI was 11. 68%, 28-day mortality was 19. 33, the one-year mortality rate was 39. 82%. This study had a slightly lower short-

term mortality compared to other studies. This may be related to the different inclusion and exclusion criteria and the number of samples. In the study by Y.R.KANG et al[9], the study population was 188 septic shock patients with hepatic dysfunction in ICU. The population included in this study was patients satisfied the criteria of Sepsis 3.0. And there is a lack of a uniform definition of liver injury in sepsis,the standard definition of liver injury used in this study was based on the previous literature[3, 4, 10, 33–36]. A prospective, observational, multicentre cohort study has demonstrated that liver failure is a factor associated with early mortality in septic patients[37]. Brun-Buisson.C. et al demonstrated that liver failure is strongly associated with mortality in the SOFA score[38]. This conclusion is consistent with the conclusions of previous studies. Although the study has demonstrated a close relationship between the occurrence and deterioration of liver injury during septic shock and long-term mortality (180-day mortality)[39], one-year mortality of SALI is still lacking to be reported.

After adjusting confounding factors, the RRs among people with sofa score < 5 were higher compared with sofa score ≥ 5. Patients with sepsis-associated liver injury had higher short-term and long-term mortality even if SOFA scores were lower. This further confirms the poor prognosis of patients with sepsis-associated liver injury. Moreover, our present study showed that in short-term outcome studies, the liver interacts with the kidney, respiratory, and cardiovascular systems, and for long-term outcome, only the kidney interacts with the liver. These results indicate that the liver and kidney might be most closely related in multiple organ failure in sepsis. It has been shown that renal failure is a common complication in cirrhotic patients with sepsis[40]. At the same time, renal injury can also cause dysfunction of extrarenal distant organs (such as liver, intestines, lung, brain, etc.), which is also called “renal and extrarenal organs crosstalk”[41]. Renal and liver crosstalk during acute kidney injury may be caused by a complex combination of soluble inflammatory mediators and cellular immunity[42]. Interestingly, septic patients without renal injury have a worse short-term or long-term prognosis if they present with liver injury. The mechanism is still unclear and needs further exploration.

This study has some limitations. Although the sample size of this study is larger than that of previous studies, the MIMIC-III database is only from a single center. Therefore, some conclusions of this study will need to be verified by multicenter studies. The diagnostic criteria for SALI used in our study were based on previous studies. At present, there is no gold standard for the diagnosis of hepatic injury of sepsis. Our study shows that, owing to the high incidence and mortality of sepsis liver injury, further clinical studies are needed to develop diagnostic criteria for liver injury in sepsis. Simultaneously, attention toward the prevention and treatment of SALI is needed. This is a retrospective study, and we extracted data from patients only for their ICU stay. As some patients may have developed sepsis before ICU admission, the exact time between sepsis and liver injury cannot be accurately calculated. This may cause bias in the results for the time of liver injury. The study included only data on the day of ICU admission and dynamic observation of continuous clinical data was absent. Our study found that total SOFA and SOFA kidney are associated with short term and long term outcoming of SALI. Also, further research was needed to clarify the potential specific mechanisms.

Conclusions

SALI was an independent risk factor for ICU mortality, 28-day mortality and 1-year mortality. So early detection of SALI as well as exploration of prognostic factors associated with SALI are extremely important to reduce mortality. In addition, this study showed that SALI was positively associated with ICU, 28-day and one-year mortality. And there is a close association between liver and kidney in sepsis, but the mechanism is still unclear and requires further study.

Abbreviations

APACHE, Acute Physiology and Chronic Health Evaluation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIDMC, Beth Israel Deaconess Medical Center; CI, confidence interval; D-Bil, direct bilirubin; ICU, intensive care unit; ICD, International Classification of Diseases; IRB, institutional review board; MIMIC-III, Medical Information Mart for Intensive Care-III; PLT, platelet count; PTT, partial thromboplastin time; RR, risk ratio; RRT, renal replacement; SOFA, sequential organ failure assessment; SALI, sepsis-associated liver injury; T-Bil, Total bilirubin.

Declarations

Ethics approval and consent to participate

Not applicable, study on existing database.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

RYD, XCM and YNM designed the study and were guarantor of the paper. HM and HL prepared the draft and finished the manuscript. HL and YNM contributed to the data analysis and interpretation of the results. YTM and CT were involved in data collection. All authors read and approved the final manuscript.

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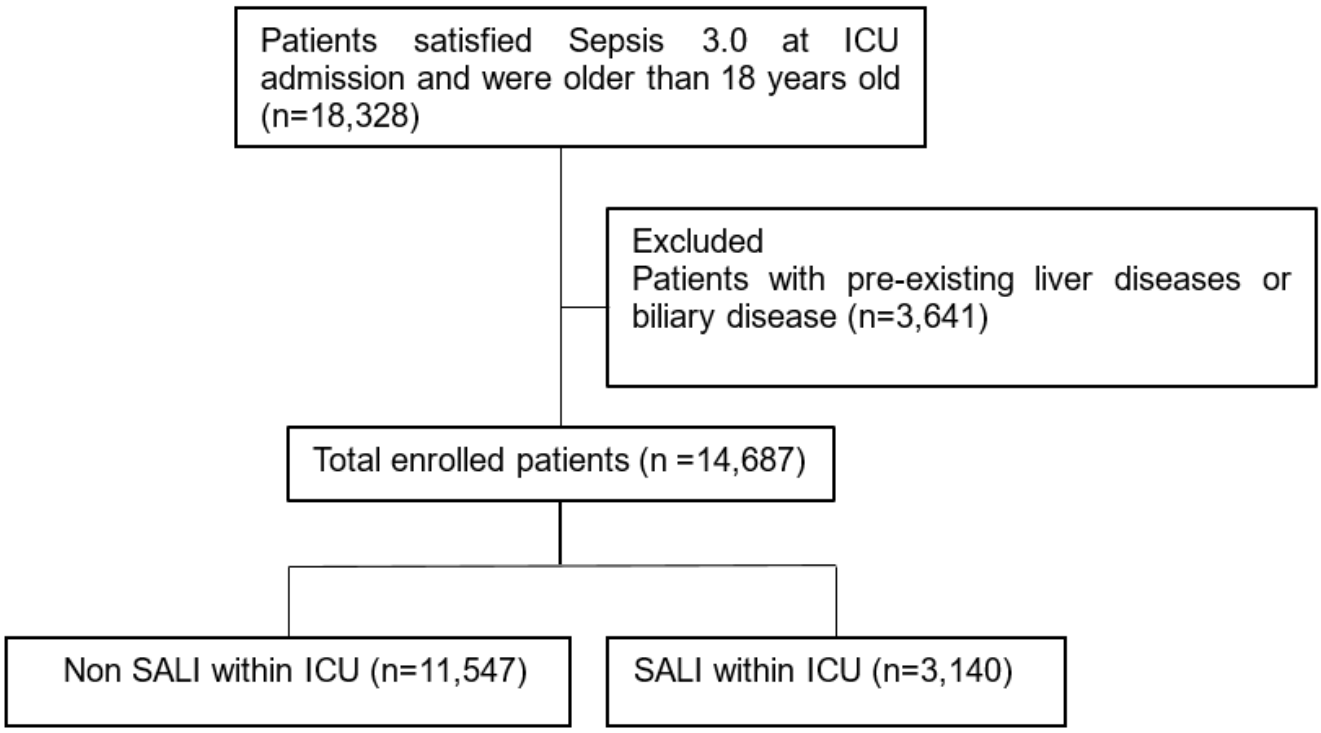
Figures



Abbreviations：ICU, intensive care unit; SALI, sepsis-associated liver injury.

Figure 1

Flow diagram for exclusion criteria in the SALI and Non SALI group.