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Sites and Causes of Infection in Patients with Sepsis-Associated Liver Dysfunction: A Population Study from the Medical Information Mart for Intensive Care III

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Background: Little is known about the relationship between the site of infection, type of pathogen, and the occurrence of sepsis-associated liver dysfunction (SALD). This population study aimed to identify the sites and types of infection in SALD patients.





Material/Methods: We conducted a retrospective observational study using the Medical Information Mart for Intensive Care III. Patients with sepsis were divided into a SALD group and a control group. We evaluated the effect of the location of culture-positive specimens and the distribution of pathogens on the occurrence of SALD and then compared the clinical outcomes.

Results: A total of 14 596 admissions were included, and the incidence of SALD was 11.96%. Positive bile culture (odds ratio [OR] 7.450, $P < 0.001$), peritoneal fluid culture (OR 3.616, $P < 0.001$), and blood culture (OR 1.957, $P < 0.001$) were correlated with the occurrence of SALD. Infection with *Enterococcus faecium* (OR 3.065, $P < 0.001$), *Bacteroides fragilis* (OR 2.061, $P < 0.001$), *Klebsiella oxytoca* (OR 2.066, $P < 0.001$), *Enterobacter aerogenes* (OR 1.92, $P = 0.001$), and *Aspergillus fumigatus* (OR 2.144, $P = 0.001$) were correlated with the occurrence of SALD. The Intensive Care Unit mortality and hospital mortality were higher in the SALD group than in the control group (24.7% vs 9.0%, $P < 0.001$; 34.2% vs 13.8%, $P < 0.001$, respectively).

Conclusions: SALD should be considered for patients with sepsis whose infection site is the biliary system, abdominal cavity, or blood and the pathogen is *Enterococcus faecium*, *B. fragilis*, *K. oxytoca*, *Enterobacter aerogenes*, or *A. fumigatus*. When SALD occurs in patients with sepsis, the above infection sites and pathogens should be considered first.

Keywords: Database • Prognosis • Sepsis

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Background

Sepsis is common in patients in the Intensive Care Unit (ICU). Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. The Surviving Sepsis Campaign guidelines indicate that improving the perfusion of tissues, including the liver, in patients with sepsis is critical to improve the prognosis [2]. Measures include timely and effective fluid resuscitation, appropriate use of vasoactive drugs, and effective treatment of primary infections, among others [2]. The liver plays an important role in maintaining metabolic and immunological homeostasis. During sepsis, the liver can regulate immune defense through mechanisms such as bacterial clearance, production of acute-phase proteins or cytokines, and metabolic adaptation to inflammation [3]. However, the liver is also affected in sepsis. During sepsis, the infection itself, hyperactivity of the inflammatory response, failure of the microcirculation, and adverse effects of treatment can cause liver injury [4]. According to the clinical presentation, sepsis-associated liver dysfunction (SALD) can be divided into 2 major patterns: hypoxic hepatitis (due to ischemia and shock) and cholestasis (due to altered bile metabolism) [3,5]. Because of the lack of uniform diagnostic criteria, the precise incidence of SALD remains difficult to determine. The mean incidence of liver dysfunction in sepsis patients is 39.9% [6]. SALD leads to increased mortality and poor prognosis in patients with sepsis. Early identification and treatment will improve the prognosis of patients with sepsis and liver injury [7]. Infection is the root cause of the occurrence and development of sepsis and SALD [8]. Different infection sites and pathogen types lead to different types of organ failure resulting from sepsis [9]. Clarifying the relationship of infection sites and pathogen types with the occurrence of SALD in patients with sepsis would aid in the early identification and treatment of SALD, and there are few such studies in the literature. Medical Information Mart for Intensive Care III (MIMIC-III) was developed at the Massachusetts Institute of Technology. MIMIC-III includes clinical data of patients admitted to the Beth Israel Deaconess Medical Center in Boston, Massachusetts, between June 2001 and October 2012, and includes 58 000 hospital admissions for 38 645 adults [10]. The current population study aimed to use data from the MIMIC-III database version 1.4 (v1.4) to identify the sites of infection and infections in patients with SALD.

Material and Methods

Patients

We conducted a retrospective study using the MIMIC-III database v1.4. The patient information in the database was deidentified for privacy protection, and the requirement for individual

informed consent was waived. One of us (Jinfeng Lin) obtained access to the database (certificate number 32304761).

Patients admitted to the hospital with sepsis were included in this study. Patients younger than 18 years and hospitalized for less than 48 h were excluded. The study subjects were divided into a control group and a SALD group. The SALD group was further divided into a hypoxic hepatitis group, a cholestasis group, and a combined hypoxic hepatitis and cholestasis group.

According to the definition of sepsis [1], we identified patients with confirmed infection (positive specimen culture) and sequential organ failure assessment (SOFA) score ≥ 2 as sepsis patients in this study.

Sepsis-associated Liver Dysfunction

Hypoxic hepatitis was defined as serum aminotransaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) levels >1000 IU/L [11]. Cholestasis was defined as a total serum bilirubin level >3 mg/dL [12]. The exclusion criteria were previous liver disease, such as autoimmune hepatitis, alcoholic cirrhosis, biliary cirrhosis, and otherwise unspecified cirrhosis, and obstruction of the bile duct.

Study Process

According to the inclusion and exclusion criteria, the subjects of this study were selected and grouped. The age, sex, SOFA score, lactate level, and white blood cell count of the 2 groups measured at admission were recorded. Moreover, the levels of ALT, AST, total bilirubin, and albumin and the international normalized ratio (INR) of each group during hospitalization were compared. We studied the location of culture-positive specimens, the distribution of pathogens, and the effect of each on the occurrence of SALD. Finally, we compared the clinical outcomes, including length of stay in the ICU and hospital, ICU and hospital mortality, and the 1-year cumulative survival rate between the 2 groups.

Statistical Analysis

Continuous variables are presented as the median and 25-75% interquartile range. Categorical data are expressed as numbers and percentages. The Mann-Whitney U test (or Kruskal-Wallis H) or chi-squared test (or Fisher's exact test) was used for univariable analysis as appropriate. An unconditional multiple logistic regression model was used to determine the relationship of infection sites and pathogen types with the occurrence of SALD. An unconditional multiple logistic regression model was used to determine the relationship between pathogens and SALD. The results of the logistic regression analysis were reported as adjusted odds ratios (ORs) with 95% confidence

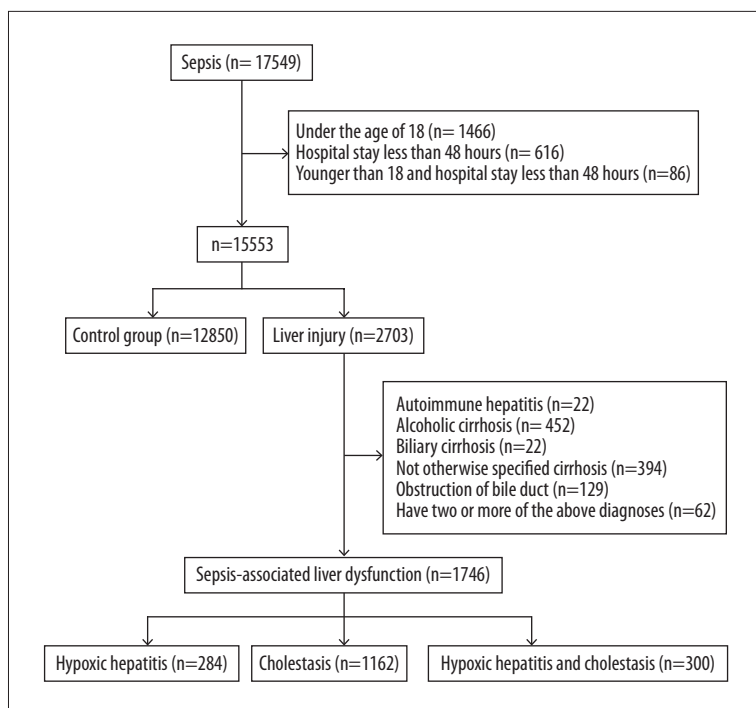


Figure 1. Flow chart for the study selection process. A total of 14 596 patients were included in this retrospective study, of which 12 850 were in the control group and 1746 were in the SALD group. The incidence of SALD was 11.96%. SALD, sepsis-associated liver dysfunction.

Table 1. Patient characteristics on admission in the two groups.

Parameter	All	Control	SALD	P value
Number of admission	14596	12850	1746	
Age (years, median, IQR)	68 (55-78)	68 (56-78)	63 (51-75)	<0.001
Male (n, %)	7904 (54.2)	6864 (53.4)	1040 (59.6)	<0.001
SOFA score (median, IQR)	5 (3-7)	4 (3-6)	7 (5-7)	<0.001
Lactate (mmol/L, median, IQR)	1.7 (1.2-2.5)	1.7 (1.2-2.5)	2.3 (1.5-4)	<0.001
WBC ($\times 10^9/L$, median, IQR)	10.6 (8.2-13.8)	10.6 (8.2-13.8)	12.2 (8.9-15.9)	<0.001

IQR – interquartile range; SOFA – score sequential organ failure assessment score; WBC – white blood cells; SALD – sepsis-associated liver dysfunction.

intervals (CIs). Kaplan-Meier curves and log-rank tests were used to compare cumulative 1-year survival rates of patients in each group. We used MS Excel and SPSS 25 (SPSS, Chicago, IL, USA) for data management and calculations. A 2-sided *P*-value <0.05 was considered statistically significant.

Result

Screening of Patients

According to the sepsis 3.0 diagnostic criteria, the number of cases with confirmed infection and a SOFA score ≥ 2 points in the MIMIC-III clinical database v1.4 was 17 549. The incidence of sepsis was 28.63%. The number of patients younger than 18 years old and/or hospitalized for less than 48 h was

1996. The number of patients with previous liver disease was 957. As a result, a total of 14 596 patients were included in this retrospective study, of which 12 850 were in the control group and 1746 were in the SALD group (284 in the hypoxic hepatitis group, 1162 in the cholestasis group, and 300 in the hypoxic hepatitis and cholestasis group). The incidence of SALD was 11.96%. The specific process is shown in **Figure 1**.

Patient Characteristics on Admission

The SOFA score (7 vs 4, $P < 0.001$), lactic acid level (2.3 vs 1.7, $P < 0.001$), and white blood cell count (12.2 vs 10.6, $P < 0.001$) of patients in the SALD group were significantly higher than those in the control group. The details are shown in **Table 1**.

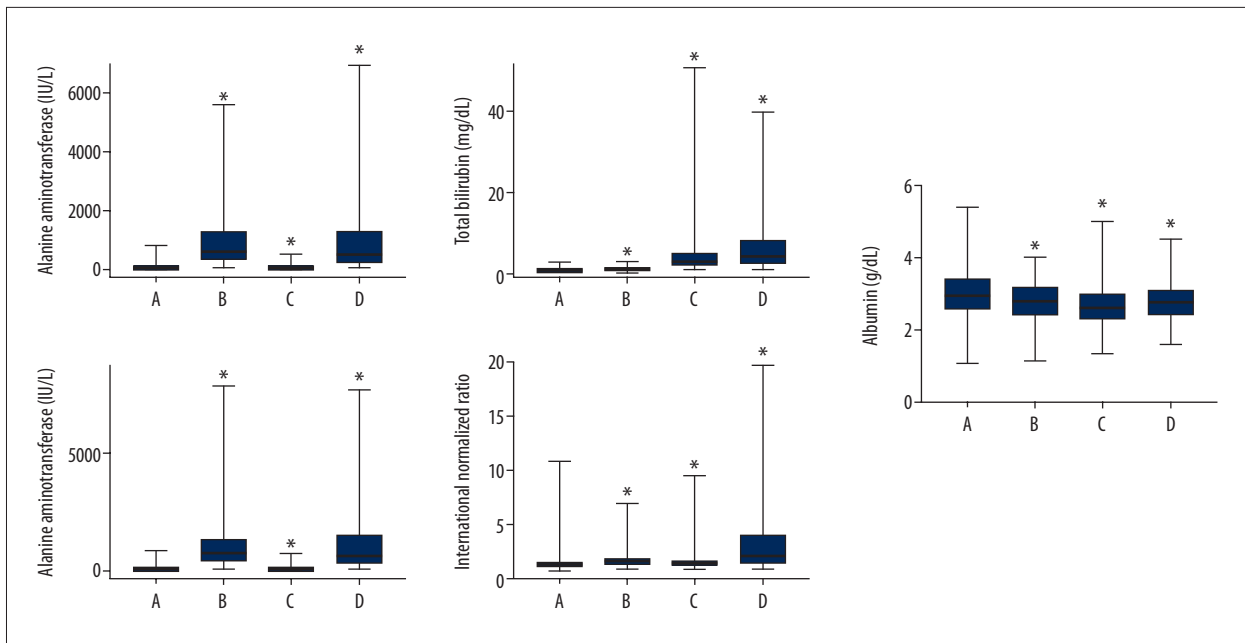


Figure 2. Liver blood laboratory data. The INR of the SALD group was higher than that of the control group ($P < 0.001$). Albumin was lower than that of the control group ($P < 0.001$). (A) control group; (B) hypoxic hepatitis; (C) cholestasis; (D) hypoxic hepatitis and cholestasis. * $P < 0.001$. ALT – alanine aminotransferase; AST – aspartate aminotransferase; INR – international normalized ratio; SALD – sepsis-associated liver dysfunction.

Liver Blood Laboratory Data

Figure 2 shows the levels of ALT, AST, total bilirubin, and albumin and the INR in each group. The INR of the SALD group was higher than that of the control group ($P < 0.001$), while albumin was lower than that of the control group ($P < 0.001$).

Location of Culture-positive Specimens

A total of 42 412 positive culture results were detected in the 2 groups. There were 35 006 cases in the control group and 7406 cases in the SALD group. The types of positive specimens in the control group were mainly sputum and urine, which accounted for 25.18% and 25.15%, respectively. The types of positive specimens in the SALD group were mainly sputum, urine, and blood, which accounted for 23.41%, 16.81%, and 16.39%, respectively. The positive rates of blood culture (16.39% vs 12.91%, $P < 0.001$), catheter tip culture (3.48% vs 2.46%, $P < 0.001$), peritoneal fluid culture (3.07% vs 0.88%, $P < 0.001$), and bile culture (2.44% vs 0.42%, $P < 0.001$) were significantly higher in the SALD group than in the control group. The details are shown in Table 2.

The Effect of the Location of Culture-positive Specimens on the Occurrence of SALD

The results of logistic regression analysis suggested that positive bile culture (OR 7.450, 95% CI 5.263-10.548, $P < 0.001$), followed by positive peritoneal fluid culture (OR 3.616, 95% CI

2.736-4.779, $P < 0.001$) and positive blood culture (OR 1.957, 95% CI 1.755-2.183, $P < 0.001$), was most closely correlated to the occurrence of SALD. The details are shown in Table 3.

Distribution of Pathogens

The pathogens of the 2 groups were mainly bacteria and fungi. In the control group, gram-positive bacteria, gram-negative bacteria, and fungi accounted for 43.06%, 29.23%, and 17.59% of the pathogens, respectively. In the SALD group, gram-positive bacteria, gram-negative bacteria, and fungi accounted for 38.06%, 29.57%, and 21.42% of the pathogens, respectively.

Gram-positive bacteria were significantly more abundant in the control group than in the SALD group (43.06% vs 38.06%, $P < 0.001$), while fungi were significantly more abundant in the SALD group than in the control group (21.42% vs 17.59%, $P < 0.001$). The details are shown in Table 4.

For gram-positive bacteria, there were more *Enterococcus* and *Enterococcus faecium* in the SALD group than in the control group (7.76% vs 6.44%, $P < 0.001$ and 1.59% vs 0.53%, $P < 0.001$, respectively). For gram-negative bacteria, *Enterobacter cloacae* was more abundant in the SALD group than in the control group (1.92% vs 1.17%, $P < 0.001$). For fungi, yeast and *Candida albicans* were more abundant in the SALD group than in the control group (16.18% vs 14.81%, $P = 0.003$ and 3.59% vs 1.90%, $P < 0.001$, respectively). The details are shown in Table 5.

Table 2. Location of culture-positive specimens in the 2 groups.

Specimen	Control (n, %)	SALD (n, %)	P value
All	35006	7406	
Sputum	8816 (25.18)	1734 (23.41)	0.001
Urine	8804 (25.15)	1245 (16.81)	<0.001
Blood	4521 (12.91)	1214 (16.39)	<0.001
Bronchial brush or washings or bronchoalveolar lavage	2066 (5.90)	404 (5.46)	0.136
Skin or tissue	1014 (2.90)	303 (4.09)	<0.001
Catheter tip	862 (2.46)	258 (3.48)	<0.001
Stool	799 (2.28)	118 (1.59)	<0.001
Peritoneal fluid	308 (0.88)	227 (3.07)	<0.001
Pleural fluid	243 (0.69)	49 (0.66)	0.801
Bile	148 (0.42)	181 (2.44)	<0.001
Cerebrospinal fluid	115 (0.33)	5 (0.07)	0.001
Joint fluid	49 (0.14)	12 (0.16)	0.614
Other	7261 (20.74)	1656 (22.36)	0.002

SALD – sepsis-associated liver dysfunction.

Table 3. The effect of location of culture-positive specimens on the occurrence of SALD.

Specimen type	Odds ratio (95% CI)	P value
Sputum	1.641 (1.474-1.827)	<0.001
Urine	0.995 (0.895-1.105)	0.918
Blood	1.957 (1.755-2.183)	<0.001
Bronchial brush or washings or bronchoalveolar lavage	1.101 (0.928-1.307)	0.271
Skin or tissue	1.496 (1.207-1.854)	<0.001
Catheter tip	1.460 (1.223-1.743)	<0.001
Stool	1.031 (0.834-1.273)	0.779
Peritoneal fluid	3.616 (2.736-4.779)	<0.001
Pleural fluid	1.163 (0.777-1.740)	0.462
Bile	7.450 (5.263-10.548)	<0.001
Cerebrospinal fluid	0.161 (0.049-0.532)	0.003
Joint fluid	1.149 (0.578-2.285)	0.691
Other	1.363 (1.213-1.533)	<0.001

SALD – sepsis-associated liver dysfunction; CI – confidence interval.

The effect of Pathogen Type on the Occurrence of SALD

Fungi were most closely correlated to the occurrence of SALD (OR 2.045, 95% CI 1.847-2.264, $P<0.001$). The details are shown in **Table 6**.

Subgroup analysis showed that *Enterococcus faecium* infection was most closely correlated to the occurrence of SALD among gram-positive bacteria (OR 3.065, 95% CI 2.344-4.008, $P<0.001$). Among gram-negative bacteria, infection with *Bacteroides fragilis* (OR 2.061, 95% CI 1.522-2.791, $P<0.001$), *Klebsiella oxytoca* (OR 2.066, 95% CI 1.511-2.824, $P<0.001$), and *Enterobacter*

Table 4. Distribution of pathogens in the 2 groups.

Specimen	Control (n, %)	SALD (n, %)	P value
All	35006	7406	
Gram-positive bacteria	15075 (43.06)	2819 (38.06)	<0.001
Gram-negative bacteria	10234 (29.23)	2190 (29.57)	0.564
Fungi	6159 (17.59)	1586 (21.42)	<0.001
Virus	179 (0.51)	53 (0.72)	0.030
Other	3359 (9.60)	758 (10.23)	0.091

SALD – sepsis-associated liver dysfunction.

Table 5. Subgroup analysis of distribution of pathogens in the 2 groups.

Pathogens	Control (n, %)	SALD (n, %)	P value
All	35006	7406	
Gram-positive bacteria			
Coagulase-positive <i>Staphylococcus aureus</i>	4910 (14.03)	740 (9.99)	<0.001
Coagulase-negative <i>Staphylococcus aureus</i>	3514 (10.04)	732 (9.88)	0.688
<i>Enterococcus</i>	2255 (6.44)	575 (7.76)	<0.001
Methicillin-resistant <i>Staphylococcus aureus</i>	805 (2.30)	84 (1.13%)	<0.001
<i>Clostridium difficile</i>	741 (2.12)	97 (1.31)	<0.001
<i>Corynebacterium species</i>	698 (1.99)	115 (1.55)	0.012
β <i>Streptococcus</i> (group B)	222 (0.63)	24 (0.32)	0.120
Viridans <i>Streptococci</i>	215 (0.61)	56 (0.76)	0.164
<i>Streptococcus pneumoniae</i>	212 (0.61)	35 (0.47)	0.182
<i>Enterococcus faecium</i>	185 (0.53)	118 (1.59)	<0.001
<i>Enterococcus faecalis</i>	165 (0.47)	37 (0.50)	0.718
β <i>Streptococci</i>	177 (0.51)	19 (0.26)	0.004
<i>Lactobacillus species</i>	138 (0.39)	50 (0.68)	0.001
α <i>Streptococci</i>	99 (0.28)	25 (0.34)	0.413
Other gram-positive bacteria	739 (2.11)	112 (1.51)	0.001
Gram-negative bacteria			
<i>Escherichia coli</i>	2210 (6.31)	387 (5.23)	<0.001
<i>Pseudomonas aeruginosa</i>	1595 (4.56)	375 (5.06)	0.060
<i>Klebsiella pneumoniae</i>	1204 (3.44)	274 (3.70)	0.267
<i>Proteus mirabilis</i>	498 (1.42)	33 (0.45)	<0.001
<i>Enterobacter cloacae</i>	408 (1.17)	142 (1.92)	<0.001
<i>Serratia marcescens</i>	306 (0.87)	79 (1.07)	0.112
<i>Haemophilus influenzae</i>	278 (0.79)	18 (0.24)	<0.001

Table 5 continued. Subgroup analysis of distribution of pathogens in the 2 groups.

Pathogens	Control (n, %)	SALD (n, %)	P value
<i>Stenotrophomonas maltophilia</i>	255 (0.73)	98 (1.32)	<0.001
<i>Bacteroides fragilis</i>	222 (0.63)	85 (1.15)	<0.001
<i>Klebsiella oxytoca</i>	209 (0.60)	77 (1.04)	<0.001
<i>Acinetobacter baumannii</i>	177 (0.51)	44 (0.59)	0.337
<i>Enterobacter aerogenes</i>	163 (0.47)	54 (0.73)	0.004
Proteus species	104 (0.30)	11 (0.15)	0.031
Other Gram-negative bacteria	2605 (7.44)	513 (6.93)	0.123
Fungi			
Yeast	5183 (14.81)	1198 (16.18)	0.003
<i>Candida tropicalis</i>	66 (0.19)	10 (0.14)	0.367
<i>Candida albicans</i>	665 (1.90)	266 (3.59)	<0.001
<i>Candida (torulopsis) glabrata</i>	148 (0.42)	73 (0.99)	<0.001
<i>Aspergillus fumigatus</i>	97 (0.28)	39 (0.53)	0.001
Virus			
Herpes simplex virus type 1	94 (0.27)	35 (0.47)	0.006
Herpes simplex virus type 2	24 (0.07)	4 (0.05)	0.807
Other virus	61 (0.17)	14 (0.19)	0.761
Other	3359 (9.60)	758 (10.23)	0.091

SALD – sepsis-associated liver dysfunction.

Table 6. The effect of pathogen type on the occurrence of SALD.

Specimen type	Odds ratio (95% CI)	P value
Gram-positive bacteria	1.337 (1.198-1.492)	<0.001
Gram-negative bacteria	1.337 (1.207-1.481)	<0.001
Fungi	2.045 (1.847-2.264)	<0.001
Virus	1.700 (1.205-2.398)	0.003
Other	1.571 (1.402-1.761)	<0.001

SALD – sepsis-associated liver dysfunction; CI – confidence interval.

aerogenes (OR 1.92, 95% CI 1.297-2.841, $P=0.001$) was closely correlated to the occurrence of SALD. Among fungi, infection with *Aspergillus fumigatus* (OR 2.144, 95% CI 1.374-3.347, $P=0.001$) was most closely correlated to the occurrence of SALD. The details are shown in **Table 7**.

Prognosis of the 2 Groups

Patients in both groups had multiple ICU stays during one hospitalization period, so the total number of all ICU stays was

greater than the number of hospital stays. The number of patients in the ICU in the 2 groups was 14 587 (control group) and 2158 (SALD group). The ICU stay (OR 6.2 [CI 2.8-14.7] vs OR 4.0 [CI 2.0-9.0], $P<0.001$) and hospital stay (OR 18.5 [CI 9.98-30.99] vs OR 12.8 [CI 7.34-21.68], $P<0.001$) of the SALD group were longer than those of the control group. Moreover, the ICU mortality and hospital mortality were significantly higher in the SALD group than in the control group (24.7% vs 9.0%, $P<0.001$; 34.2% vs 13.8%, $P<0.001$, respectively). The details are shown in **Table 8**.

Table 7. Subgroup analysis of the effect of pathogen type on the occurrence of SALD.

Pathogens	Odds ratio (95% CI)	P value
Gram-positive bacteria		
Coagulase-positive <i>Staphylococcus aureus</i>	0.945 (0.838-1.064)	0.350
Coagulase-negative <i>Staphylococcus aureus</i>	1.324 (1.177-1.489)	<0.001
<i>Enterococcus</i>	1.287 (1.126-1.471)	<0.001
Methicillin-resistant <i>Staphylococcus aureus</i>	0.903 (0.713-1.144)	0.398
<i>Clostridium difficile</i>	0.879 (0.701-1.103)	0.265
<i>Corynebacterium</i> species	0.867 (0.684-1.097)	0.235
β <i>Streptococcus</i> (group B)	0.859 (0.534-1.380)	0.529
Viridans <i>Streptococci</i>	1.435 (1.019-2.019)	0.038
<i>Streptococcus pneumoniae</i>	1.305 (0.867-1.966)	0.202
<i>Enterococcus faecium</i>	3.065 (2.344-4.008)	<0.001
<i>Enterococcus faecalis</i>	1.049 (0.708-1.556)	0.810
β <i>Streptococci</i>	0.798 (0.486-1.31)	0.372
<i>Lactobacillus</i> species	1.801 (1.235-2.627)	0.002
α <i>Streptococci</i>	0.89 (0.518-1.527)	0.671
Gram-negative bacteria		
<i>Escherichia coli</i>	1.242 (1.077-1.431)	0.003
<i>Pseudomonas aeruginosa</i>	1.066 (0.902-1.259)	0.453
<i>Klebsiella pneumoniae</i>	1.292 (1.087-1.534)	0.004
<i>Proteus mirabilis</i>	0.52 (0.348-0.777)	0.001
<i>Enterobacter cloacae</i>	1.454 (1.119-1.889)	0.005
<i>Serratia marcescens</i>	1.482 (1.076-2.042)	0.016
<i>Haemophilus influenzae</i>	0.557 (0.341-0.912)	0.020
<i>Stenotrophomonas maltophilia</i>	1.521 (1.126-2.054)	0.006
<i>Bacteroides fragilis</i>	2.061 (1.522-2.791)	<0.001
<i>Klebsiella oxytoca</i>	2.066 (1.511-2.824)	<0.001
<i>Acinetobacter baumannii</i>	1.094 (0.72-1.663)	0.674
<i>Enterobacter aerogenes</i>	1.92 (1.297-2.841)	0.001
<i>Proteus</i> species	0.625 (0.303-1.288)	0.203
Fungi		
Yeast	1.606 (1.441-1.79)	<0.001
<i>Candida tropicalis</i>	0.485 (0.211-1.116)	0.089
<i>Candida albicans</i>	1.616 (1.328-1.967)	<0.001
<i>Candida (torulopsis) glabrata</i>	1.793 (1.255-2.563)	0.001
<i>Aspergillus fumigatus</i>	2.144 (1.374-3.347)	0.001
Virus		
Herpes simplex virus type 1	1.918 (1.23-2.992)	0.004
Herpes simplex virus type 2	0.65 (0.209-2.025)	0.457

SALD – sepsis-associated liver dysfunction; CI – confidence interval.

Table 8. Prognosis of the 2 groups.

Parameter	Control	SALD	P value
ICU LOS (days, median, IQR)	4.0 (2.0-9.0)	6.2 (2.8-14.7)	<0.001
Hospital LOS (days, median, IQR)	12.8 (7.34-21.68)	18.5 (9.98-30.99)	<0.001
ICU mortality (n, %)	1314 (9.0)	533 (24.7)	<0.001
Hospital mortality (n, %)	1731 (13.8)	597 (34.2)	<0.001

SALD – sepsis-associated liver dysfunction; ICU – Intensive Care Unit; LOS – length of stay; IQR – interquartile range.

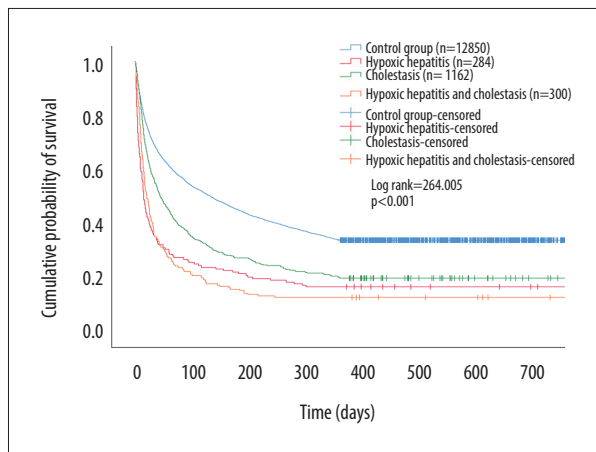


Figure 3. Kaplan-Meier survival curves of each groups. The 1-year cumulative probability of survival for the control group was significantly higher than that for the SALD group (log-rank=264.005; $P<0.001$). SALD – sepsis-associated liver dysfunction.

Kaplan-Meier curves and log-rank tests showed that the 1-year cumulative probability of survival for the control group was significantly higher than for the SALD group (log-rank=264.005; $P<0.001$). In the SALD group, the 1-year cumulative probability of survival for the cholestasis subgroup was the highest. The details are shown in **Figure 3**.

Discussion

We conducted retrospective research using the MIMIC-III database to study the correlation of infection sites and pathogen types with the occurrence of SALD. The results showed that the incidence of SALD was 11.96%. Infection in the biliary tract, abdominal cavity, or blood and infection with *Enterococcus faecium*, *B. fragilis*, *K. oxytoca*, *Enterobacter aerogenes*, or *A. fumigatus* were correlated with the occurrence of SALD. Compared with the control group, patients in the SALD group had a higher ICU mortality (24.7% vs 9.0%, $P<0.001$) and hospital mortality (34.2% vs 13.8%, $P<0.001$).

According to the clinical presentation, SALD can be divided into 2 major patterns: cholestatic dysfunction and hypoxic hepatitis [5]. Some studies define hypoxic hepatitis as an acute elevation of serum aminotransferase levels (20-fold the upper limit of normal) [11,13]. In our research, we defined SALD as elevation of ALT and/or AST levels >1000 IU/L and/or total serum bilirubin levels >3 mg/dL. The incidence of SALD remains imprecisely known, most likely because of the lack of unified diagnostic criteria. The incidence of sepsis-associated liver dysfunction or liver failure ranges from 1.3% to 46% in all patients with sepsis [6]. In this study, according to the above diagnostic criteria, the incidence of SALD was 11.96%.

The persistence or development of liver failure after sepsis is strongly associated with outcome [14], and the mortality rate of sepsis patients with liver dysfunction or failure ranges from 54% to 68% [6]. Raurich et al [15] retrospectively studied 181 patients with septic shock. They found that the mortality of patients with ischemic hepatitis (defined as having a value of serum aminotransferases ≥ 1000 IU/L) was 84.0%. In our study, the hospital mortality of SALD patients was 34.2%. The mortality was lower than that found by Raurich et al [15], which may be related to the different research subjects. In that study [15], the research subjects were patients with septic shock, and their conditions were more serious than those of the patients in our study.

In MIMIC-III, the median length of ICU stay is 2.1 days (Q1-Q3: 1.2-4.6), and the median length of hospital stay is 6.9 days (Q1-Q3: 4.1-11.9) [10]. In the current study, the median length of ICU stay was 6.2 days (Q1-Q3: 2.8-14.7) in the SALD group and 4.0 days (Q1-Q3: 2.0-9.0) in the control group, and the median length of hospital stay was 18.5 days (Q1-Q3: 9.98-30.99) and 12.8 days (Q1-Q3: 7.34-21.68), respectively. Compared with other critically ill patients in the MIMIC-III database, patients in the SALD group had the longest ICU and hospital stays, followed by the patients in the control group and MIMIC-III.

Infection is the root cause of sepsis. We suspected that the infection site and the type of pathogen were related to the occurrence of SALD. In our study, we found that the positive rate of peritoneal fluid, bile, and blood culture in the SALD group

was significantly higher than in the control group. The results of the distribution of infection sites were similar to the results of Raurich et al [15] (mainly abdominal infection).

There are a few studies on the correlation between infection sites and the occurrence of SALD. Most previous studies have focused on the role of bacterial infections in the occurrence of acute-on-chronic liver failure (ACLF). The results show that spontaneous peritonitis is the most common cause of ACLF [16-18], which is different from the results of our study. In the current study, biliary infection was most closely correlated with the occurrence of SALD (OR 7.450), followed by abdominal infection (OR 3.616) and bloodstream infection (OR 1.957). The specific mechanism needs to be clarified by relevant basic research.

Similarly, few studies exist on the relationship between different pathogens and the occurrence of SALD. The main organisms triggering ACLF are gram-positive bacteria, followed by gram-negative bacteria [19]. In a study by Mücke et al [17], the ACLF-inducing bacteria were gram-positive bacteria (52.1%, *Enterococcus*, *Staphylococcus aureus*, and coagulase-negative staphylococci) and gram-negative bacteria (47.9%, *Escherichia coli*, *Enterobacteriaceae*, *Pseudomonas*, and *Klebsiella*). Fernández et al [18] found that the bacteria that induce ACLF are mainly *E. coli*, *Klebsiella pneumoniae*, and *Enterobacter* (gram-negative bacteria) and *S. aureus*, *Enterococcus faecalis*, and *Enterococcus faecium* (gram-positive bacteria). There is a certain difference between the above research results and ours.

The above 5 pathogens were 4 bacteria and 1 fungus with distinct pathogenic characteristics. These 4 bacteria possess

certain common characteristics. Most of them are opportunistic pathogenic bacteria and can cause abdominal and bloodstream infections. These common features may be part of the mechanism leading to SALD. In immunocompromised mice, *A. fumigatus* can spread to the liver 24 h after inoculation, resulting in severe liver inflammation [20]. The above studies have shown that these pathogens are related to the occurrence of liver injury. The definite mechanism of SALD caused by the above pathogens needs further study.

The current study is a retrospective study, and there may be data bias. The conclusion needs to be confirmed through more prospective multi-center randomized controlled trials. Second, this study is an observational study, and the specific mechanism needs further investigation.

Conclusions

An awareness of SALD should be maintained for sepsis patients whose infection site is the bile, abdominal cavity, or blood and the pathogen is *Enterococcus faecium*, *B. fragilis*, *K. oxytoca*, *Enterobacter aerogenes*, or *A. fumigatus*. When SALD occurs in sepsis patients, the above infection sites and pathogens should be considered first.

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