Development and validation of a predictive model for in-hospital mortality in patients with sepsis-associated liver injury

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Background: Sepsis is often accompanied by organ dysfunction and acute organ failure, among which the liver is commonly involved. Sepsis patients suffering from liver injury have a greater risk of mortality than patients suffering from general sepsis. As of now, there are no tools that are specifically designed for assessing the prognosis of such patients. This study aimed to develop and validate a model to predict the risk of in-hospital mortality in patients with sepsis-associated liver injury (SALI).

Methods: Data were obtained from the Medical Information Mart for Intensive Care (MIMIC)-IV database. In the analysis, all patients with SALI who met the inclusion and exclusion criteria were included. A primary outcome was in-hospital mortality, and clinical data were extracted for these patients. In a ratio of 8:2, the data were divided into training and validation groups at random. Least absolute shrinkage and selection operator (LASSO) regression was used for data dimension reduction and feature selection, and independent factors related to prognosis were identified through multi-factor logistics analysis. A nomogram was developed to visualize the model, and the performance of the model was evaluated by the area under the curve (AUC) as well as calibration and decision curve analysis (DCA) through internal verification.

Results: A total of 616 and 154 patients with SALI were included in the training and validation cohorts, respectively. The LASSO regression and logistic multivariate analysis showed that nine factors were associated with in-hospital mortality in patients with SALI. Both the training and validation cohorts had higher AUCs than sequential organ failure assessment (SOFA) and simplified acute physiology score 2 (SAPS2): 0.753 (95% CI: 0.715–0.791) and 0.783 (95% CI: 0.749–0.817), respectively. Both the training and validation cohorts showed good calibration results for the prediction model. In terms of clinical practicability, DCA of the predictive model demonstrated greater net benefits than the SOFA and SAPS2 scores.

Conclusions: We developed a predictive model that can effectively predict the in-hospital mortality of SALI patients, with satisfactory performance and clinical practicability. This model can assist clinicians in the early identification of high-risk patients and provide a reference for clinical treatment strategies.

Keywords: Sepsis-associated liver injury (SALI); hypoxic hepatitis (HH); sepsis; nomogram

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Introduction

Sepsis is a major disease in intensive care units (ICU) worldwide, with high rates of morbidity and mortality (1). According to the International Surviving Sepsis Campaign, sepsis is defined as life-threatening organ dysfunction caused by the host response to infection disorders and is characterized by systemic inflammation that is commonly associated with organ dysfunction or failure (2). The liver is the central organ of the body in terms of defense against exogenous infection, with a large collection of phagocytic cells present. Also, the liver sinusoids are rich in various types of lymphocytes, which enable the identification and capture of antigens from the gastrointestinal tract and blood. Moreover, the liver is an important site of adaptive immunity (3,4), and is intimately related to the maintenance of the microbial barrier of the gastrointestinal tract. Additionally, it can also secrete bile acids and regulate the intestinal flora through the hepato-enteric axis (5). In infectious diseases, after the intestinal-epithelial barrier, the liver constitutes the second line of defense to clear invading bacteria and bacterial products and limit the further spread of bacteria into the body. During sepsis, the release of a large number of inflammatory factors inhibits the expression of tight junction proteins and upregulates intestinal epithelial cell apoptosis, resulting in increased permeability of the intestinal barrier. A large number of intestinal microbes enter the blood and the liver through the portal vein, which directly aggravates liver injury (6). In addition, a vigorous immunogenic response within the liver, while contributing to the clearance of microbial products, may also lead to liver injury due to overwhelming systemic inflammatory responses (7).

Sepsis-associated liver injury (SALI) is a result of the combined effects of multiple mechanisms, including the systemic inflammatory response, immune dysregulation, and microcirculatory disturbance (8). SALI primarily manifests in two forms: hypoxic hepatitis (HH) and cholestasis (9). HH is often accompanied by circulatory and respiratory failure, and acute heart failure and septic shock are the most common predisposing factors (10). The occurrence of cholestasis is closely related to the dysfunction and inflammation of liver and bile duct cells caused by proinflammatory cytokines and inflammatory mediators. Impaired cells lead to the down-regulation of the transport system function and the normal operation of bile is impaired, which leads to cholestasis flow (11).

Sepsis is one of the leading causes of HH and cholestasis

in the ICU. Two multicenter studies of acquired HH in the ICU reported that 32% and 33% of patients had HH combined with septic shock, respectively (12,13), while the proportion of cholestasis triggered by septic shock was approximately 28–33% (3,14). At present, there is a lack of clear diagnostic criteria for SALI. The incidence of SALI varies according to different diagnostic criteria; Kobashi *et al.* reported an incidence rate of 34.7% (15). Severe sepsis can lead to a high mortality rate in intensive care units due to a variety of factors, including multiple visceral damage and dysfunction due to inflammation that has not been controlled, multidrug-resistant bacterial infections, and ineffective anti-infection treatments (2). Besides the risks associated with sepsis, liver injury poses a number of additional risks, including comorbid organ injury in synergy with the liver, increased drug toxicity as a result of decreased liver biotransformation function, which may result in a higher death rate. Without exception, all of the studies on HH, cholestasis, or SALI have reported extremely high mortality rates (up to 53–61.5%) (12,13,16). Given the severe adverse consequences for SALI patients, the early identification of patients with a high risk of death can help clinicians optimize the clinical diagnosis and treatment strategies, which is crucial to improving the prognosis of patients. To date, prediction models have been applied to predict the mortality risk of sepsis patients. Prediction models based on the clinical data of the patients were developed by Ren and Zeng to assess the in-hospital mortality of sepsis patients and the 90-day mortality of those patients. Previously, prediction models were designed to cover the entire spectrum of sepsis patients, whereas the models may not be applicable to this particular group of patients in SALI (17,18). At present, there are few studies on SALI and no short-term predictive models for SALI patients. Furthermore, there are currently no large-scale studies or accurate short-term predictive models for SALI patients. The present study aims to address this. We present the following article in accordance with the TRIPOD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4319/rc).

Methods

Data source

Data for this retrospective study were obtained from the Medical Information Mart for Intensive Care (MIMIC)-IV

database (Version 1.0). This public database is maintained by the Computational Physiology Laboratory of the Massachusetts Institute of Technology (Massachusetts Institute of Technology, Cambridge, Massachusetts, USA), and includes the clinical information of patients admitted to the ICU of the Beth Israel Women's Medical Center (BIDMC, Boston, Massachusetts, USA) from 2008 to 2019 (19).

The included patients were de-identified according to the Health Insurance Portability and Accountability Act (HIPAA). Since the current project does not affect clinical nursing, the requirement for individual patient consent was waived. Members of the team (Run Sun) were given access to the database and were responsible for the data extraction (CITE number: 45997657).

Patient population

The inclusion criteria were as follows: (I) patients with sepsis; (II) patients age ≥18; (III) patients who remained in the ICU for at least 48 hours; and (IV) patients who met the SALI diagnostic criteria at least once. Sepsis was defined according to the Sepsis3.0 guidelines. The first record was selected for patients with multiple admissions to the ICU during hospitalization.

The exclusion criteria were as follows (20-23): (I) patients without liver injury; (II) those with primary liver diseases, such as acute or chronic viral hepatitis, cirrhosis and chronic liver diseases, acute or chronic liver failure, and liver necrosis; (III) patients with liver trauma; (IV) those with autoimmune hepatitis; (V) patients with hepatic vascular infarction; (VI) patients with toxic hepatitis; (VII) those with cholangitis and acute cholecystitis with biliary obstruction; (VIII) patients with bile duct obstruction; (IX) patients with bile duct and ampullary tumors (Table S1); (X) length of ICU stay <48 hours.

SALI

There are currently no definite diagnostic criteria for SALI. Based on previous studies, SALI patients included in this study were further divided into HH and cholestasis groups. HH was defined as a 10-fold increase in the levels of alanine aminotransferase or aspartate aminotransferase above the upper limit of normal (400 U/dL) (20), and the cholestasis group was defined as serum bilirubin >2 mg/dL (21,23). The time that the patient entered the ICU was set as 0 h, and the time of the first recording of SALI was defined as the liver injury occurrence time.

Data extraction and management

Data were extracted in a structured query language (SQL) using Navicat Premium version 15.0.12 (PremiumSoft CyberTech Ltd, Hongkong), and codes in the database were all available on GitHub (https://github.com/MIT-LCp/mimic-code). In order to facilitate the practical application and generalization of predictive models, variable extraction is considered on the basis of early acquisition and easy acquisition. We retrospectively collected the following data: (I) demographic data, including age and gender; (II) type and occurrence time of liver injury; (III) chronic complications: chronic complications were defined according to International Classification of Diseases 9 (ICD) and ICD-10, and included hypertension, hyperlipidemia, diabetes both with and without complication, atrial fibrillation, old myocardial infarction, chronic heart failure, chronic pulmonary disease, chronic renal disease, peripheral vascular disease, cerebrovascular disease, malignant cancer, and hypothyroidism; (IV) septic shock, anemia after acute hemorrhage, and acute organ injury; (V) infection site and pathogenic microorganism; (VI) vital signs and urine output within 24 hours of hospitalization in the ICU, in which the vital signs were expressed as the mean; (VII) the first laboratory examination data after ICU hospitalization; (VIII) supportive treatments including mechanical ventilation and renal replacement therapy; (IX) drugs and other treatments, such as blood transfusion, vasoactive drugs, cardiovascular drugs, frozen plasma, extraintestinal nutrition, and anticoagulants; and (V) the first Simplified Acute Physiology Score2 (SAPS2) and sequential organ failure assessment (SOFA) score in the ICU.

The determination of infection site and pathogenic microorganism culture results were lagging, so it was not applicable to incorporate them into the predictive model. The SOFA and SAPS2 scores are commonly used in ICU to evaluate severity and patient prognosis, which were used for comparison with the performance of the predictive model in this study. Continuous variables with more than 20% missingness were removed, and the remaining missing data were filled by interpolation (Table S2, Figure S1).

Statistical analysis

The Shapiro-Wilk test was applied to evaluate whether the samples conformed to a normal distribution. Normally distributed continuous variables were expressed as the mean ± standard deviation (SD), while those that did not

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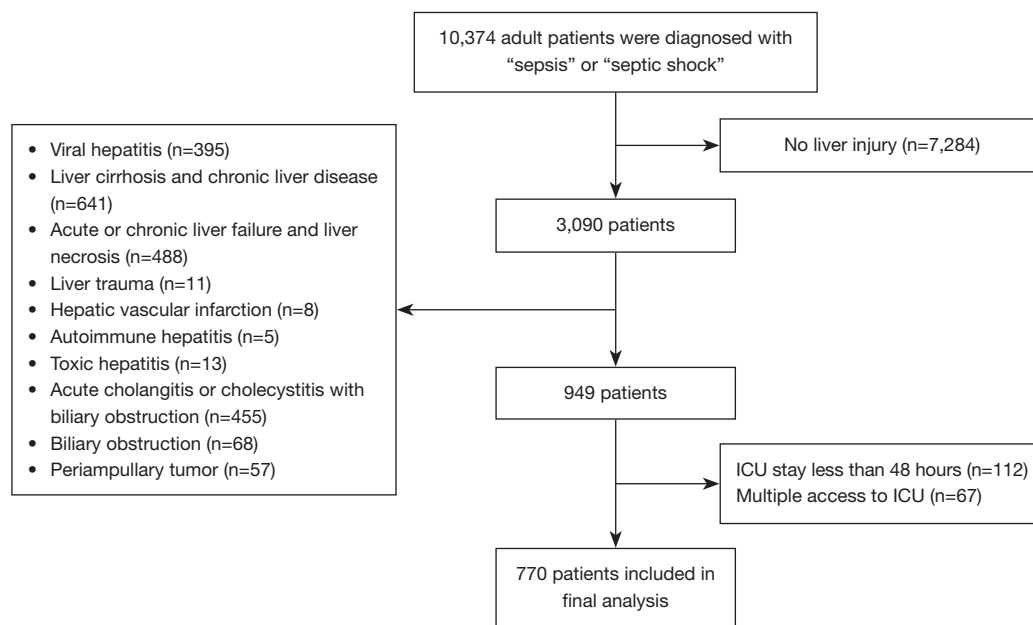
Figure 1 Inclusion and exclusion process. ICU, intensive care unit.

conform to a normal distribution were expressed as the median (interquartile range, IQR). Classified variables were expressed as frequency and percentage. The non-parametric test (Mann-Whitney U test) was used to analyze data with non-normal distribution or heterogeneity of variance, and the Pearson chi-square test was used to classify the variables.

Feature selection and model development

In the clinic, SAPS II and SOFA scores are commonly used for assessing patient outcomes, and their inclusion as variables in predictive models will undoubtedly enhance the accuracy of the models. In actual clinical work, obtaining the exact score depends on the completeness of information regarding its composition, and including the score in model building can actually decrease its usefulness. As a result, in this study, the score was not used in variable screening and model construction, but was used to contrast with the model. To remove redundant variants, the least absolute shrinkage and selection operator (LASSO) regression was applied to feature the selection of prognostic-related variables. Multivariate logistic regression analysis was performed on the variable combinations corresponding to the minimum mean square error (MMSE), and independent factors with statistically significant differences were used to construct the predictive model. Patients were randomly assigned to a training (80%) or validation (20%) cohort,

and nomograms were developed based on the training cohort to visualize the model. The predicted outcome was the patient's risk of in-hospital mortality. To evaluate the performance of the model, the area under the curve (AUC) and bootstrap resampling methods (1,000 iterations) were applied. Also, the clinical practicability and net profit of the predictive model were evaluated by Decision Curve Analysis (DCA). IBM SPSS Statistics version 26.0 (SPSS Inc., Chicago, IL, USA, 2019) was used for data analysis and (R Foundation for Statistical Computing, Vienna, Austria) was utilized for model construction and validation. A two-sided P value smaller than 0.05 suggested statistical significance. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Baseline characteristics of the survival and non-survival groups

Figure 1 shows the detailed patient recruitment process. Based on the inclusion and exclusion criteria, 770 patients were included in the final analysis.

The baseline characteristics of the survival and non-survival groups are shown in *Table 1*. The survival group had a longer hospitalization time but there was no significant difference in the ICU hospitalization time between the two

Table 1 Patients' baseline characteristics

Variables	All (n=770)	Survival group (n=435)	Non-survival group (n=335)	P value
Hospital stay (days)				
LOS-hospital	19.7 [10.2, 33.0]	22.0 [12.8, 34.6]	15.1 [7.0, 30.1]	<0.001
LOS-ICU	8.5 [4.3, 16.1]	8.5 [4.2, 16.3]	8.5 [4.5, 16.1]	0.998
Liver injury				
Type, n (%)				
Cholestasis	652 (84.7)	387 (89.0)	265 (79.1)	<0.001
Hypoxia	118 (15.3)	48 (11.0)	70 (20.9)	
Occurrence time (hours)	20.0 [4.0, 73.0]	12.0 [2.0, 51.0]	32.0 [8.0, 95.0]	<0.001
Demography				
Age (years)	67.1 [56.9, 76.5]	65.1 [54.3, 74.7]	68.2 [60.0, 78.5]	<0.001
Gender, n (%)				
Female	324 (42.1)	176 (40.5)	148 (44.2)	0.3
Male	446 (57.9)	259 (59.5)	187 (55.8)	
Comorbidity, n (%)				
Hypertension	495 (64.3)	275 (63.2)	220 (65.7)	0.481
Hyperlipidemia	238 (30.9)	131 (30.1)	107 (31.9)	0.587
Diabetes without complication	190 (24.7)	95 (21.8)	95 (28.4)	0.038
Diabetes with complication	75 (9.7)	36 (8.3)	39 (11.6)	0.118
Atrial fibrillation	288 (37.4)	137 (31.5)	151 (45.1)	<0.001
Old myocardial infarction	64 (8.3)	33 (7.6)	31 (9.3)	0.406
Chronic heart failure	209 (27.1)	102 (23.4)	107 (31.9)	0.009
Chronic pulmonary disease	209 (27.1)	99 (22.8)	110 (32.8)	0.002
Chronic renal disease	212 (27.5)	111 (25.5)	101 (30.1)	0.154
Peripheral vascular disease	114 (14.8)	54 (12.4)	60 (17.9)	0.033
Cerebrovascular disease	78 (10.1)	36 (8.3)	42 (12.5)	0.052
Malignant cancer	122 (15.8)	56 (12.9)	66 (19.7)	0.01
Hypothyroidism	108 (14.0)	55 (12.6)	53 (15.8)	0.208
Acute organ injury, n (%)				
Acute heart failure	207 (26.9)	97 (22.3)	110 (32.8)	0.001
Septic shock	543 (70.5)	296 (68.0)	247 (73.7)	0.086
Acute myocardial infarction	87 (11.3)	29 (6.7)	58 (17.3)	<0.001
Acute respiratory failure	471 (61.2)	238 (54.7)	233 (69.6)	<0.001
Acute renal failure	547 (71.0)	297 (68.7)	250 (74.6)	0.054
Coagulation disorder	288 (37.4)	144 (33.1)	144 (43.0)	0.005
Acute post-hemorrhagic anemia	170 (22.1)	91 (20.9)	79 (23.6)	0.377
Toxic encephalopathy	100 (13.0)	50 (11.5)	50 (14.9)	0.16

Continuous variables in the table did not follow a normal distribution and are expressed as median [interquartile range] and categorical variables as frequencies (percentages). LOS, length of stay; ICU, intensive care unit.

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Table 2 Patients' characteristics of pathogenic microorganisms and infection sites

Variables	All (n=770)	Survival group (n=435)	Non-survival group (n=335)	P value
Pathogenic microorganism, n (%)				
Escherichia coli	87 (11.3)	62 (14.3)	25 (7.5)	0.003
Streptococcus	70 (9.1)	47 (10.8)	23 (6.9)	0.059
Methicillin-susceptible staphylococcus	87 (11.3)	52 (12.0)	35 (10.4)	0.513
Other gram-negative bacteria	78 (10.1)	50 (11.5)	28 (8.4)	0.153
Methicillin-resistant staphylococcus	51 (6.6)	25 (5.7)	26 (7.8)	0.265
Pseudomonad	50 (6.5)	27 (6.2)	23 (6.9)	0.713
Candida	54 (7.0)	34 (7.8)	20 (6.0)	0.32
Klebsiella pneumoniae	41 (5.3)	25 (5.7)	16 (4.8)	0.552
Enterococcus	17 (2.2)	13 (3.0)	4 (1.2)	0.093
Other staphylococci	32 (4.2)	18 (4.1)	14 (4.2)	0.977
Infection site, n (%)				
Lung	374 (48.6)	188 (43.2)	186 (55.5)	<0.001
Subcutaneous skin and soft tissue	219 (28.4)	117 (26.9)	102 (30.4)	0.279
Urinary tract	158 (20.5)	97 (22.3)	61 (18.2)	0.164
Abdominal cavity	177 (23.0)	112 (25.7)	65 (19.4)	0.038
Catheter correlation	145 (18.8)	86 (19.8)	59 (17.6)	0.448

groups. In addition, the non-survival group had a higher proportion of liver injury in the form of HH, and liver injury occurred later. In terms of chronic complications, the non-survival group had a higher proportion of diabetes without complications, atrial fibrillation, chronic heart failure, chronic pulmonary disease, peripheral vascular disease, and cancer. Acute organ injury was more common in the non-survival group, with a higher proportion of acute heart failure, acute myocardial infrastructure, acute respiratory failure, and coagulation disorder.

The microbial results and infection site characteristics of the two groups are shown in *Table 2*. The five pathogens with the highest detection rate were as follows: Escherichia coli, Methicillin-susceptible staphylococcus, other gram-negative bacteria, Streptococcus and Candida. The proportion of Escherichia coli in the non-survival group was lower than that in the survival group, and there were no significant differences in the proportions of the other pathogenic microorganisms between the two groups. The most common site of infection was the lung (pulmonary infection). The non-survival group had more pulmonary infections and fewer abdominal infections compared to the survival group.

The characteristics of the two groups during ICU hospitalization are shown in *Table 3*. In terms of vital characteristics, there were no significant differences in heart rate and blood pressure between the two groups, but the non-survival group had a lower body temperature and 24-hour urine output. Laboratory examinations revealed that the non-survival group had lower red blood cell, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and total bilirubin levels, and higher levels of RDW, lactate dehydrogenase, blood urea nitrogen (BUN), partial thromboplastin time (PTT), and bicarbonate. Moreover, the proportion of non-survivors who required supportive treatment was higher, and more patients in this group underwent invasive ventilation and renal replacement therapy. In terms of treatment, a higher proportion of patients in the non-survival group received blood transfusion, vasoactive drugs, and frozen plasma infusion. As for the disease scores, patients in the non-survival group had higher SAPS2 scores but there were no

Table 3 Patients' characteristics at ICU admission

Variables	All (n=770)	Survival group (n=435)	Non-survival group (n=335)	P value
Vital sign				
Heart rate (bpm)	96.0 [84.0, 108.0]	97.0 [84.0, 109.0]	96.0 [83.0, 107.0]	0.743
Systolic pressure (mmHg)	106.0 [99.0, 114.0]	106.0 [99.0, 113.0]	105.0 [99.0, 116.0]	0.764
Diastolic pressure (mmHg)	58.0 [53.0, 65.0]	59.0 [54.0, 65.0]	58.0 [52.0, 65.0]	0.119
Mean arterial pressure (mmHg)	72.0 [67.0, 78.0]	73.0 [68.0, 78.0]	71.0 [66.0, 78.0]	0.098
Respiratory rate (bpm)	22.0 [18.0, 25.0]	22.0 [19.0, 25.0]	22.0 [18.0, 25.0]	0.033
Temperature (℃)	36.90 [36.58, 37.40]	37.04 [36.69, 37.51]	36.76 [36.48, 37.18]	<0.001
SPO_2 (%)	97.1 [95.8, 98.5]	97.1 [95.7, 98.5]	97.1 [95.8, 98.7]	0.62
Urine output (mL/24 h)	1,195 [615, 1,980]	1,378 [817, 2,200]	870 [380, 1675]	<0.001
Laboratory results				
Red blood cell (m/UL)	3.3 [2.8, 3.9]	3.4 [2.9, 4.0]	3.2 [2.7, 3.8]	0.017
Hemoglobin (g/dL)	9.8 [8.3, 11.4]	10.2 [8.4, 11.8]	9.5 [8.1, 11.1]	0.011
Hematocrit (%)	30.3 [25.7, 35.1]	30.8 [26.1, 35.8]	29.6 [25.3, 34.3]	0.123
MCV (fl)	91.0 [87.0, 96.0]	91.0 [87.0, 95.0]	92.0 [87.0, 98.0]	0.005
MCH (pg)	30.0 [28.5, 31.4]	29.9 [28.3, 31.3]	30.2 [28.6, 31.4]	0.275
MCHC (g/dL)	32.6 [31.5, 33.7]	32.8 [31.6, 33.8]	32.3 [31.3, 33.5]	<0.001
RDW (%)	15.7 [14.3, 17.8]	15.3 [13.9, 17.2]	16.5 [14.8, 18.8]	<0.001
Platelet (K/UL)	170.0 [98.0, 247.0]	179.0 [104.0, 249.0]	156.0 [94.0, 239.0]	0.099
White blood cell (K/UL)	12.7 [7.3, 19.5]	13.0 [7.3, 20.0]	12.4 [7.4, 19.0]	0.613
Neutrophils (%)	81.6 [71.2, 87.7]	80.5 [71.0, 87.270]	82.1 [72.5, 88.0]	0.114
Monocytes (%)	4.0 [2.4, 6.8]	4.0 [2.5, 6.4]	4.0 [2.3, 7.0]	0.981
Lymphocytes (%)	7.0 [3.9, 11.0]	7.150 [4.0, 11.0]	6.6 [3.7, 11.0]	0.528
Eosinophils (%)	0.1 [0.0, 1.0]	0.1 [0.0, 1.0]	0.05 [0.0, 1.0]	0.416
Basophils (%)	0.0 [0.0, 0.2]	0.0 [0.0, 0.2]	0.0 [0.0, 0.2]	0.727
Albumin (g/dL)	2.6 [2.2, 3.0]	2.6 [2.2, 3.0]	2.5 [2.2, 2.9]	0.214
ALT (IU/L)	36.0 [20.0, 78.0]	37.0 [21.0, 84.0]	35.0 [19.0, 75.0]	0.358
AST (IU/L)	58.0 [33.0, 132.0]	59.0 [33.0, 123.0]	55.0 [33.0, 144.0]	0.765
ALP (IU/L)	100.0 [64.0, 174.0]	99.0 [63.0, 166.0]	102.0 [65.0, 183.0]	0.194
Total bilirubin (mg/dL)	2.1 [1.0, 3.0]	2.2 [1.1, 3.2]	1.6 [0.7, 2.9]	<0.001
LDH (IU/L)	358.0 [249.0, 572.0]	323.0 [237.0, 513.0]	415.0 [282.0, 695.0]	<0.001
BUN (mg/dL)	31.0 [19.0, 52.0]	29.0 [18.0, 48.0]	35.0 [21.0, 54.0]	0.008
Creatinine (mg/dL)	1.4 [0.9, 2.5]	1.4 [0.9, 2.4]	1.4 [0.9, 2.7]	0.652
Glucose (mg/dL)	131.0 [104.0, 170.0]	129.0 [105.0, 161.0]	137.0 [103.0, 176.0]	0.324
Potassium (mEq/L)	4.1 [3.7, 4.6]	4.1 [3.7, 4.5]	4.1 [3.7, 4.7]	0.473
Sodium (mEq/L)	137.0 [134.0, 141.0]	137.0 [134.0, 141.0]	137.0 [134.0, 141.0]	0.247

Table 3 (*continued*)

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Table 3 (*continued*)

Variables	All (n=770)	Survival group (n=435)	Non-survival group (n=335)	P value
Chloride (mEq/L)	103.0 [99.0, 108.0]	104.0 [99.0, 109.0]	103.0 [99.0, 108.0]	0.642
Calcium (mg/dL)	7.9 [7.3, 8.5]	7.9 [7.3, 8.4]	8.0 [7.4, 8.5]	0.053
PT (s)	16.2 [14.0, 19.6]	16.2 [14.1, 18.9]	16.3 [13.8, 20.8]	0.488
PTT (s)	34.3 [30.0, 44.6]	33.1 [29.4, 42.1]	36.4 [31.2, 50.2]	<0.001
INR	1.5 [1.3, 1.8]	1.5 [1.3, 1.7]	1.5 [1.3, 1.9]	0.472
PO_2 (mmHg)	85.0 [49.0, 154.0]	88.0 [50.0, 161.0]	81.0 [47.0, 139.0]	0.276
PCO_2 (mmHg)	39.0 [33.0, 47.0]	39.0 [33.0, 45.0]	40.0 [33.0, 48.0]	0.133
PH	7.35 [7.28, 7.41]	7.35 [7.28, 7.41]	7.35 [7.27, 7.42]	0.821
Total CO_2 (mEq/L)	23.0 [19.0, 26.0]	22.0 [19.0, 26.0]	23.0 [20.0, 27.0]	0.162
Base excess (mEq/L)	−3.0 [−7.0, 0.0]	−3.0 [−7.0, 0.0]	−3.0 [−7.0, 0.0]	0.468
Bicarbonate (mEq/L)	21.0 [18.0, 24.0]	20.0 [17.0, 23.0]	21.0 [18.0, 24.0]	0.034
Anion gap (mEq/L)	16.0 [13.0, 19.0]	16.0 [13.0, 19.0]	16.0 [13.0, 19.0]	0.335
Lactate (mmol/L)	2.3 [1.5, 3.5]	2.2 [1.5, 3.5]	2.3 [1.5, 3.6]	0.349
Treatment, n (%)				
Invasive ventilation	584 (75.844)	311 (71.494)	273 (81.493)	0.001
Renal replacement therapy	246 (31.948)	106 (24.368)	140 (41.791)	<0.001
Blood transfusion	494 (64.156)	264 (60.690)	230 (68.657)	0.022
Vasoactive drugs	662 (85.974)	361 (82.989)	301 (89.851)	0.007
Cardiotonic drugs	73 (9.481)	35 (8.046)	38 (11.343)	0.122
Frozen plasma	257 (33.377)	125 (28.736)	132 (39.403)	0.002
Extraintestinal nutrition	158 (20.519)	85 (19.540)	73 (21.791)	0.443
Anticoagulant	115 (14.935)	59 (13.563)	56 (16.716)	0.224
Severity score				
SOFA	9.0 [6.0, 11.0]	9.0 [6.0, 11.0]	9.0 [6.0, 12.0]	0.358
SAPSII	48.0 [39.0, 58.0]	45.0 [36.0, 54.0]	51.0 [43.0, 60.0]	<0.001

Continuous variables in the table did not follow a normal distribution and are expressed as median [interquartile range] and categorical variables as frequencies (percentages). ICU, intensive care unit; SPO_2, saturation of pulse oxygen; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; PO_2, oxygen partial pressure; PCO_2, carbon dioxide partial pressure; PH, potential of hydrogen; SAPS2, simplified acute physiology score II (SAPSII); SOFA, sequential organ failure assessment score.

significant differences in the SOFA scores between the two groups (P>0.05).

Feature selection

The 79 variables related to prognosis were screened by LASSO regression and 10-fold cross-validation (*Figure 2A*). In the minimum mean square errors (λ=0.038), the number of features was reduced to 11 (*Figure 2B*), including age, SALI type, occurrence time, atrial fibrillation acute respiratory failure, acute myocardial infarction, temperature, urine output, RDW, PTT, and renal replacement therapy.
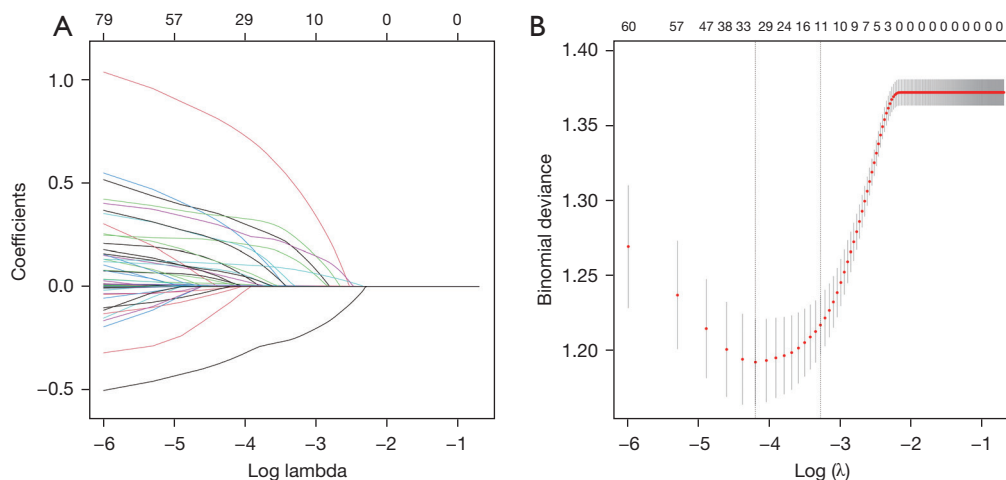
Figure 2 LASSO regression for feature selection. (A) Trajectories of change in coefficients for each variable in the lasso regression. (B) Min mean square error (left dotted line) and min distance (right dotted line) for the lambda values and number of variables. LASSO, least absolute shrinkage and selection operator.

Table 4 Multivariate logistic analysis

Variables	OR	95% CI		P value
		Lower	Upper	
Age	1.006	0.994	1.018	0.365
Type	1.653	1.048	2.617	0.031
Occurrence time	1.006	1.004	1.009	<0.001
Atrial fibrillation	1.425	1.000	2.032	0.05
Acute respiratory failure	1.781	1.269	2.509	0.001
Acute myocardial infarction	2.703	1.617	4.603	<0.001
Temperature	0.667	0.512	0.863	0.002
Urine output	1.000	1.000	1.000	0.003
RDW	1.167	1.103	1.238	<0.001
PTT	1.007	1.001	1.014	0.035
Renal replacement therapy	1.441	1.001	2.073	0.049

OR, odds ratio; CI, confidence interval; RDW, red blood cell distribution width; PTT, partial thromboplastin time.

The regression coefficients for variables in the LASSO regression were presented in Table S3.

Multivariable logistic analysis

Multivariate logistic analysis was performed to analyze the 11 potential predictors (*Table 4*). The results showed that SALI type, occurrence time, acute respiratory failure, acute myocardial infarction, temperature, urine output, RDW, PTT, and renal replacement therapy were independent prognostic factors for SALI patients (P<0.05).

Nomogram development

Nine independent variables were used to develop a model to predict the in-hospital mortality of SALI patients, which was presented in the form of a visual nomogram (*Figure 3*). By establishing the hazard ratios of these risk factors, the prognosis of each patient can be scored, and the sum of scores of each variable can be used to evaluate the risk of in-hospital mortality of SALI patients.

Discrimination and calibration

The AUC of the prediction model in the training and validation cohorts were 0.753 (95% CI: 0.715–0.791) and 0.783 (95% CI: 0.749–0.817), respectively, which were significantly better than the SOFA score (AUC of the training cohort: 0.516, 95% CI: 0.47–0.563; AUC of the validation cohort: 0.531, 95% CI: 0.438–0.624) and SAPS2 score (AUC of the training cohort: 0.612, 95% CI: 0.567–0.657; AUC of the validation cohort: 0.629, 95% CI: 0.537–0.718). Compared with the SOFA and SAPS2 scores, the predictive model showed better discrimination in predicting the risk of in-hospital death of SALI patients (*Figure 4*). The specificity and sensitivity of the predictive model were 0.704 and 0.698, respectively. The 1,000 bootstrap method was adopted to calibrate the model. In

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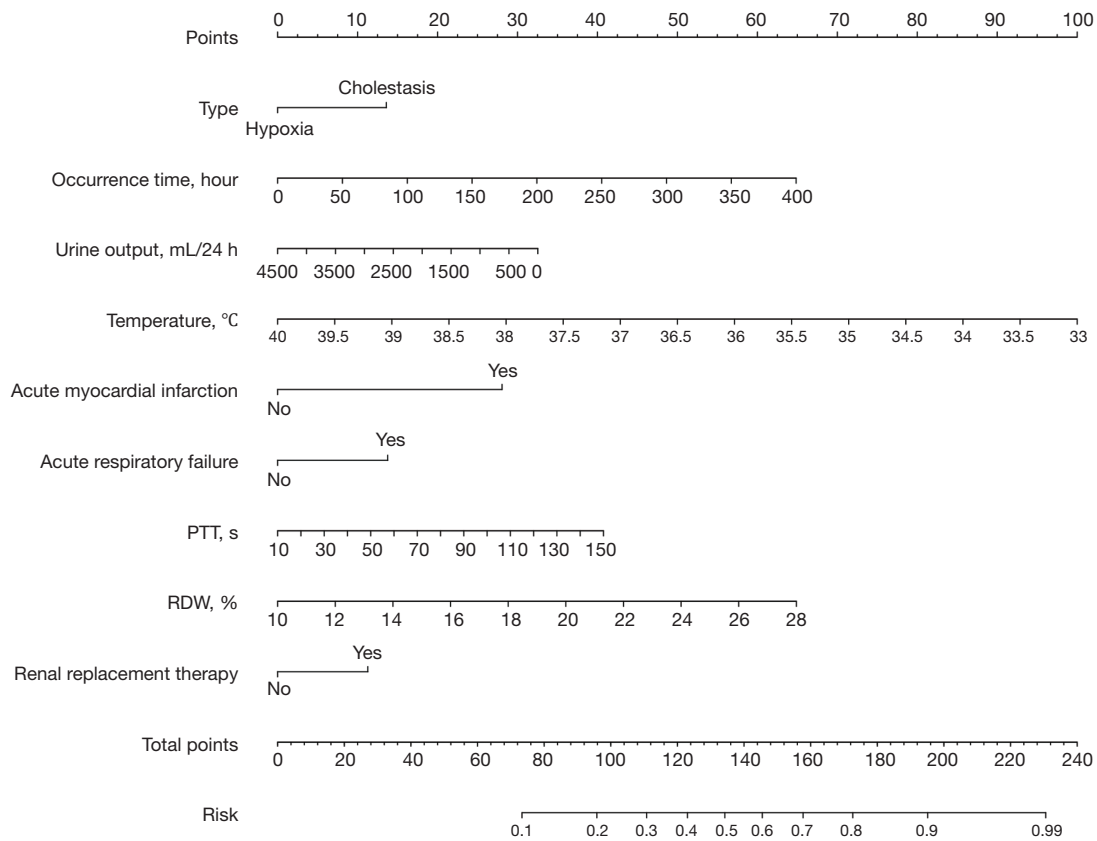
Figure 3 Nomogram for predicting the in-hospital mortality of SALI patients. PTT, partial thromboplastin time; RDW, red blood cell distribution width; SALI, sepsis-associated liver injury.
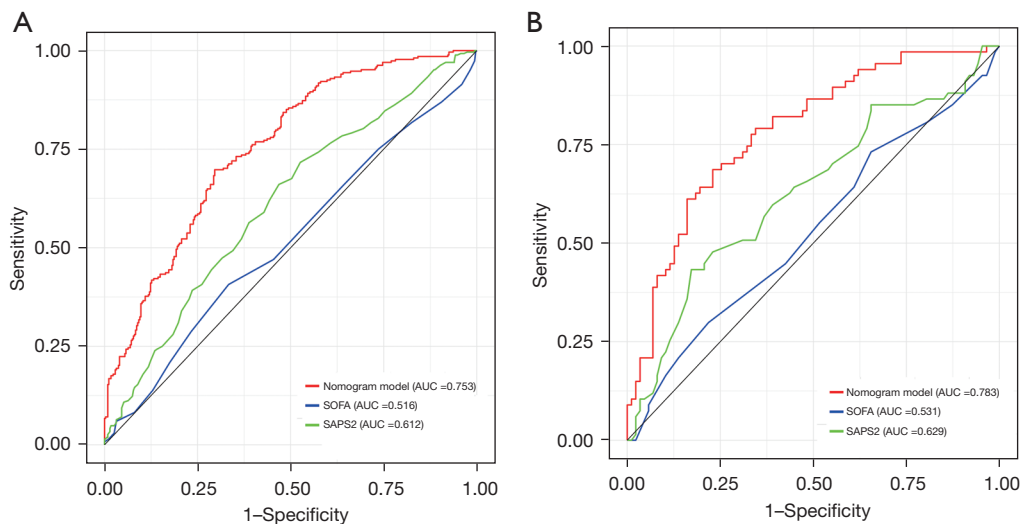
Figure 4 ROC curves of the predictive model, SOFA and SAPS2 scores. (A) Training cohort; (B) validation cohort. ROC, receiver operating characteristic curve; AUC, area under the curve; SOFA, sequential organ failure assessment score; SAPS2, simplified acute physiology score II.
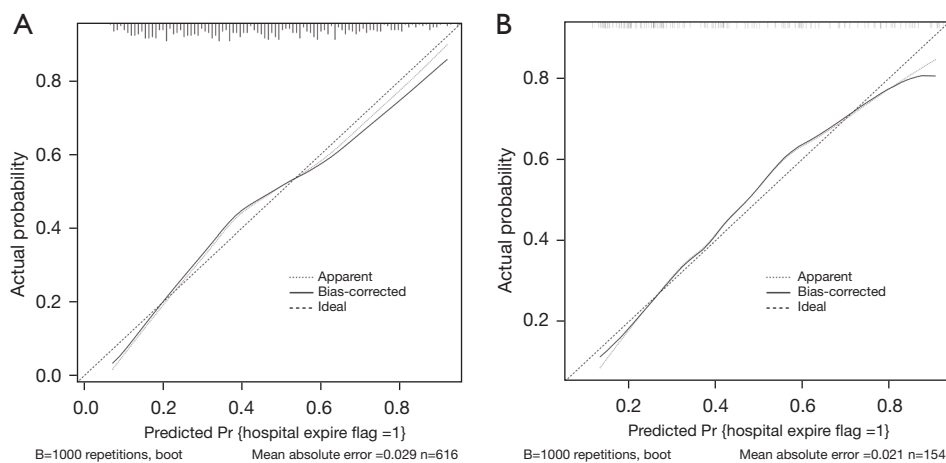
Figure 5 Calibration of the predictive model. (A) Training cohort; (B) validation cohort.
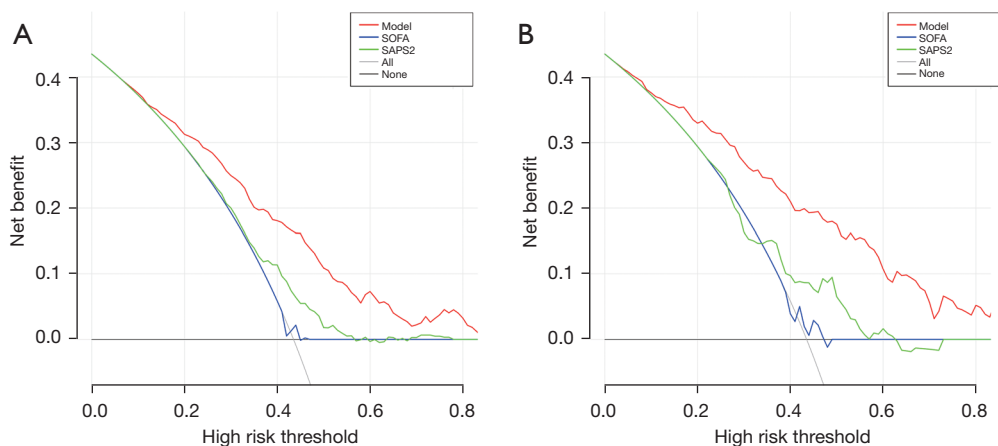
Figure 6 DCA curves of the predictive model *vs.* the SOFA, and SAPS2 scoring methods. (A) Training cohort; (B) validation cohort. DCA, decision curve analysis; SOFA, sequential organ failure assessment score; SAPS2, simplified acute physiology score II.

both cohorts, the calibration curves were slightly deviated, but good consistency between observation and prediction was still observed, with Brier scores of 0.199 and 0.188, respectively (*Figure 5*).

Clinical utility

DCA was applied to evaluate the clinical utility of the predictive model and scoring methods. In the training cohort, when the probability threshold (PT) was greater than 0.1, the medical intervention guided by the nomogram was found to provide a superior net benefit than the SOFA and SAPS2 scores (*Figure 6A*). In the validation cohort, when the PT was greater than 0.1, the treatment guided by

the nomogram could provide a higher net benefit than the SOFA and SAPS2 scores (*Figure 6B*).

Discussion

According to our results, 29.8% of sepsis patients had a liver injury (3,090 of 10,374 patients), but after strict exclusion of other factors that could cause liver dysfunction, the incidence of SALI decreased to 9.15 %, which was lower than that reported by Kobashi *et al.* and Saini *et al.* This discrepancy was due to the different diagnostic criteria for hypoxic injury; the inclusion criteria for hypoxic injury used in Kobashi *et al.* were alanine aminotransferase (ALT), aspartate aminotransferase (AST), and G-glutamyl

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transferase (GGT) exceeding the upper limit of normal values, while that applied in Saini *et al.* was a two-fold exceeding of the upper limit of ALT (15,24). One of the characteristics of HH is the massive and transient increase in serum transaminase activity caused by hypoxic necrosis of hepatocytes in the centrilobular region. The standard chosen in multiple studies of HH in the ICU involves ALT or AST levels exceeding the upper limit of normal value by 10–20-fold (25-29). In this study, the inclusion criterion of the HH group was a >10-fold increase to reflect this unique liver injury. Without exception, and consistent with most studies on SALI, HH, and cholestasis, the present study also observed a high mortality rate; the overall in-hospital mortality rate of SALI patients was 43.5%, and the mortality rate in the HH group was remarkably high (up to 59.3%). However, there are currently few studies on the prognostic aspects of SALI patients, and the development of a predictive model that can effectively provide an early prediction of a patient's risk is helpful for clinicians to comprehensively assess the true risk of death and offer a clear statement of the condition to families of SALI patients.

The SOFA and SAPS2 scores are the most commonly used disease scores in clinical practice and are widely applied in internal medicine wards and the ICU for predicting the short-term mortality of patients with sepsis (30,31). Surprisingly, these two scores did not show good performance in the prognosis of SALI patients, with the SOFA score showing worse efficacy, indicating that these two scores may not apply to the prognostic prediction of this special group of sepsis patients. In our prediction model, body temperature plays an important role. Higher body temperature was found to be associated with improved prognosis in this study. As reported by Young *et al.*, the early peak temperature in infected patients was associated with a reduced risk of in-hospital mortality, even if the peak temperature exceeded 40.0 ℃ (32). Similar results were also observed by Lee *et al.* in a prospective study, which showed that higher body temperature was associated with better clinical outcomes (33). Fever is the body's protective response to infection. In infectious diseases, endogenous and exogenous heat sources lead to an increased body temperature, which is the response of the body against exogenous microorganisms (34). It has also been found that hypothermia increases the occurrence of adverse outcomes in septic patients, which is consistent with our findings (35).

Another important factor is the liver injury occurrence time. Two studies have suggested that the mortality rate of patients with prolonged liver injury is higher, but no other studies have explored the relationship between the liver injury occurrence time and the prognosis of patients (12,27). To facilitate the liver injury occurrence time calculation, we set the time at which patients entered the ICU as 0 hour, and found that compared with the survival group, the time of liver injury in the non-survival group was later. We speculate that the earlier liver dysfunction is triggered by an inflammatory response and hepatic microcirculation disturbance under infection, which can be restored after infection control. Later liver dysfunction may be one of the manifestations of systemic organ failure caused by severe sepsis or may be a concurrent result of other organ injuries. Animal experiments have shown that acute kidney injury (AKI) can trigger liver inflammation by activating kappa B (NF-κF) (36). In addition, acidosis and drug metabolism disorders caused by renal injury can directly or indirectly induce liver injury, increasing the mortality of patients (37). Meanwhile, a subset of patients experiences multiple injuries as the liver injury disease progresses; Jäger *et al.* reported that new onset jaundice in patients with HH increased the mortality of patients (38). However, more studies are needed to discover the reasons for this discrepancy; further clarifying the existence and causes of this difference by imaging examination or other standards will facilitate a more accurate determination of the liver injury occurrence time and allow for contrasting the differences in the occurrence time of different types of liver injury.

Another more important factor is RDW, which was originally used as a diagnostic indicator of anemia. At present, it is believed that excessive oxidative stress and inflammatory response can not only induce the premature death of red blood cells but also inhibit the maturation of red blood cells, resulting in the premature release of red blood cells into the circulation, ultimately leading to increased RDW, which is suggestive of red blood cell heterogeneity (39). In this study, we found that higher RDW was associated with adverse outcomes. Similarly, a previous study has confirmed the role of RDW in the prognosis of patients with sepsis (40).

Our research has some limitations that should be noted. Firstly, this is a single-center retrospective study, which lacks multi-center participation and external verification, which limits the reliability of research conclusions. Secondly, for the microbial culture information and infection sites that needed to be identified over a long period, we conducted only a preliminary statistical description and did not use this as an alternative predictor, which may have led to some powerful factors not

being included in the model. In addition, the imaging examination information is missing. Therefore, in future studies, we will conduct external validation and include some potentially significant factors to further enhance the stability and performance of our model.

Conclusions

In this study, a predictive model for the in-hospital mortality of SALI patients was established, which showed good accuracy and clinical usefulness. This model can help clinicians identify high-risk patients and reduce the incidence of adverse events.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4319/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4319/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Open Access Statement: This is an Open Access article

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