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Development and Validation of a Nomogram for Predicting Sepsis-Induced Coagulopathy in Septic Patients: Mixed Retrospective and Prospective Cohort Study

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Abstract

Background Sepsis-induced coagulopathy (SIC) is a common cause of poor prognosis in critically ill patients in the intensive care unit (ICU). However, currently there are no tools specifically designed for predicting the occurrence of SIC in septic patients earlier. This study aimed to develop a predictive nomogram incorporating clinical markers and scoring systems to individually predict the probability of SIC in septic patients.

Methods Patients consecutively recruited in the stage between January 2022 and April 2023 constituted the development cohort for retrospective analysis to internally test the nomogram, and patients in the stage between May 2023 to November 2023 constituted the validation cohort for prospective analysis to externally validate the nomogram. Univariate logistic regression analysis of the development cohort was performed firstly, and then multivariate logistic regression analysis was performed using backward stepwise method to determine the best-fitting model and obtain the nomogram from it. The nomogram was validated in an independent external validation cohort, involving discrimination and calibration. A decision curve analysis was also performed to evaluate the net benefit of the insertion decision with this nomogram.

Results A total of 548 and 245 patients, 55.1 and 49.4% with SIC occurrence, were included in the development and validation cohorts, respectively. Predictors contained in the prediction nomogram included shock, platelets, and international normalized ratio (INR). Patients with shock (odds ratio [OR]: 4.499; 95% confidence interval [CI]: 2.730–7.414; $p < 0.001$), higher INR (OR: 349.384; 95% CI: 62.337–1958.221; $p < 0.001$), and lower platelet (OR: 0.985; 95% CI: 0.982–0.988; $p < 0.001$) had higher probabilities of SIC. The development model showed good discrimination, with an area under the receiver operating characteristic curve (AUROC) of 0.879 (95% CI: 0.850–0.908) and good calibration. Application of the nomogram in the validation cohort also gave good discrimination with an AUROC of 0.872 (95% CI: 0.826–0.917) and good

Keywords
- sepsis
- sepsis-induced coagulopathy
- nomogram
- prediction
- intensive care unit

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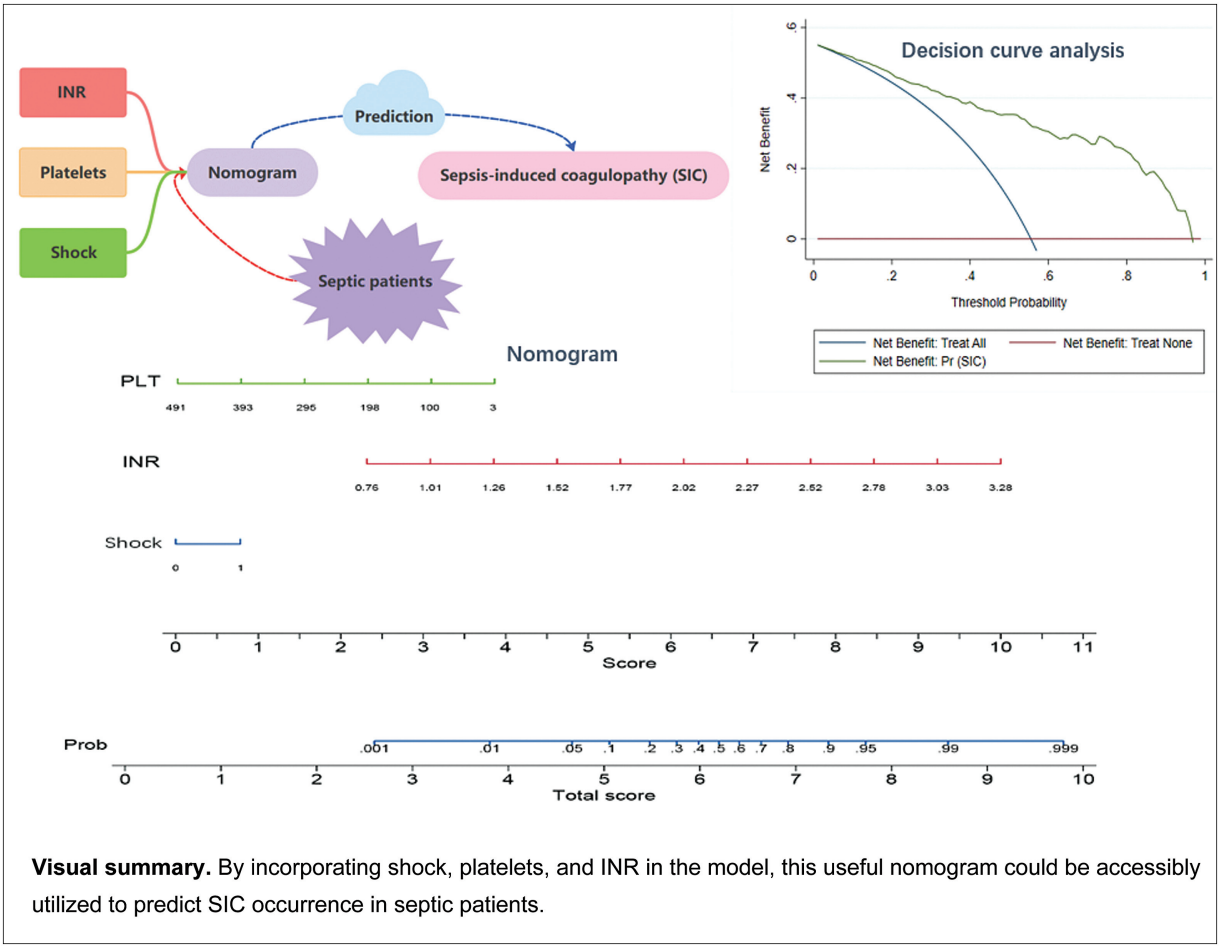

Visual summary. By incorporating shock, platelets, and INR in the model, this useful nomogram could be accessibly utilized to predict SIC occurrence in septic patients.

calibration. The decision curve analysis of the nomogram provided better net benefit than the alternate options (intervention or no intervention).

Conclusion By incorporating shock, platelets, and INR in the model, this useful nomogram could be accessibly utilized to predict SIC occurrence in septic patients. However, external validation is still required for further generalizability improvement of this nomogram.

Background

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] It poses a significant threat to the survival of patients admitted to the intensive care unit (ICU). The incidence and mortality of sepsis remain high and it is one of the leading causes of death in the ICU worldwide.[2] The incidence of coagulopathy, which is reportedly responsible for poor outcomes, is commonly seen among patients with sepsis.[3,4] Sepsis-induced coagulopathy (SIC) was proposed in 2017 by the Scientific Standardization Committee on Disseminated Intravascular Coagulopathy (DIC) of the International Society on Thrombosis and Haemostasis to categorize patients with "sepsis and coagulation disorders" and was designed to fit the new sepsis definition. So far, the diagnostic criteria of SIC consist of three items, namely, platelet count, international normalized ratio (INR), and total Sequential Organ Failure Assessment (SOFA) score which only contains four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA). The score of total SOFA is defined as 2 if the total score exceeded 2. SIC is defined as a score $\geq$4 and the score system for SIC is listed in ►**Supplementary Table S1** (available in the online version).[5]

In a recent observational survey conducted in Japan, 29% of 1,895 sepsis patients treated in ICUs were diagnosed with SIC.[6] A secondary analysis of two randomized controlled trials in Europe demonstrated that SIC prevalence was 22.1% (the HYPRESS trial) and 24.2% (the SISPCT trial).[7] Coagulation abnormalities are a serious complication in almost all septic patients.[8] The clinical manifestations of coagulation abnormalities range from early thrombocytopenia to late DIC,

which often leads to multiple organ dysfunction syndrome and a higher mortality rate.[9] Previous multicenter retrospective observational trials have shown a significant correlation between SIC and poor prognosis.[10,11] SIC is regarded as an early phase of DIC because it includes most cases of overt DIC, which provides the possibility for early clinical intervention of sepsis.[12]

Although several studies have shown that coagulopathy is one of the major complications of sepsis, leading to a higher risk of thrombosis, the deterioration of organ failure, and an increased mortality rate,[13–15] so far there are almost no tools specifically designed for predicting the occurrence of SIC in septic patients earlier. Since SIC is associated with poor prognosis in patients with sepsis, this study aimed to develop a predictive nomogram incorporating clinical markers and scoring systems to individually predict the probability of SIC in septic patients, so as to provide evidence for early diagnosis and treatment of SIC.

Materials and Methods

Study Design

This study was conducted in two stages. In the development stage, a retrospective research approach was employed to screen all patients admitted to the ICU of a tertiary general hospital (The First Hospital of Jilin University in Changchun, China) from January 2022 to April 2023. Clinical data of septic patients were collected through the electronic medical records system. Patients who met the inclusion criteria and did not meet the exclusion criteria were included in the development cohort to establish a clinical model for predicting SIC. In the validation stage, a prospective observational study was conducted, including septic patients admitted to the ICU of the First Hospital of Jilin University from May 2023 to November 2023. All participants in validation cohort provided written informed consent. This study has been approved by the Ethics Committee of the First Hospital of Jilin University [Approval number: 2022(013)].

Study Population

Adult patients fulfilling the diagnostic criteria for sepsis stated in the third international consensus definitions for sepsis and septic shock (Sepsis-3)[1] were collected.

The inclusion criteria are: (1) adult ($\geq$18 years old); (2) met the definition of Sepsis 3.0 criteria, which is defined as a suspected infection combined with an acute increase in SOFA score $\geq$2; (3) the length of ICU stay is greater than 48 hours.

The exclusion criteria are: (1) age $<$18 years; (2) ICU length of stay $<$48 hours; (3) history of heparin-induced thrombocytopenia; (4) patients with various cancers combined with abnormal coagulation function; (5) decompensated liver cirrhosis; (6) concomitant anticoagulant treatment of warfarin; (7) missing data $>$10%; (8) patient refusal to sign the informed consent form or request for withdrawal during the second stage. The patients were divided into SIC group and non-SIC group according to whether the SIC score was $\geq$4.[5]

Data Collection

The collected data included age, gender, body weight, the Acute Physiology and Chronic Health Evaluation (APACHE) II score based on the worst values obtained within 24 hours after the onset of sepsis, SOFA score, past medical history, and site of infection. In addition, procalcitonin, C-reactive protein, white blood cells, platelets, INR, fibrinogen, prothrombin time (PT), creatinine, D-dimer, fibrin degradation products, neutrophil-to-lymphocyte ratio, total bilirubin, lactate, and oxygenation index (PaO_2/FiO_2) were also collected within 24 hours after the onset of sepsis. Furthermore, we also collected continuous renal replacement therapy (CRRT) proportion, mechanical ventilation proportion, and shock ratio. According to Sepsis-3, patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L ($>$18 mg/dL) in the absence of hypovolemia.[1]

Sample Size Consideration

The sample size was calculated based on the rule of thumb proposed by Harrell et al[16] and Peduzzi et al,[17] which suggest a minimum of 20 outcome events per predictor variable in a multivariate regression model. In our model development, we considered approximately 2 to 3 critical clinical factors and 2 to 3 scores.

To accurately predict the occurrence of the SIC, a minimum sample size of 120 patients (6×20) with the event (SIC) was required. This ensured an adequate number of patients who experienced the outcome event relative to the predictor variables and allows for more reliable predictions of SIC incidence.

Statistical Analysis

The Shapiro–Wilk test was employed to identify the normal distribution of continuous variables,[18,19] expressed as the median and standard deviation. The Wilcoxon–Mann–Whitney U-test was performed on the skew distribution, defined as the median and interquartile range. Categorical variables were described using frequency (percentage) and compared using Pearson's Chi-square tests or Fisher precision tests according to appropriateness. Variables showing significance at the 0.1 level in the univariate analysis were taken into account. Spearman correlation and Belsley collinearity tests were used to assess collinearity across all covariables.

To develop a predictive nomogram indicating the probability of developing SIC in patients with sepsis, we initially performed a multivariate logistic regression analysis using a backward stepwise approach. The analysis aimed to identify simplified models in the development cohort. The covariates considered in the analysis included diabetes mellitus, shock, platelet, and INR. We obtained estimated odds ratios (ORs) and 95% confidence intervals (CIs). A nomogram was then constructed based on the simplified model, including the identified predictors. Each predictor in the nomogram was assigned points by drawing a vertical line from the corresponding factor to the point axis. The sum of all points from

all the predictors was then calculated to generate the total points. By drawing a vertical line from the total point axis to the risk of SIC axis, the probability of SIC occurrence can be estimated. The differentiation was assessed by calculating the area under the receiver operating characteristic curve (AUROC) derived from the conventional receiver operating characteristic curves (ROC). In order to evaluate the classification accuracy of these two models, AUROC was compared using the nonparametric method of DeLong and Clarke-Pearson.[20]

The best-fitting model and the nomogram were verified and calibrated using bootstrap techniques.[17] The bootstrap method was applied to 1,000 resamples, and the AUROC and 95% CI of the obtained bootstrap correction were reported. We used Hosmer–Lemeshow test to evaluate the calibration plot of the nomogram. The identification and calibration of the nomogram models were verified in an independent external validation cohort. In addition, in the validation cohort, decision curve analysis was performed using a nomogram at different threshold probabilities to assess the net benefit of SIC treatment decisions. All statistical analyses were performed using SPSS 26.0 and Stata 16.0.

Results

Development Cohort

Of 697 patients recruited in the first stage, 33 patients with incomplete data were excluded from the analysis. In addition, 67 patients were excluded due to hospitalization in the ICU for less than 48 hours, 21 patients were excluded due to diagnosis of hematological malignancy, and 28 patients were excluded due to diagnosis of Child–Pugh grade C cirrhosis. Thus, a total of 548 patients were included in the development cohort, in which 302 (55.1%) patients occurred SIC (►**Table 1**).

Validation Cohort

Of 265 patients prospectively recruited in the second stage, 12 patients were excluded due to hospitalization in the ICU for less than 48 hours, 4 patients were excluded due to diagnosis of hematological malignancy, and 4 patients were excluded due to diagnosis of Child–Pugh grade C cirrhosis. Then a total of 245 patients were involved in the validation cohort, in which 121 (49.4%) patients occurred SIC (►**Table 1**). The clinical and demographic data differences between development and validation cohorts are also presented in ►**Table 1**. The flowchart for the patient selection is shown in ►**Fig. 1** (►**Fig. 1A** is the flowchart of development cohort; ►**Fig. 1B** is the flowchart of validation cohort).

Development of the Nomogram Model

As shown in ►**Table 1**, variables presenting significance including diabetes, shock, average red blood cell volume, platelets, and INR were selected to the univariate logistic regression. After univariate logistic regression analysis, shock, platelets, and INR might represent the risk factors for SIC ($p < 0.05$) (►**Table 2**). Shock, platelets, and INR were recognized as independent predictors in the multivariate logistic regression analysis (►**Table 3**). Patients with shock (OR: 4.499; 95% CI: 2.730–7.414; $p < 0.001$) or higher INR (OR: 349.384; 95% CI: 62.337–1958.221; $p < 0.001$) had higher probabilities of SIC. By contrast, the higher the platelet (OR: 0.985; 95% CI: 0.982–0.988; $p < 0.001$), the less likely the SIC was to be occurred (►**Table 3**).

The nomogram, which incorporated these predictors, was developed and presented as shown (►**Fig. 2**). To obtain the nomogram-predicted probability, whether the patient is in shock, the patient's platelet and INR should be mapped onto the axes of the nomogram-predictive factors. A vertical line is drawn on the axes to identify the score for each variable value. By summing up the scores for all variables and locating the corresponding total on the total point line, the individual probability of SIC occurrence can be assessed. For example, let's consider a patient with shock, platelet 100×10^9/L, and an INR of 1.01. The corresponding points on the axes of the nomogram-predictive factors are as follows: 1 point for the shock, 3 points for platelet, and 3 points for INR. Adding up these points, the total score is 7 ($1 + 3 + 3$) points. According to this nomogram, the probability of SIC occurrence for this patient is over 80%.

Validation of the Nomogram Model

ROC analysis was conducted on the predictors of SIC occurrence in both the development cohort and validation cohort. The area under the curve (AUC) of the development group was 0.879 (95% CI: 0.850–0.908) (►**Fig. 3**), while the AUC of the validation group was 0.872 (95% CI: 0.826–0.917) (►**Fig. 4**). There was no significant difference observed (DeLong test, $p = 0.372$). These results initially confirm the favorable discriminative ability of the nomogram model. This model enables the prediction of SIC occurrence probability in diverse septic patients.

To further evaluate the calibration performance of the nomogram model, the calibration curve was described using the bootstrap method for both the development cohort (►**Fig. 5**) and validation cohort (►**Fig. 6**). The *x*-axis represents the predicted risk of SIC occurring, while the *y*-axis represents the actual risk of SIC occurring. The diagonal dotted lines represent prediction models with perfect predictive power. A closer alignment between the calibration curve and the diagonal dashed line indicates a higher prediction accuracy of the nomogram model. It is worth noting that both curves show slight linearity, indicating that the model has excellent calibration performance.

Clinical Use

The decision curve analysis of the nomogram of SIC occurrence risk in the development cohort is shown in ►**Fig. 7**. The *y*-axis represents the net benefit, while the *x*-axis represents the threshold probability that the ICU physician believes SIC is likely to occur. The blue dashed line represents a scenario in which all patients receive the intervention, while the red dashed line represents a scenario in which no patients receive the intervention, resulting in a net benefit of 0. The net benefit is calculated by subtracting the percentage of patients with false positives from the percentage of patients

Table 1 Clinical and demographic data for development and validation cohort

Variables	Development cohort				Validation cohort			
	Total ($n=548$)	SIC ($n=302$)	Non-SIC ($n=246$)	*p*-Value	Total ($n=245$)	SIC ($n=121$)	Non-SIC ($n=124$)	*p*-Value
Age (y)	60.4 ± 16.7[a]	60.5 ± 16.9	60.1 ± 16.4	0.158	63.5 ± 15.5[a]	63.9 ± 15.1	63.1 ± 16.0	0.451
Gender				0.880				0.128
Male, *n* (%)	334 (60.9)	177 (58.6)	157 (63.8)		154 (62.9)	80 (66.1)	74 (59.7)	
Female, *n* (%)	214 (39.1)	125 (41.4)	89 (36.2)		91 (37.1)	41 (33.9)	50 (40.3)	
Body weight (kg)	67.4 ± 13.8[b]	67.2 ± 13.3	67.7 ± 14.4	0.990	73.5 ± 15.1[b]	73.8 ± 14.9	73.2 ± 15.4	0.652
Past medical history, *n* (%)								
Diabetes mellitus	167 (30.5)	86 (28.5)	81 (32.9)	0.011	62 (25.3)	40 (33.1)	22 (17.7)	0.078
Hypertension	246 (44.9)	129 (41.7)	117 (47.6)	0.235	116 (47.3)	54 (44.6)	62 (50.0)	0.208
Coronary artery disease	99 (18.1)	60 (19.9)	39 (15.9)	0.067	49 (20.0)	20 (16.5)	29 (23.3)	0.085
Site of infection, *n* (%)				0.628				0.607
Blood	55 (10.0)	41 (13.6)	14 (5.7)		30 (12.2)	22 (18.2)	8 (6.5)	
Pulmonary	346 (63.1)	179 (59.3)	167 (67.9)		150 (61.2)	66 (54.5)	84 (67.7)	
Intra-abdominal	85 (15.5)	46 (15.2)	39 (15.9)		27 (11.0)	20 (16.5)	7 (5.6)	
Genitourinary	22 (4.0)	15 (5.0)	7 (2.8)		7 (2.9)	3 (2.5)	4 (3.2)	
Others	40 (7.3)	21 (7.0)	19 (7.7)		31 (12.7)	10 (8.3)	21 (16.9)	
APACHE II	15.0 ± 6.1	16.0 ± 6.4	13.8 ± 5.6	0.608	14.8 ± 6.0	16.5 ± 6.1	13.1 ± 5.5	0.152
SOFA	5.8 ± 3.2	6.4 ± 3.5	5.1 ± 2.6	0.859	6.4 ± 3.5	7.6 ± 4.0	5.2 ± 2.6	0.207
Mechanical ventilation, *n* (%)	307 (56.0)	185 (61.3)	122 (49.6)	0.236	164 (66.9)	91 (75.2)	73 (58.9)	0.385
CRRT, *n* (%)	144 (26.3)	107 (35.4)	37 (15.0)	0.530	55 (22.4)	37 (30.6)	18 (14.5)	0.175
Shock, *n* (%)	236 (43.1)	174 (57.6)	62 (25.2)	0.019	120 (49.0)	84 (69.4)	36 (29.0)	0.002
PCT (ng/mL)	12.8 ± 25.0	18.1 ± 29.7	5.9 ± 14.6	0.704	12.4 ± 23.3	18.4 ± 28.8	6.6 ± 14.3	0.174
Lac (mmol/L)	2.1 ± 2.2	2.6 ± 2.7	1.5 ± 1.1	0.320	2.2 ± 2.0	2.7 ± 2.5	1.7 ± 1.2	0.510
CRP (mg/L)	134.0 ± 11.9	150.9 ± 120.5	113.7 ± 99.7	0.516	125.8 ± 97.2	142.8 ± 100.9	109.5 ± 91.0	0.503
WBC ($\times 10^9$/L)	12.8 ± 11.9	13.7 ± 15.1	11.6 ± 5.9	0.150	12.6 ± 6.5	12.9 ± 7.0	12.4 ± 6.0	0.176
NLR	20.0 ± 69.8	24.5 ± 93.2	14.4 ± 12.2	0.115	19.7 ± 16.8	22.1 ± 18.7	17.4 ± 14.3	0.679
RDW (%)	14.5 ± 2.4	14.8 ± 2.5	14.1 ± 2.1	0.915	14.1 ± 2.3	14.4 ± 2.8	13.7 ± 1.5	0.472
MCV (fL)	91.0 ± 7.1[c]	91.2 ± 7.9	90.72 ± 6.0	0.014	89.6 ± 7.6[c]	90.9 ± 5.6	88.4 ± 9.0	0.040
PLT ($\times 10^9$/L)	170.7 ± 94.4	130.0 ± 82.1	220.8 ± 84.0	<0.001	187.0 ± 100.3	155.8 ± 109.0	217.8 ± 80.1	0.035

(*Continued*)

Table 1 (*Continued*)

Variables	Development cohort				Validation cohort			
	Total ($n = 548$)	SIC ($n = 302$)	Non-SIC ($n = 246$)	*p*-Value	Total ($n = 245$)	SIC ($n = 121$)	Non-SIC ($n = 124$)	*p*-Value
AST (U/L)	25.9 (15.9–52.5)	27.3 (18.6–62.2)	24.6 (14.4–45.2)	0.440	39.9 (26.1–76.5)	53.1 (33.0–103.0)	32.0 (23.0–47.1)	0.685
ALT (U/L)	38.7 (22.7–69.2)	47.4 (27.4–89.5)	30.0 (19.3–52.6)	0.831	31.5 (19.6–58.3)	39.2 (22.2–88.3)	25.6 (16.8–43.3)	0.682
Variables	Development cohort				Validation cohort			
	Total ($n = 548$)	SIC ($n = 302$)	Non-SIC ($n = 246$)	*p*-Value	Total ($n = 245$)	SIC ($n = 121$)	Non-SIC ($n = 124$)	*p*-Value
ALP (U/L)	106.1 ± 70.3	107.9 ± 73.6	104.0 ± 66.2	0.073	96.8 ± 76.7	98.5 ± 90.9	95.1 ± 59.9	0.072
Albumin (g/L)	29.5 ± 5.8	28.4 ± 5.6	30.8 ± 5.8	0.910	30.1 ± 5.6	28.4 ± 5.9	31.7 ± 4.7	0.727
TBIL (μmol/L)	27.7 ± 50.8	35.6 ± 64.9	18.0 ± 20.5	0.995	25.9 ± 43.1	36.2 ± 58.9	15.9 ± 9.7	0.594
CRE (μmol/L)	202.7 ± 253.1[a]	229.8 ± 247.6	169.0 ± 258.3	0.300	135.1 ± 164.8[a]	160.4 ± 153.6	110.2 ± 172.1	0.405
BUN (mmol/L)	14.0 ± 11.3[c]	15.8 ± 11.7	11.8 ± 10.5	0.741	11.3 ± 7.6[c]	13.7 ± 8.3	9.0 ± 6.1	0.144
INR	1.22 ± 0.45	1.33 ± 0.57	1.08 ± 0.12	0.020	1.21 ± 0.51	1.36 ± 0.69	1.06 ± 0.12	0.037
FBG (g/L)	4.6 ± 2.3	4.4 ± 2.4	4.9 ± 2.2	0.486	4.9 ± 2.1	4.7 ± 2.0	5.0 ± 2.1	0.963
PT (s)	14.1 ± 4.6	15.2 ± 5.9	12.8 ± 1.4	0.361	13.9 ± 5.9	15.7 ± 8.0	12.2 ± 1.2	0.610
D-D (mg/L)	10.4 ± 21.0	12.7 ± 24.7	7.5 ± 14.7	0.389	8.5 ± 12.6	11.7 ± 14.9	5.4 ± 8.8	0.526
FDP (ug/mL)	29.2 ± 61.1	36.3 ± 71.5	20.5 ± 43.6	0.466	23.4 ± 34.2	32.1 ± 40.0	14.7 ± 25.1	0.605
PaO_2/FiO_2 (mmHg)	246.8 ± 124.3	232.3 ± 121.6	264.5 ± 125.4	0.273	228.0 ± 130.2	226.5 ± 131.4	229.5 ± 129.6	0.964

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APACHE II, Acute Physiology and Chronic Health Evaluation II; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRE, creatinine; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; D-D, D-dimer; FBG, fibrinogen; FDP, fibrin degradation product; INR, international normalized ratio; IQR, interquartile range; Lac, lactate; MCV, mean corpuscular volume; NLR, neutrophil-to-lymphocyte ratio; PaO_2/FiO_2, oxygenation index; PCT, procalcitonin; PLT, platelets; PT, prothrombin time; RDW, red blood cell volume distribution width; SOFA, Sequential Organ Failure Assessment; TBIL, total bilirubin; WBC, white blood cells.

Note: Data presented as mean ± standard deviation, median (IQR) or *n* (%).

[a]Represents $p < 0.01$.

[b]Represents $p < 0.001$.

[c]Represents the difference between the development cohort and the validation cohort; represents $p < 0.05$.

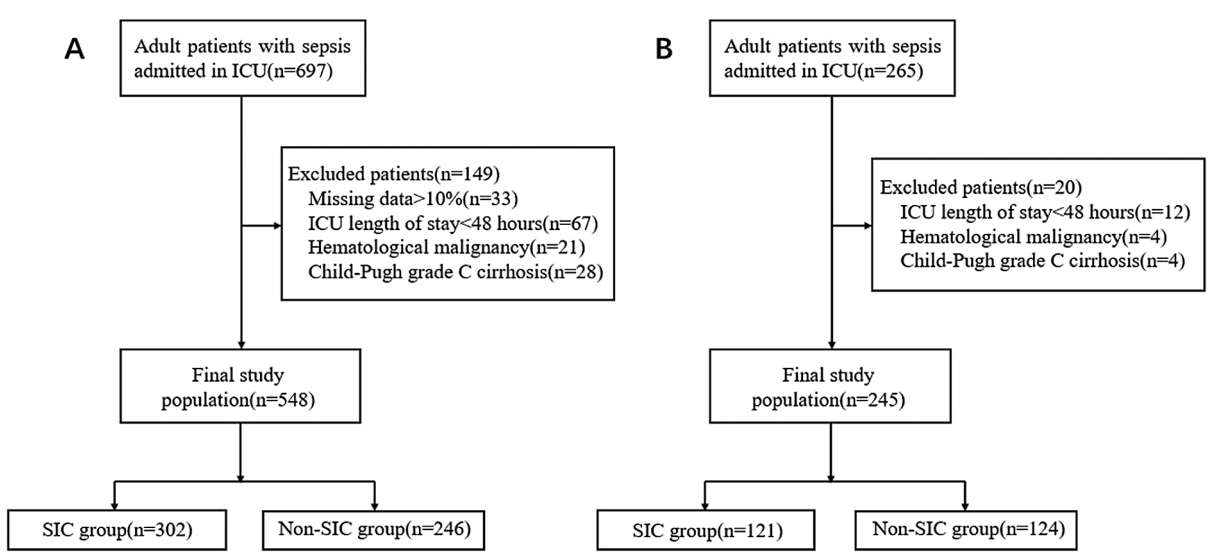

Fig. 1 The flowchart for the patient selection.

Table 2 Univariate logistic regression analysis of predictors for SIC in the development cohort

Predictive factors	OR (95% CI)	*p*-Value
Diabetes	1.233 (0.856–1.776)	0.261
MCV	1.011 (0.987–1.035)	0.384
Shock	4.034 (2.794–5.825)	<0.001
Platelets	0.988 (0.986–0.991)	<0.001
INR	470.555 (110.903–1996.529)	<0.001

Abbreviations: CI, confidence interval; INR, international normalized ratio; MCV, mean corpuscular volume; OR, odds ratio; SIC, sepsis-induced coagulopathy.

Table 3 Multivariate logistic regression analysis of predictors for SIC in the development cohort

Predictive factors	OR (95% CI)	*p*-Value
Shock	4.499 (2.730–7.414)	<0.001
Platelets	0.985 (0.982–0.988)	<0.001
INR	349.384 (62.337–1,958.221)	<0.001

Abbreviations: CI, confidence interval; INR, international normalized ratio; OR, odds ratio.

with true positives, weighted according to the relative harm of refusing treatment versus the negative consequences of unnecessary treatment. The threshold probability indicates the likelihood that SIC will occur and guides the critical care physician in deciding whether to treat SIC based on this probability.

The decision curve shows that if the threshold probability of SIC occurrence is 8% or higher, covering the clinically acceptable range (the incidence of SIC is about 50%), employing the nomogram for SIC intervention yields greater benefits compared to no intervention.

The decision curve analysis of the nomogram of SIC occurrence risk in the validation cohort is shown in ►**Fig. 8**. The decision curve shows that if the threshold probability of SIC occurrence is 17% or higher, employing the nomogram for SIC intervention yields greater benefits compared to no intervention.

Discussion

This study demonstrated that shock, platelets, and INR were independent predictors for the occurrence of SIC, and developed an user-friendly nomogram with clinical usefulness to predict the individual probability of SIC in septic patients. This mixed retrospective and prospective cohort study indicated that the incidence of SIC is 53.3% (423/793) in patients with sepsis, this is slightly higher than the previously reported incidence of SIC in Japan (29%) and Europe (22.1% in the HYPRESS trial and 24.2% in the SISPCT trial).[6,7] Coagulation dysfunction is common in sepsis and is often

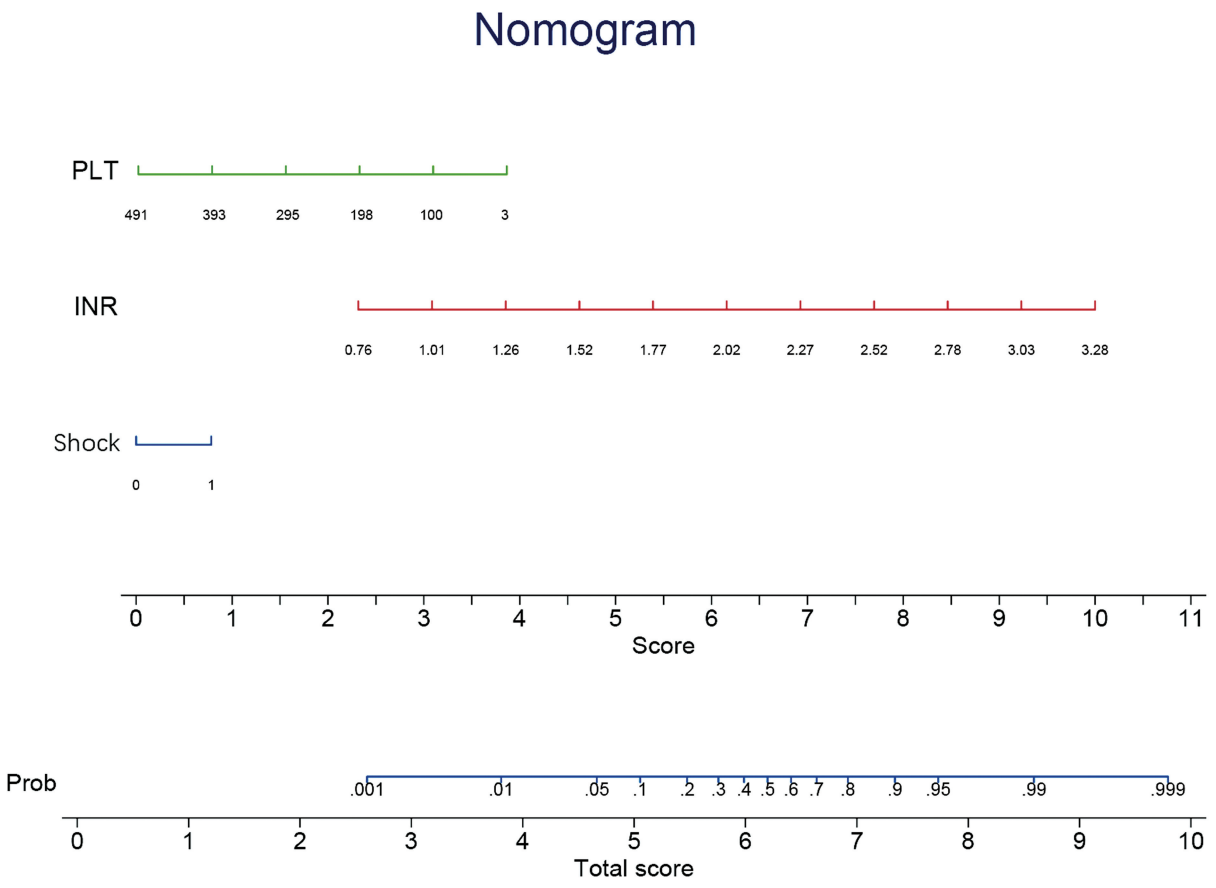

Fig. 2 Nomogram of sepsis-induced coagulopathy.

associated with poor prognosis caused by multiple organ dysfunction syndrome and microvascular thrombosis.[21] Coagulopathy in sepsis may take the form of SIC or sepsis-associated DIC. About 93.9% of patients who were diagnosed with SIC went on to develop sepsis-associated DIC within the next 2 to 4 days.[10] Coagulopathy in septic patients is caused by a complex relationship between immune, inflammatory, and coagulation systems, characterized by coagulation activation, disorder of the anticoagulant system, and excessive inhibition of fibrinolysis. The activation of coagulation and inflammation is a necessary response for host defense during sepsis.[22] Engelmann and Massberg proposed the concept of "immunothrombosis," which refers to the close interaction between coagulation and innate immunity.[23] The combined effects of these processes lead to coagulation disorders worsening into sepsis-related DIC.[24] Since SIC is closely associated with poor prognosis in septic patients and the incidence of which is high, it is important to identify SIC

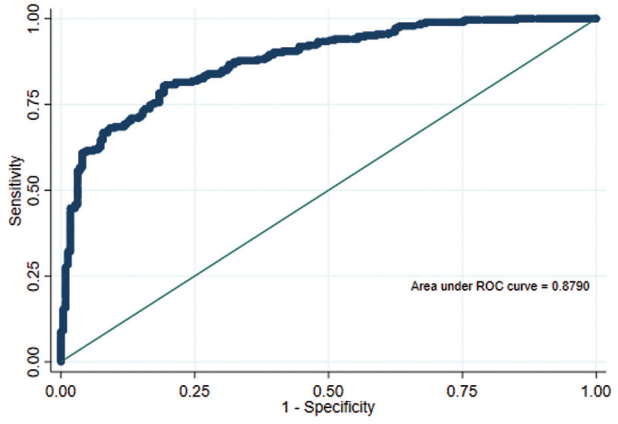

Fig. 3 Receiver operating characteristic curve analysis of predictors for SIC in the development cohort. SIC, sepsis-induced coagulopathy.

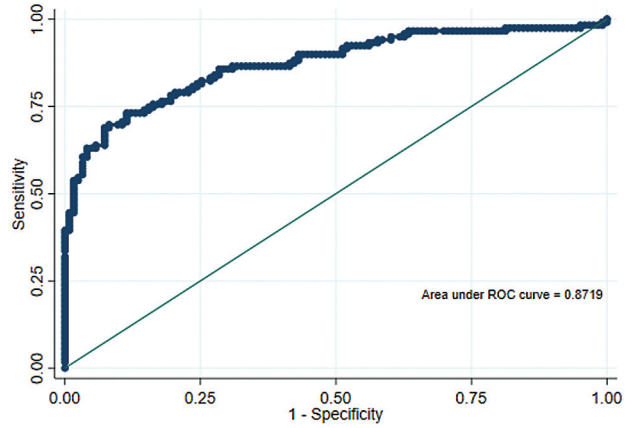

Fig. 4 Receiver operating characteristic curve analysis of predictors for SIC in the validation cohort. SIC, sepsis-induced coagulopathy.

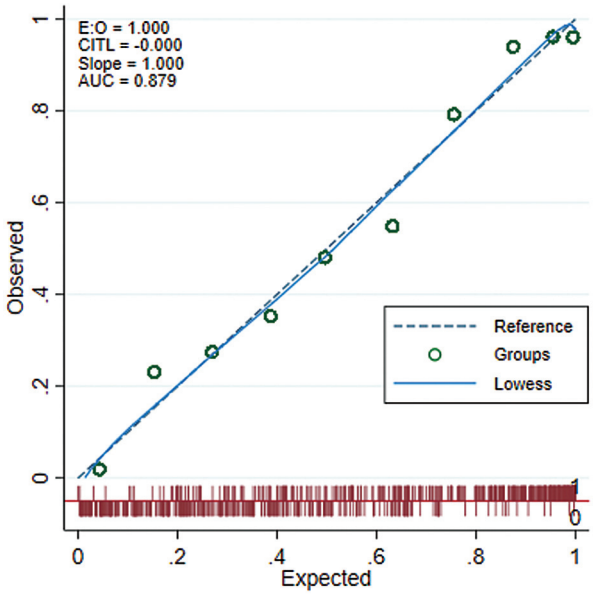

Fig. 5 Calibration plot for nomogram in the development cohort.

early, as at this stage of coagulopathy anticoagulants may be of the greatest benefit.[25]

The current SIC criteria are a scoring system designed to identify patients with sepsis and coagulation disorders. With the concept of "infection-induced organ dysfunction and coagulopathy, " SIC diagnostic criteria include SOFA score, platelet count, and INR. SIC is defined as a score of $\geq$4 points.[5] The SOFA score included in the SIC diagnostic criteria is used to confirm the presence of sepsis. Because the SOFA score is limited to two points, it does not reflect the severity of sepsis.[26] Coagulopathy in sepsis may take the form of SIC (early stage) or sepsis-associated DIC (late stage). Thrombocytopenia is usually a clue to the presence of DIC, with reported platelet counts below 50×10^9/L is closely related to poor prognosis in

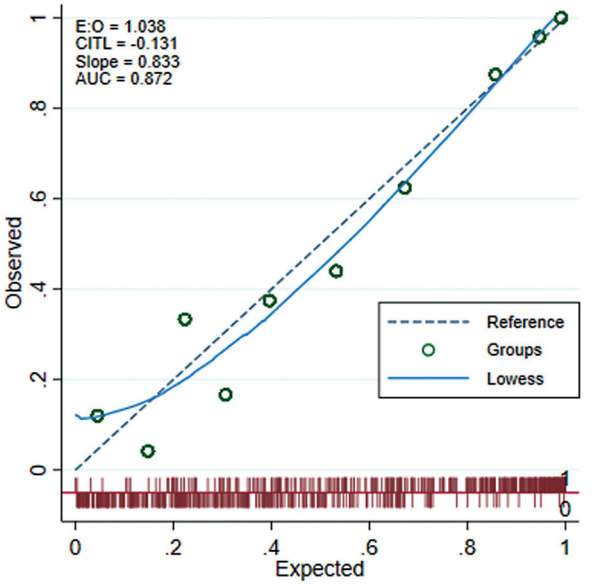

Fig. 6 Calibration plot for nomogram in the validation cohort.

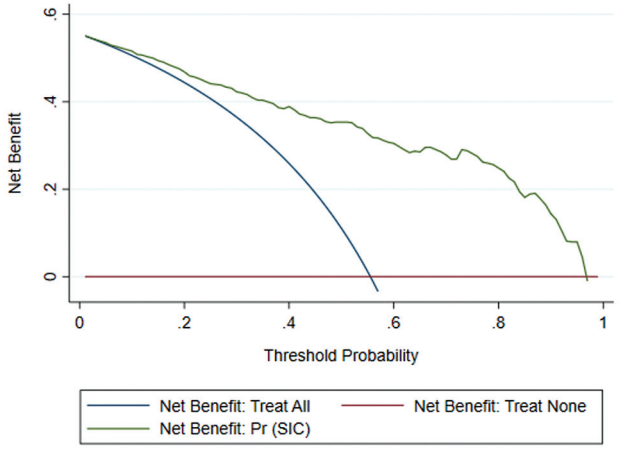

Fig. 7 Decision curve analysis of the nomogram of SIC occurrence risk in the development cohort. SIC, sepsis-induced coagulopathy.

patients with sepsis.[27] Study suggests that INR is a moderate diagnostic tool for infectious shock and sepsis. In addition, INR has been proven to be an appropriate prognostic tool for 30-day all-cause mortality. INR >1.5 is associated with an increased risk of all-cause death at 30 days, as observed in patients with sepsis and septic shock.[28] During sepsis, the hemostatic balance is significantly disrupted. The coagulation process is activated, while anticoagulant mechanisms are suppressed. Traditional laboratory findings of sepsis, including thrombocytopenia, increased PT and fibrin degradation products, and decreased fibrinogen, only present late in the course of sepsis.[29] This nomogram can predict the incidence of SIC through platelet and INR levels at an earlier stage when changes to coagulation status are still reversible. Different from our study, another nomogram including 13 conventional clinical variables provided an optimal prediction of the 28-day mortality risk in SIC patients through the internal validation. Using this model, the 28-day mortality risk of an individual SIC patient can be determined, which may lead to an improved mortality assessment.[30]

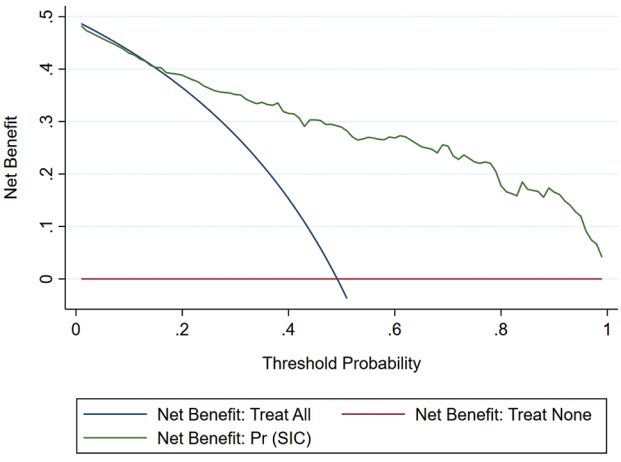

Fig. 8 Decision curve analysis of the nomogram of SIC occurrence risk in the validation cohort. SIC, sepsis-induced coagulopathy.

There were 144 patients in the development cohort and 55 patients in the validation cohort who received CRRT. These patients received local external anticoagulant therapy with sodium citrate. Sodium citrate is an anticoagulant drug whose pharmacological action is mainly to exert anticoagulant effect by inhibiting coagulation factors in the blood. Specifically, citrate ions in sodium citrate combine with calcium ions in the blood to form the refractory soluble complex calcium citrate. Although this complex is soluble in water, it is not easily dissociated, resulting in a decrease in calcium ions in the blood, which inhibits the clotting process and prevents the blood from clotting. Citrate is partially removed by filtration or dialysis, and the remaining amount is rapidly metabolized in the citric acid cycle, especially in the liver, muscle, and renal cortex, while the chelated calcium is released and the lost calcium is replaced. Systemic coagulation is unaffected.[31] Therefore, sodium citrate has little effect on INR and platelets. In addition, there was no statistical difference in the proportion of CRRT between SIC and non-SIC patients in both the development and validation cohorts. As a result, the ratios of sodium citrate use in SIC and non-SIC patients in the development and validation cohorts were also matched.

INR has provided higher value for predicting occurrence of SIC than platelets in the nomogram, which may be due to several reasons. First, INR can reflect the coagulation state more comprehensively. INR takes into account not only the number of platelets, but also the synthesis and function of other clotting factors, thus providing a more complete picture of a patient's clotting status. Second, INR is more sensitive to coagulation dysfunction. Since INR is an indicator of PT, it is more sensitive to coagulation disorders and can detect coagulation abnormalities earlier. Third, INR is less disturbed. Compared with platelets, INR is less affected by some interfering factors (such as drugs, blood transfusion, etc.), so it can more accurately reflect the patient's clotting status. Previous study has found that there was a strong correlation between INR value and SOFA score.[32] The SOFA score was correlated with the prognosis of SIC, which also suggested that INR had a good predictive value of SIC from another perspective.

Shock was also an independent predictive factor for SIC in our study. Septic shock is commonly associated with a wide spectrum of coagulation abnormalities with the most severe form being DIC. This is the result of a complex interplay between proinflammatory cytokines, procoagulant factors, anticoagulant factors, and endothelial dysfunction.[13] Patients who needed vasopressors were considered to have septic shock. Previous study has demonstrated that SIC developed in 66.4% of patients who used vasopressors and 42.2% of patients who did not. The in-hospital mortality difference between the SIC and non-SIC groups was statistically significant in those who needed vasopressors (35.8% vs. 27.9%). In addition, SIC was significantly correlated with mortality risk in patients who used vasopressors.[33] Although shock does not have a high score in our nomogram, patients with septic shock need to be highly vigilant about the occurrence of SIC.

There are several limitations in our study. First, it is a mixed retrospective and prospective cohort study, the participants with missing variables in the retrospective cohort study are excluded, hence suffers from potential selection and ascertainment bias. Second, the variables included in the model are mainly common indicators of SIC; some new coagulation markers and examinations, including soluble thrombomodulin, thrombin–antithrombin complex, tissue plasminogen activator–inhibitor complex, α2-plasmin inhibitor–plasmin complex, antithrombin III, and thromboelastography, are becoming useful tools in coagulopathy diagnosis.[34–37] However, these tests have not been widely and routinely conducted in clinical practice at present, so complete results cannot be obtained. Third, due to the single-center nature and small heterogeneous patient population, the generalizability of our results is limited. Therefore, larger-scale and multicenter research is still required in the future. Fourth, it is crucial to assess the significance of SIC in less severe patients, not only the patients treated in the ICU but also the patients in the emergency room or general ward should be evaluated and screened for early warning in the future study.

Conclusion

By incorporating shock, platelets, and INR in the model, this useful nomogram could be accessibly utilized to predict SIC occurrence in septic patients earlier. However, external validation is still required for further generalizability improvement of this nomogram.

What is known about this topic?

- Sepsis-induced coagulopathy (SIC) is a common cause of poor prognosis in critically ill patients in the intensive care unit (ICU).
- So far the diagnostic criteria of SIC consist of three items, namely, platelet count, international normalized ratio (INR), and Sequential Organ Failure Assessment (SOFA) score.
- However, currently there are no tools specifically designed for predicting the occurrence of SIC in septic patients earlier.

What does this paper add?

- This study developed an user-friendly nomogram with clinical usefulness to predict the individual probability of SIC in septic patients.
- By incorporating shock, platelets, and INR in the model, this useful nomogram could be accessibly utilized to predict SIC occurrence in septic patients earlier.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

Y.L. and D.Z. conceived the study. L.Z., C.Z., M.G., and Y.Z. designed and conducted data collection. Y.W. conducted data analysis, and provided interpretations of the data. Y.L. drafted the first version of the manuscript. All authors critically revised the manuscript for intellectually important content and approved the final version to be published.

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Conflict of Interest

None declared.

References

1 Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(08):801–810
2 Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet 2018;392(10141):75–87
3 Moore HB, Winfield RD, Aibiki M, Neal MD. Is coagulopathy an appropriate therapeutic target during critical illness such as trauma or sepsis? Shock 2017;48(02):159–167
4 Lyons PG, Micek ST, Hampton N, Kollef MH. Sepsis-associated coagulopathy severity predicts hospital mortality. Crit Care Med 2018;46(05):736–742
5 Iba T, Nisio MD, Levy JH, Kitamura N, Thachil J. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. BMJ Open 2017;7(09):e017046
6 Saito S, Uchino S, Hayakawa M, et al; Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) study group. Epidemiology of disseminated intravascular coagulation in sepsis and validation of scoring systems. J Crit Care 2019;50:23–30
7 Schmoch T, Möhnle P, Weigand MA, et al; SepNet–Critical Care Trials Group. The prevalence of sepsis-induced coagulopathy in patients with sepsis - a secondary analysis of two German multicenter randomized controlled trials. Ann Intensive Care 2023;13(01):3
8 Simmons J, Pittet JF. The coagulopathy of acute sepsis. Curr Opin Anaesthesiol 2015;28(02):227–236
9 Lipinska-Gediga M. Coagulopathy in sepsis - a new look at an old problem. Anaesthesiol Intensive Ther 2016;48(05):352–359
10 Tiru B, DiNino EK, Orenstein A, et al. The economic and humanistic burden of severe sepsis. PharmacoEconomics 2015;33(09):925–937
11 Jhang WK, Park SJ. Evaluation of sepsis-induced coagulopathy in critically ill pediatric patients with septic shock. Thromb Haemost 2021;121(04):457–463
12 Iba T, Arakawa M, Di Nisio M, et al. Newly proposed sepsis-induced coagulopathy precedes international society on thrombosis and haemostasis overt-disseminated intravascular coagulation and predicts high mortality. J Intensive Care Med 2020;35(07):643–649
13 Levi M, van der Poll T. Coagulation and sepsis. Thromb Res 2017;149:38–44
14 Levi M, Ten Cate H. Disseminated intravascular coagulation. N Engl J Med 1999;341(08):586–592
15 Zhao H, Cai X, Liu N, Zhang Z. Thromboelastography as a tool for monitoring blood coagulation dysfunction after adequate fluid resuscitation can predict poor outcomes in patients with septic shock. J Chin Med Assoc 2020;83(07):674–677
16 Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15(04):361–387
17 Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48(12):1503–1510
18 Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). Biometrika 1965;52(3–4):591–611
19 Razali NM, Wah YB. Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests. J Stat Model Anal. 2011;2(01):21–33
20 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44(03):837–845
21 Fourrier F. Severe sepsis, coagulation, and fibrinolysis: dead end or one way? Crit Care Med 2012;40(09):2704–2708
22 Iba T, Levi M, Levy JH. Sepsis-induced coagulopathy and disseminated intravascular coagulation. Semin Thromb Hemost 2020;46(01):89–95
23 Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. Nat Rev Immunol 2013;13(01):34–45
24 Iba T, Ogura H. Role of extracellular vesicles in the development of sepsis-induced coagulopathy. J Intensive Care 2018;6:68
25 Czempik PF, Wiórek A. Management strategies in septic coagulopathy: a review of the current literature. Healthcare (Basel) 2023;11(02):227
26 Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi MScientific and Standardization Committee on DIC, and the Scientific and Standardization Committee on Perioperative and Critical Care of the International Society on Thrombosis and Haemostasis. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost 2019;17(11):1989–1994
27 Thiery-Antier N, Binquet C, Vinault S, Meziani F, Boisramé-Helms J, Quenot JPEPIdemiology of Septic Shock Group. Is thrombocytopenia an early prognostic marker in septic shock? Crit Care Med 2016;44(04):764–772
28 Schupp T, Weidner K, Rusnak J, et al. Diagnostic and prognostic significance of the prothrombin time/international normalized ratio in sepsis and septic shock. Clin Appl Thromb Hemost 2022;28:10760296221137893
29 Tsantes AG, Parastatidou S, Tsantes EA, et al. Sepsis-induced coagulopathy: an update on pathophysiology, biomarkers, and current guidelines. Life (Basel) 2023;13(02):350
30 Lu Z, Zhang J, Hong J, et al. Development of a nomogram to predict 28-day mortality of patients with sepsis-induced coagulopathy: an analysis of the MIMIC-III database. Front Med (Lausanne) 2021;8:661710
31 Oudemans-van Straaten HM, Kellum JA, Bellomo R. Clinical review: anticoagulation for continuous renal replacement therapy–heparin or citrate? Crit Care 2011;15(01):202
32 Zhang J, Du HM, Cheng MX, He FM, Niu BL. Role of international normalized ratio in nonpulmonary sepsis screening: an observational study. World J Clin Cases 2021;9(25):7405–7416

33 Tanaka C, Tagami T, Kudo S, et al. Validation of sepsis-induced coagulopathy score in critically ill patients with septic shock: post hoc analysis of a nationwide multicenter observational study in Japan. Int J Hematol 2021;114(02):164–171
34 Li Y, Li H, Wang Y, Guo J, Zhang D. Potential biomarkers for early diagnosis, evaluation, and prognosis of sepsis-induced coagulopathy. Clin Appl Thromb Hemost 2023;29:10760296 231195089
35 Zhang J, Xue M, Chen Y, et al. Identification of soluble thrombomodulin and tissue plasminogen activator-inhibitor complex as biomarkers for prognosis and early evaluation of septic shock and sepsis-induced disseminated intravascular coagulation. Ann Palliat Med 2021;10(10):10170–10184
36 Gardner AJ, Kirkin DJ, Rodriguez-Villar S, Leoz Abellanas G, Tee A, Valentin A. Antithrombin III deficiency-induced coagulopathy in the context of COVID-19: a case series. Br J Haematol 2021;194 (06):1007–1009
37 Müller MC, Meijers JC, Vroom MB, Juffermans NP. Utility of thromboelastography and/or thromboelastometry in adults with sepsis: a systematic review. Crit Care 2014;18(01):R30

