Prognostic accuracy of SIC, JAAM DIC, and ISTH overt-DIC for 28-day all-cause mortality among patients with sepsis and coagulation abnormalities: a retrospective study

Yuwei Chen
Ruijin Hospital
Weiwei Chen
Ruijin Hospital
Fuhua Ba
Ruijin Hospital
Yanjun Zheng
Ruijin Hospital
Yi Zhou
Ruijin Hospital
Wen Shi
Ruijin Hospital
Jian Li
Ruijin Hospital
Zhitao Yang
Ruijin Hospital
Ying Chen (bichatlion@163.com)
Ruijin Hospital
Enqiang Mao
Ruijin Hospital
Erzhen Chen
Ruijin Hospital

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Abstract

Background

There is no gold standard for the diagnosis of coagulation dysfunction in sepsis, and the use of the current scoring systems is still controversial. The purpose of this study was to externally validate and assess the discriminatory capacities of SIC, JAAM DIC, and ISTH overt DIC for outcomes among patients with sepsis and coagulation abnormalities.

Methods

This retrospective study included patients with sepsis and coagulation abnormalities admitted to the general wards and ICU in Ruijin Hospital, Shanghai Jiaotong University School of Medicine from 2017 through 2019. The SIC, JAAM DIC, and ISTH overt-DIC criteria were applied to data collection during admission. The relationship between each scoring system and 28-day all-cause mortality was observed.

Results

Among 452 patients (mean age, 65 [48,76] years), 306 [66.7%] were men, the median SOFA score was 6 [4, 9], and the median APACHE II score was 15 [11, 22]. A total of 132 patients (29.2%) died within 28 days. SIC was positive in 25.4% of the patients, 44.7% of the patients manifested with JAAM DIC, and 12.2% had ISTH overt-DIC. Both the diagnosis of SIC (AUROC, 0.779 [95% CI, 0.728–0.830], $P < 0.001$) and ISTH overt-DIC (AUROC, 0.782 [95% CI, 0.732–0.833], $P < 0.001$) performed equally well in the discrimination of 28-day all-cause mortality (between-group difference: SIC *vs.* ISTH overt-DIC, -0.003 [95% CI, -0.025-0.018], $P = 0.766$). It is remarkably, however, the SIC demonstrated greater calibration for 28-day all-cause mortality than ISTH overt-DIC (the coincidence of the calibration curve of the former is higher than that of the latter). The diagnosis of JAAM DIC was not independently associated with 28-day all-cause mortality in sepsis (RR, 1.115, [95% CI 0.660–1.182], $P = 0.684$).

Conclusions

Combined with the results of distinction and calibration, the SIC scoring system demonstrated superior prognostic prediction ability for 28-day all-cause mortality among patients with sepsis and coagulation abnormalities than either JAAM DIC or ISTH overt-DIC. (309 words)

Introduction

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, is listed as one of the major global public health issues by the World Health Organization (WHO) due to its high prevalence, high mortality, high costs, complex pathogenesis, clinical heterogeneity and so on[1,2]. Studies have shown that the interaction of inflammation and coagulation during sepsis can lead to coagulation dysfunction by causing excessive activation of the coagulation system, damage to the anticoagulation system, inhibition of the fibrinolytic system, damage to vascular endothelial cells, and abnormal activation and aggregation of platelets[3–5]. As one of the common complications, coagulation dysfunction, deemed to be a systemic response that compromises tissue circulation to cause multiorgan dysfunction, often manifests in the early stage of sepsis, runs through, and even worsens with disease progression[6]. The latest data show that the incidence of coagulation dysfunction is as high as 50–70%, of which approximately 35% of cases can be secondary to disseminated intravascular coagulation (DIC), and the mortality rate of patients with DIC is as high as 28–43%[7–9]. Therefore, early identification and diagnosis of coagulation dysfunction and timely initiation of corresponding treatment are critical to improving the prognosis of patients with sepsis.

However, there is no gold standard for the diagnosis of coagulation disorders because of their extremely complex pathophysiological mechanisms and considerably dynamic changes[10]. In addition, neither any clinical manifestation nor single biomarker has been found to have adequate sensitivity, specificity, and reliability to diagnose or exclude coagulation disorders[11]. Thus, at present, the use of scoring systems for diagnosis and monitoring is recommended internationally. The commonly used scoring systems include the sepsis-induced coagulopathy (SIC) scoring system[12], the Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) scoring system[13], and the International Society on Thrombosis and Hemostasis overt Disseminated Intravascular Coagulation (ISTH overt-DIC) scoring system[14]. Each scoring system has advantages and disadvantages, and there remains controversy about their applications in previous clinical studies.

The current study aimed to assess the effect of the SIC scoring system, the JAAM DIC scoring system, and the ISTH overt-DIC scoring system within the first 24 hours in discriminating 28-day all-cause mortality among patients with sepsis and coagulation abnormalities.

Patients and Methods

Study Design and Participants

This is a retrospective observational study that was conducted at a single center. Patients with sepsis and coagulation abnormalities were also admitted to Ruijin Hospital, Shanghai Jiao Tong University School of Medicine from January 2017 to December 2019. Each patient was included once.

The protocol for this study was reviewed and approved by the Ethics Committee of Ruijin Hospital of Shanghai Jiao Tong University School of Medicine, China (approval number: 20191101; approval date: August 20, 2020). Due to retrospective, observational design, waivers of informed consent and HIPAA authorization were granted. Procedures followed in this study were in accordance with the ethical standards of the Helsinki Declaration of 1975, as most recently amended. The datasets used during the current study are available from the corresponding author on reasonable request.

The inclusion criteria were as follows: (1) young and older adults (aged ≥ 18 years); (2) diagnosed with sepsis, according to the International Guidelines for Management of Sepsis and Septic Shock 2021[2]; (3) combined with coagulation abnormalities (meeting any of the following criteria) on the day of sepsis diagnosis: platelet count (PLT) < 150×10^9/L or > 300×10^9/L, activated partial thromboplastin time (APTT) > 38.7 s, prothrombin time (PT) > 16.0 s, fibrinogen (FIB) < 1.8 g/L or > 3.5 g/L, fibrin or fibrinogen degradation products (FDP) > 5.0 mg/L, and D-dimer (DDI) > 0.55 mg/L.

The exclusion criteria were as follows: (1) a history of hematological diseases (such as hematological malignancies, idiopathic thrombocytopenia, hemophilia, etc. ; (2) history of liver damage (Child—Pugh class C); (3) history of chronic renal failure requiring long-term renal replacement therapy; (4) history of long-term use of steroids or immunosuppressants; (5) history of long-term use of anticoagulation or antiplatelet drugs; (6) received chemotherapy or radiotherapy within 1 month before diagnosis; (7) complicated emergency bleeding or thromboembolic events (such as acute myocardial infarction, etc. ; (8) received cardiopulmonary resuscitation or emergency surgery within 12 hours before diagnosis; and (9) pregnant or breastfeeding. It should be noted that when the individual components of SIC, JAAM DIC, and ISTH overt DIC were unknown, the patient was assigned a missing score and was excluded from the analysis.

Data Collection

The following data were extracted: (1) demographic information: age, sex, and BMI (body mass index); (2) clinical information: the initial site of infection, whether blood product were transfused (on the day of diagnosis), whether renal replacement therapy was received (on the day of diagnosis), whether respiratory support was required (invasive mechanical ventilation, noninvasive mechanical ventilation, or no respiratory support; on the day of diagnosis), whether anticoagulation therapy was taken (on the day of diagnosis), whether antiplatelet therapy was taken (on the day of diagnosis), the average daily cost of treatment; (3) scoring systems calculated by physiological and laboratory parameters recorded from on the day of the sepsis diagnosis: SIRS status (range, 0[best] to 4[worst] criteria), SOFA scores (range, 0[best] to 24[worst] points), APACHE II scores (range, 0[best] to

71[worst] points), SIC scores (range, 0[best] to 6[worst] points;), JAAM DIC scores (range, 0[best] to 8[worst] points), ISTH overt-DIC (range, 0[best] to 8[worst] points).The SIC criteria, JAAM DIC criteria, and ISTH overt-DIC criteria are listed in Table s1.

The primary outcome of this study was 28-day all-cause mortality.

Statistical Analysis

The mean values and standard deviation were calculated for continuous variables; the median and interquartile ranges were calculated for nonparametric data; and the frequency and percentage were calculated for categorical variables. Group comparisons were conducted using Pearson's chi-square tests or Fisher's exact tests for equal proportions, t tests for normally distributed data, and Mann—Whitney U tests otherwise. A correlation analysis was performed using scatter plots and Spearman's rank correlation. Multinomial logistic regression models were used to adjust for differences in prognostic variables and severity of disease, using age, BMI, APACHE II score, intra-abdominal infection, respiratory infection, bone and soft tissue infection, receiving renal replacement therapy, transfusion of blood product, taking anticoagulation therapy, and receiving invasive mechanical ventilation on the day of diagnosis as covariates. Model calibration was assessed using the Hosmer—Lemeshow goodness-of-fit test ($P > 0.05$) and calibration plots. Discriminatory power was determined by comparing the area under the receiver operating characteristic curve (AUROC) for each score individually (adjusted analysis). A P value < 0.05 was considered to be statistically significant unless otherwise specified. All analyses were performed using IBM SPSS Statistics 26.0.

Results

Study Population

Data pertaining to 877 adult admissions were recorded, and a final cohort of 452 patients was identified (Fig. 1). As shown in Table 1, the median age was 65 (48,76) years, 67.7% (n = 306) were male, and the most common site of infection was intra-abdominal (50.9%), followed by the respiratory tract (25.2%). The initial APACHE II score was 15 (11, 22) points, the initial SOFA score was 6 (4.9) points, and both were significantly higher among the nonsurvivors ($P < 0.001$). The average cost of treatment was approximately RMB 3567.39 (2390.05, 5650.66) yuan per day, and the cost for the nonsurvivors was higher ($P < 0.001$). There were 132 patients (29.2%) who had died within 28 days after the diagnosis of sepsis.

Table 1
Baseline characteristics of patients.

	All (n = 452)	Survivor (n = 320)	Non-survivor (n = 132)	*P*
Male	306 (67.7)	218 (68.1)	88 (66.7)	0.763[b]
Age (years)	65 (48,76)	63 (45,76)	67 (55,77)	0.010[a]
BMI (Kg/m^2)	23.4 (20.3,26.0)	23.8 (20.8,26.3)	22.5 (19.3,24.5)	0.001[a]
The initial site of infection				
Intra-abdominal	230 (50.9)	175 (54.7)	55 (41.7)	0.012[b]
Respiratory	114 (25.2)	68 (21.3)	46 (34.8)	0.002[b]
Bone and soft tissue	31 (6.9)	15 (11.4)	16 (5.0)	0.015[b]
Bloodstream	26 (5.8)	20 (6.3)	6 (4.5)	0.479[b]
Urinary tract	22 (4.9)	20 (6.3)	6 (4.5)	0.033[b]
Others	52 (11.5)	38 (11.9)	14 (10.6)	0.701[b]
SIRS	2 (2,3)	3 (2,3)	2 (2,3)	0.831[a]
SOFA	6 (4,9)	6 (4,9)	8 (5,13)	< 0.001[a]
APACHE II	15 (11,22)	14 (10,19)	18 (14,25)	< 0.001[a]
Laboratory parameters				
PLT (∗10^9/L)	131 (81,219)	128 (82,209)	146 (70,229)	0.622[a]
APTT (s)	33.1 (29.1,37.9)	32.5 (28.6,36.8)	35.3 (30.0,45.0)	< 0.001[a]
PT (s)	14.5 (13.1,16.2)	14.1 (13.0,15.5)	15.9 (13.4,19.4)	< 0.001[a]
PT-INR	1.24 (1.12,1.39)	1.20 (1.11,1.32)	1.36 (1.14,1.65)	< 0.001[a]
FIB (g/L)	4.2 (2.7,5.7)	4.5 (3.1,5.9)	3.5 (2.0,5.3)	< 0.001[a]
FDP (mg/L)	15.80 (7.73,37.53)	14.90 (7.33,34.40)	17.40 (8.40,44.40)	0.124[a]
DD (mg/L)	4.50 (2.22,11.86)	4.34 (2.22,10.27)	4.95 (2.27,13.59)	0.232[a]
The diagnosis of coagulopathy				

BMI: body mass index; SIRS: Systemic Inflammatory Response Syndrome; SOFA: Sequential Organ Failure Assessment; APACHE ：Acute Physiology and Chronic Health Evaluation ；PLT: platelet count; APTT: activated partial thromboplastin time; PT: prothrombin time; PT-INR: prothrombin time international normalized ration; FIB: fibrinogen; FDP: fibrin or fibrinogen degradation products; DD: D-dimer

[a] Mann-Whitney U test; [b] Pearson's chi-square tests; [c] Fisher's exact tests

	All (n = 452)	Survivor (n = 320)	Non-survivor (n = 132)	*P*
SIC	115 (25.4)	64 (20.0)	51 (38.6)	< 0.001[b]
JAAM DIC	202 (44.7)	137 (42.8)	65 (49.2)	0.211[b]
ISTH overt-DIC	55 (12.2)	24 (7.5)	31 (23.5)	< 0.001[b]
Treatment on the day of diagnosis				
Renal replacement	16 (3.5)	6 (1.9)	10 (7.6)	0.009[c]
Blood product	85 (18.8)	48 (15.0)	37 (28.0)	0.001[b]
Anticoagulation	92 (20.4)	73 (22.8)	19 (14.4)	0.043[b]
Antiplatelet	8 (1.8)	7 (2.2)	1 (0.8)	0.447[c]
Respiratory support			0.001[b]	
Invasive	112 (24.8)	63 (19.7)	49 (37.1)	< 0.001[b]
Noninvasive	274 (60.6)	206 (64.4)	68 (51.5)	0.011[b]
no	66 (14.6)	51 (15.9)	15 (11.4)	0.211[b]
The average daily cost (RMB yuan/day)	3567.39 (2390.05,5650.66)	2996.43 (2152.56,4530.24)	6484.51 (4403.76,10648.10)	< 0.001[a]

BMI: body mass index; SIRS: Systemic Inflammatory Response Syndrome; SOFA: Sequential Organ Failure Assessment; APACHE ：Acute Physiology and Chronic Health Evaluation ；PLT: platelet count; APTT: activated partial thromboplastin time; PT: prothrombin time; PT-INR: prothrombin time international normalized ration; FIB: fibrinogen; FDP: fibrin or fibrinogen degradation products; DD: D-dimer

[a] Mann-Whitney U test; [b] Pearson's chi-square tests; [c] Fisher's exact tests

SIC, JAAM DIC, ISTH overt DIC, and Coagulation Parameters

Of the study cohort, 115 patients (25.4%) were diagnosed as positive for SIC, 202 patients (44.7%) had a diagnosis of JAAM DIC, and 55 patients (12.2%) had disease that was consistent with ISTH overt DIC (Table 1). There was a significant difference in the positive rate of SIC and ISTH overt DIC between the survivors and the nonsurvivors (20.0% *vs.* 38.6%, $P < 0.001$ and 23.5% *vs.* 7.5%, $P < 0.001$, respectively), while there was no significant difference in the positive rate of JAAM DIC between the two groups (42.8% *vs.* 49.2%, $P = 0.211$) (Table 1). The 28-day all-cause mortality of the patients with SIC was 44.3% (51 of 115 patients) *vs.* 24.0% (81 of 337 patients), $P < 0.001$ (between-group difference). For those who satisfied ISTH overt DIC, mortality was 56.4% (31 of 55 patients) *vs.* 25.4% (101 of 397 patients), $P < 0.001$ (between-group difference), when compared with the negative group. No significant difference in mortality between the JAAM DIC-positive and JAAM DIC-negative groups was observed (32.3% *vs.* 26.8%, $P = 0.211$). The distributions of each score and their relationship with 28-day all-cause mortality are presented in Figure s1.

For the coagulation parameters at baseline (Table 1), APTT, PT and PT-INR were higher ($P < 0.001$), and FIB was lower ($P < 0.001$) among the nonsurvivors. In contrast, PLT, FDP and DD did not differ between the survivors and the nonsurvivors ($P = 0.622$, $P = 0.124$, $P = 0.232$, respectively). The distribution of each coagulation parameter is detailed in Figure s2.

Univariate and multivariate analyses of 28-day all-cause mortality

Both univariate logistic regression analyses and multivariate analyses were performed to examine the association between mortality and each variable (Table 2). The multivariate analyses showed that the diagnosis of SIC and ISTH overt DIC were independently associated with 28-day all-cause mortality (RR, 2.493 [95% CI 1.414–4.396], $P = 0.002$ and RR, 3.925 [95% CI 1.810–8.512], $P = 0.001$), in contrast to the diagnosis of JAAM DIC (RR, 1.115, [95% CI 0.660–1.182], $P = 0.684$).

Table 2
The univariate and multivariate analyses of 28-day All-cause Mortality.

Predictor	Univariate		Multivariate					
			Model-1		Model-2		Model-3	
	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Male	1.069 (0.695,1.645)	0.091						
Age (years)	1.015 (1.004,1.027)	0.008	1.011 (0.995,1.027)	0.183	1.010 (0.995,1.026)	0.198	1.015 (0.999,1.032)	0.070
BMI (Kg/m^2)	0.931 (0.889,0.976)	0.003	0.952 (0.901,1.007)	0.086	0.953 (0.902,1.007)	0.088	0.959 (0.906,1.014)	0.141
The initial site of infection								
Intra-abdominal	0.592 (0.393,0.892)	0.012	1.281 (0.557,2.948)	0.560	1.242 (0.548,2.817)	0.604	1.543 (0.652,3.654)	0.324
Respiratory	1.982 (1.268,3.100)	0.003	3.032 (1.221,7.530)	0.017	2.852 (1.163,6.995)	0.022	3.439 (1.355,8.728)	0.009
Bone and soft tissue	2.436 (1.167,5.085)	0.018	4.166 (1.308,13.263)	0.016	3.718 (1195,11.563)	0.023	5.018 (1.545,16.297)	0.007
Bloodstream	0.714 (0.280,1.821)	0.481						
Urinary tract	0.231 (0.053,1.002)	0.050						
Others	0.880 (0.460,1.685)	0.701						
SIRS	0.989 (0.823,1.188)	0.905						
SOFA	1.176 (1.117,1.238)	< 0.001						
APACHE II	1.097 (1.061,1.134)	< 0.001	1.067 (1.018,1.117)	0.006	1.075 (1.027,1.125)	0.002	1.060 (1.011,1.110)	0.015
Laboratory parameters								
PLT (∗10^9/L)	1.001 (0.999,1.003)	0.483						
APTT (s)	1.021 (1.007,1.035)	0.003						
PT (s)	1.203 (1.128,1.284)	< 0.001						
PT-INR	7.943 (3.810,16.558)	< 0.001						
FIB (g/L)	0.774 (0.668,0.871)	< 0.001						
FDP (mg/L)	1.007 (1.000,1.014)	0.044						

BMI: body mass index; SIRS: Systemic Inflammatory Response Syndrome; SOFA: Sequential Organ Failure Assessment; APACHE ：Acute Physiology and Chronic Health Evaluation ；PLT: platelet count; APTT: activated partial thromboplastin time; PT: prothrombin time; PT-INR: prothrombin time international normalized ration; FIB: fibrinogen; FDP: fibrin or fibrinogen degradation products; DD: D-dimer; RR: relative risk; 95% CI: 95% confidence interval.

Predictor	Univariate		Multivariate					
			Model-1		Model-2		Model-3	
	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
DD (mg/L)	1.020 (1.000,1.040)	0.055						
The diagnosis of coagulopathy								
SIC	2.519 (1.614,3.929)	< 0.001	2.493 (1.414,4.396)	0.002				
JAAM DIC	1.296 (0.863,1.946)	0.212			1.115 (0.660,1.882)	0.684		
ISTH overt-DIC	3.785 (2.122,6.753)	< 0.001					3.925 (1.810,8.512)	0.001
Treatment on the day of diagnosis								
Renal replacement	4.290 (1.526,12.058)	0.006	5.392 (1.538,18.898)	0.008	5.880 (1.748,19.783)	0.004	6.850 (1.939,24.202)	0.003
Blood product	2.207 (1.354,3.596)	0.001	1.733 (0.861,3.488)	0.123	2.014 (1.032,3.930)	0.040	1.804 (0.897,3.629)	0.098
Anticoagulation	0.569 (0.328,0.988)	0.045	0.253 (0.121,0.531)	< 0.001	0.921 (0.453,1.871)	0.820	0.238 (0.112,0.508)	< 0.001
Antiplatelet	0.341 (0.042,2.802)	0.317						
Respiratory support								
Invasive	2.644 (1.332,5.252)	0.005	0.959 (0.461,1.992)	0.910	1.115 (0.660,1.882)	0.684	0.980 (00.471,2.039)	0.957
Noninvasive	1.122 (0.593,2.123)	0.723						
no	-	0.001						

BMI: body mass index; SIRS: Systemic Inflammatory Response Syndrome; SOFA: Sequential Organ Failure Assessment; APACHE Ⅱ: Acute Physiology and Chronic Health Evaluation Ⅱ; PLT: platelet count; APTT: activated partial thromboplastin time; PT: prothrombin time; PT-INR: prothrombin time international normalized ration; FIB: fibrinogen; FDP: fibrin or fibrinogen degradation products; DD: D-dimer; RR: relative risk; 95% CI: 95% confidence interval.

Calibration and Discrimination For SIC and ISTH overt-DIC (Adjust Analysis)

The calibration of 28-day all-cause mortality was significantly higher using SIC (χ^2 = 3.222, P = 0.920) than ISTH overt-DIC (χ^2 = 14.090, P = 0.079), with the difference being statistically significant (the former's expected curve was more coincident with its observed curve) when considered in conjunction with baseline prediction mortality (Fig. 2). Both the diagnosis of SIC (AUROC, 0.779 [95% CI, 0.728–0.830], P< 0.001) and ISTH overt-DIC (AUROC, 0.782 [95% CI, 0.732–0.833], P< 0.001) performed equally well in the discrimination of 28-day all-cause mortality (between-group difference: SIC *vs.* ISTH overt-DIC, -0.003 [95% CI, -0.025-0.018], P = 0.766) when adjusted (Fig. 3).

The calibration and discrimination of the JAAM DIC diagnosis were not reported in this article because it was not defined as an independent predictor of death, as previously described.

Discussion

In the early onset of sepsis, along with inflammation, the coagulation system is usually activated in the host as a defensive role to absorb and remove microorganisms. However, as inflammation continues, coagulation dysfunction occurs because of the widely activated coagulation system, the collapsed anticoagulation system, and so on. Coagulation dysfunction, manifested by thrombosis and the consumption of platelets and clotting factors, is considered to be an important factor leading to poor prognosis in sepsis. Therefore, the establishment of diagnostic criteria is crucial for identifying patients, guiding treatment, and determining prognosis.

However, there is no gold standard, and the results of previous studies are controversial. Although with high specificity, ISTH overt DIC may lead to a delayed diagnosis and missed opportunities for intervention by ignoring the different characteristics of coagulopathy under their basic etiologies[15]. JAAM DIC, reflecting the interaction of inflammation and coagulation, is rarely used outside Japan due to its low sensitivity[13]. SIC, which is easy to calculate and consistent with the pathophysiology of fibrinolytic inhibition and high organ dysfunction in sepsis, has been proven to be controversial[12,16]. For example, a retrospective study conducted in the ICU of The First Hospital of China Medical University showed that there was no significant difference in the prevalence of SIC between survivors and nonsurvivors (62.9% *vs.* 74.3%, $P = 0.055$), and the predictive accuracy of SIC was less than that of ISTH overt-DIC (AUROC, 0.658±0.036 *vs.* 0.684±0.033)[17]. This study retrospectively evaluated the application of SIC, JAAM DIC, and ISTH overt-SIC scoring systems in patients with sepsis.

In this study, a total of 452 patients were included, whose mortality was 29.9%, which was similar to the 24.4%-35.5% reported previously[18–21]. The positive rates of each scoring system were lower than those of previous studies (60.8%-84.8% for SIC[12,17,22–24], 61.0%-91.4% for JAAM DIC[13,14,22,25], and 20.3%-29.3% for ISTH overt-DIC[14,17,22,23,25]), which may be because the patients included in the previous studies, whose SOFA and APACHE II scores were higher than those in this research, were only admissible from the ICU, in addition to the general wards[17,22–26]. Consistent with previous studies, the positive rate of SIC in this current study was approximately twice that of ISTH overt DIC[22,27,28], which may be related to the inclusion of FIB in the latter. FIB is an acute-phase protein important to the coagulation cascade[29], but studies of its cutoff in sepsis with coagulopathy are inconclusive[30]. Previous studies and this study have shown that FIB levels are elevated in the early stage of sepsis, which may result from the release of plasminogen activation inhibitor-1 (PAI-1), and the activation of thrombin activates fibrinolytic inhibitors (TAFI)[31,32]. Therefore, the cutoff value of FIB $\leq$ 1.0 g/L in the ISTH overt-DIC scoring system may reduce the diagnostic efficacy[33,34]. It is worth mentioning that the prognostic calibration of SIC in this study was higher than that of ISTH overt DIC, and there were no previous studies available for comparison.

We found that the positive rate of JAAM DIC was not significantly different between the survivors and the nonsurvivors, as was the mortality between the JAAM DIC positive and negative groups. We also found that the diagnosis of JAAM DIC was not independently associated with 28-day all-cause mortality in sepsis. These negative results should be related to the statistical indifference in SIRS (3 *vs.* 2 points, $P = 0.831$), FDP (14.90 *vs.* 17.40 mg/L, $P = 0.124$) and DD (4.34 *vs.* 4.95 mg/L, $P = 0.232$). Several cohort studies have shown that the SIRS criteria, with its high sensitivity and low specificity, can lead to overdiagnosis and overtreatment[35,36]. In recent years, it has been found that FDP and DD, which are biomarkers of hypercoagulability and fibrinolysis, are generally elevated in patients with infection or suspected infection, regardless of the severity[37].

In conclusion, compared with JAAM DIC and ISTH overt-DIC, the SIC scoring system had the best prognostic prediction ability and was the simplest to calculate. However, questions such as the pathophysiological state of patients with the diagnosis of SIC and whether the SIC can be used to guide the selection of intervention timing still need further research. In addition, the combination of novel biomarkers (e.g., neutrophil extracellular traps, NETs), emerging detection technologies (e.g., thromboelastometry, TEG), or machine learning and traditional indicators is expected to be a new direction of research[38–42].

Strengths

This study had several strengths. First, this study, in which all of the patients in general wards and ICUs were included, covered a wider range of patients than other studies, which included patients with ICU admission only. Second, this study offered a more

comprehensive and objective summary that can be useful in guiding clinical practice by conducting pairwise comparisons of different scoring systems.

Limitations

First, this study is a single-center, retrospective study of low quality, and the conclusions still need further verification by prospective, multicenter, and large-sample studies. Second, in this study, the relationship between continuous dynamic changes in coagulation function and prognosis could not be explored, and only the clinical data on the day of enrollment could be collected. Third, this study only evaluated the prognostic prediction performance of each scoring system, and whether each of them can be used to guide anticoagulation therapy needs further observation. Fourth, deep vein thrombosis, bleeding, and other indices were not included in this study due to data limitations.

Conclusions

In our study, the SIC scoring system, in comparison with JAAM DIC and ISTH overt-DIC, demonstrated superior prognostic prediction ability for 28-day all-cause mortality among patients with sepsis and abnormal coagulation. Research with a larger sample size, more comprehensive outcomes, and further confounders is necessary.

Non-standard Abbreviations And Acronyms

Abbreviations And Acronyms	Full name
SIC	Sepsis Induced Coagulopathy
JAAM	Japanese Association of Acute Medicine
ISTH	International Society on Thrombosis and Hemostasis
DIC	Disseminated Intravascular Coagulation
ICU	Intensive Care Units
GBD	the Global Burden of Diseases, Injuries, and Risk Factors Study
WHO	World Health Organization
SOFA	Sequential Organ Failure Assessment
APTT	Activated Partial Thromboplastin Time
PT	Prothrombin Time
Fg	Fibrinogen
FDP	Fibrin or Fibrinogen Degradation Products
DD	D-dimer
BMI	Body Mass Index
SIRS	Systemic Inflammatory Response Syndrome
APACHE-II	Acute Physiology and Chronic Health Evaluation
PT-INR	Prothrombin Time International Normalized Ration
PPT	Prolonged Prothrombin Time
Tol	Tolerance
VIF	Variance Inflation Factor
ROC	Receiver Operating Characteristic Curve
AUROC	the Area Under the Receiver Operating Characteristic Curve
CI	Confidence Interval
rTM	Recombinant Human-Soluble Thrombomodulin
PAI-1	Plasminogen Activation Inhibitors-1
TAFI	Thrombin Activates Fibrinolytic Inhibitors
HMGB1	High Mobility Group Box 1 Protein
NETs	Neutrophil Extracellular Traps
PF4	Platelet Factor 4
MPs	Microparticles
MP-TF	Microparticle-Associated Tissue Factor
TEG	Rotational Thromboelastography
ROTEM	Thromboelastometry
RF	Random Forests

Abbreviations And Acronyms	Full name
SVM	Support Vector Machines
NN	Neural Networks
vs.	Versus

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ruijin Hospital of Shanghai Jiao Tong University School of Medicine, China (approval number: 20191101; approval date: August 20, 2020).

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

Chen YW and Chen WW contributed equally to this article. Chen EZ and Mao EQ conceived the idea for this project. Chen Y, Yang ZT, Chen WW and Chen YW designed the study. Ba FH, Zheng YJ, Zhou Yi and Shi W contributed to the data analysis and synthesis. Chen YW and Li J performed the statistical analyses. Chen YW and Chen WW wrote the paper. All authors contributed to the survey development, pilot phase, the revision of the paper and approval of the final version for submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

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Figures

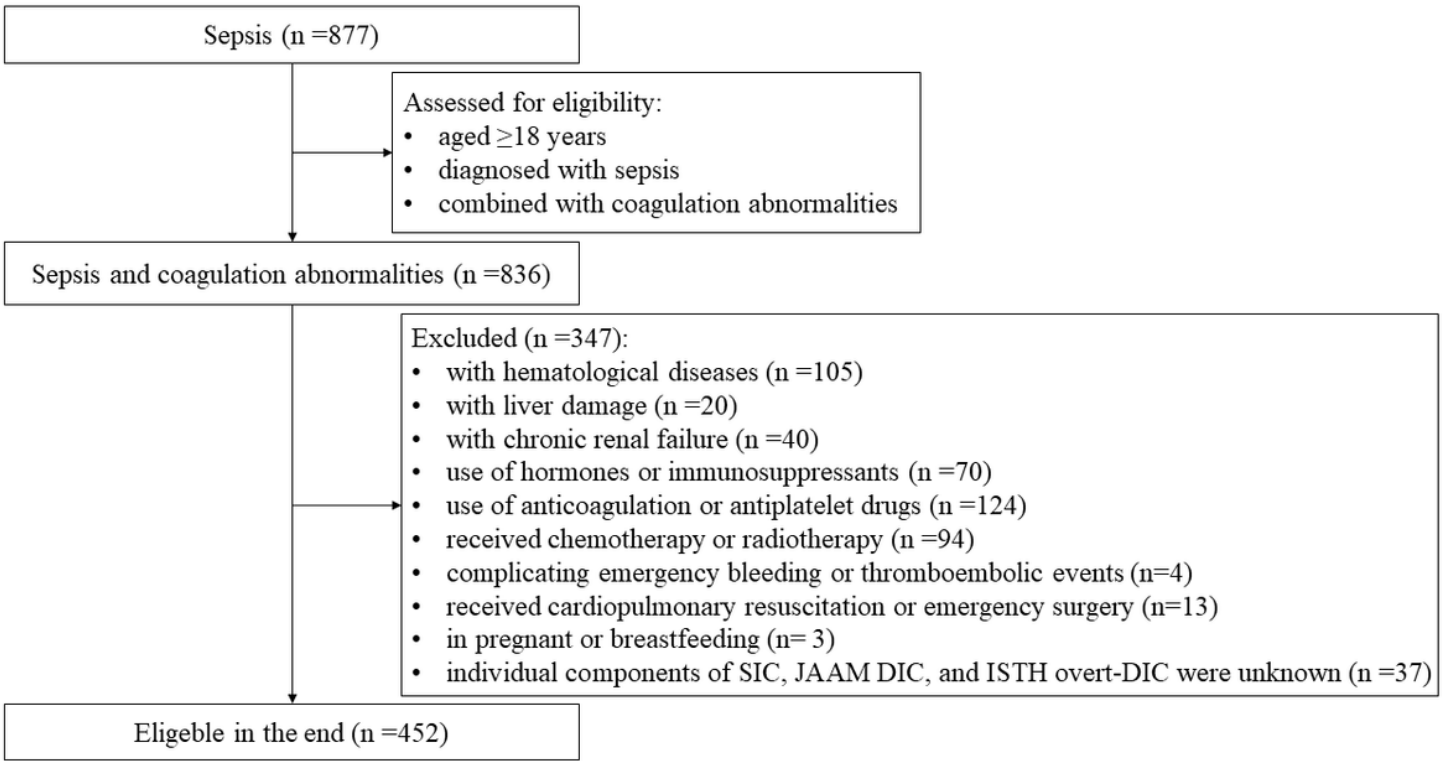


Figure 1

Eligible population and exclusion criteria. Data pertaining to 836 adult admissions were recorded for the period 2017-2019, drawn from general wards and ICU in Ruijin Hospital, Shanghai Jiaotong University School of Medicine. Following restriction, a final cohort of 452 cases was identified.

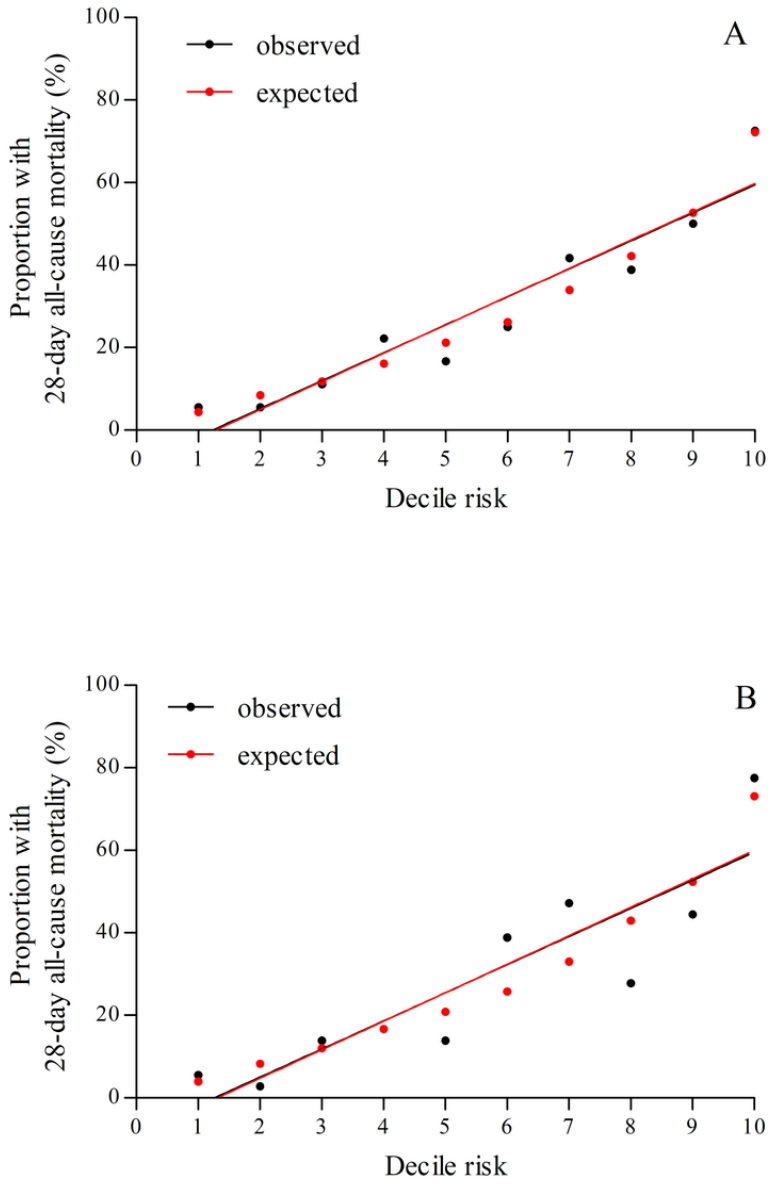
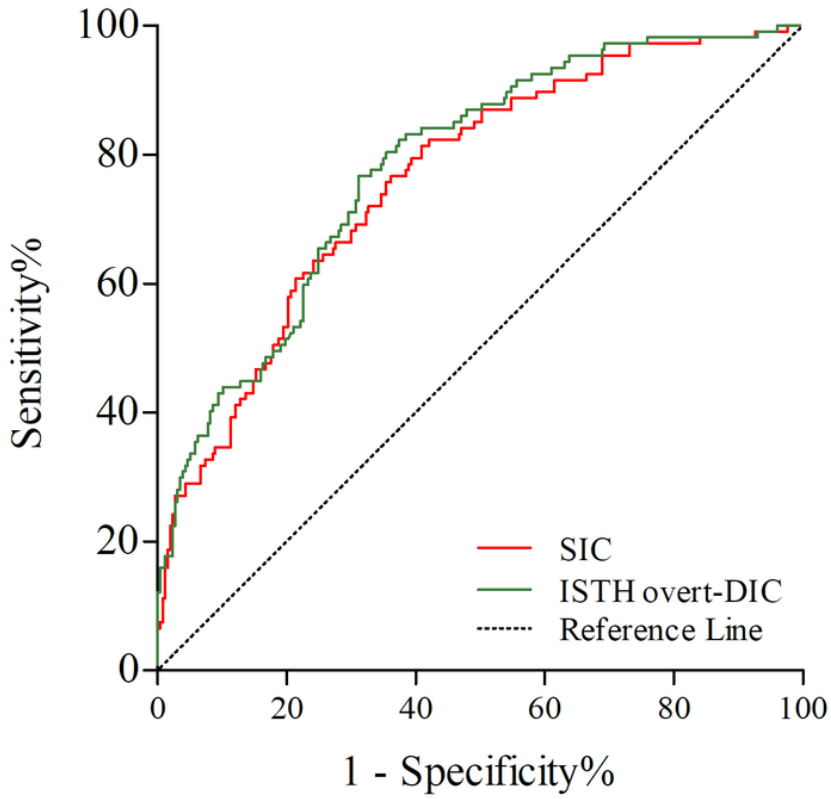


Figure 2

A-B. SIC and ISTH overt-DIC calibration plot of expected vs observed rates of 28-day all-cause mortality (n =364 after adjustment).

A. SIC calibration plot of expected vs observed rates of 28-day all-cause mortality; B. ISTH overt-DIC calibration plot of expected vs observed rates of 28-day all-cause mortality. Black dots represent the observed outcome risk, and red dots represent the expected outcome risk.



SIC		ISTH overt-DIC		Between-Group Difference (SIC vs. ISTH overt-DIC)	
AUROC (95% CI)	*P*	AUROC (95% CI)	*P*	AUROC (95% CI)	*P*
0.779 (0.728-0.830)	<0.001	0.782 (0.732-0.833)	<0.001	-0.003 (-0.025-0.018)	0.766

Figure 3

Area under the receiver operating characteristic Curves (AUROCs) for discriminatory capacity for 28-day all-cause mortality for SIC and ISTH overt-DIC (diagnose of each scoring system) (n =364 after adjustment)

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