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ORIGINAL RESEARCH

Sepsis-induced coagulopathy (SIC) score is an independent predictor of mortality and overt-disseminated intravascular coagulation in emergency department patients with sepsis

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Abstract

Sepsis is frequently associated with coagulation anomalies which can contribute to multiple organ dysfunction and death through a mechanism of microvascular thrombosis and possible evolution to consumption coagulopathy. The recently introduced SIC (sepsis-induced coagulopathy) score was developed for the early identification of sepsis-associated coagulopathy. This study aims to evaluate the predictive value of the SIC score for in-hospital mortality and clinically significant complications in emergency department (ED) patients with sepsis. This is a retrospective, observational cohort study including patients with a diagnosis of sepsis admitted to the hospital after an ED evaluation in a period of one year (January 2021 to December 2021). The SIC score was retrospectively calculated from the electronic clinical records of our hospital. The primary outcome was in-hospital mortality; secondary outcomes were coagulopathy-related clinical complications (disseminated intravascular coagulation, bleeding, thrombosis, blood component transfusion, and organ injury). Univariate and multivariate logistic regression analyses were used to assess the association between a positive SIC score and the study endpoints. The study cohort consisted of 357 septic patients. Overall, 82 (23.0%) patients died during hospital stay, and 27 patients (7.6%) developed overt disseminated intravascular coagulation (DIC) At multivariate logistic regression analysis, a positive SIC score at ED admission was an independent predictor of in-hospital mortality, with an Odd Ratio (OR) of 2.28 (95% confidence interval, 1.16–4.48). In addition, the SIC score was an independent predictor for the development of overt-DIC (OR 10.39, (95% CI, 4.08–26.46)), new organ injury (OR 6.33, (95% CI, 2.90–13.83)), bleeding (OR 4.83, (95% CI, 2.22–10.50)) and thrombotic events (OR 9.48, (95% CI, 2.95–30.40)), as well as the need for blood component transfusion (OR 5.28, (95% CI, 2.35–11.83)). In ED patients with sepsis, the SIC score is an early predictor of in-hospital mortality and the development of severe coagulopathy-related complications.

Keywords

Sepsis; Septic coagulopathy; Disseminated intravascular coagulation; SIC score; Emergency department

1. Background

Sepsis is frequently accompanied by coagulation anomalies, probably as an expression of the cross-talk between inflammation and coagulation that occurs as part of the life-threatening host response to infection [1, 2]. Coagulation abnormalities in sepsis can range from a subtle hypercoagulable state that is virtually undetectable by routine laboratory markers to a stronger activation in coagulation that can be detected by a subclinical and indolent prolongation of coagulation times and a slight decrease in platelet count, up to devastating clinical scenarios as seen in disseminated intravascular coagulation (DIC) with widespread thrombosis and profuse bleeding [3]. It has been speculated that the systemic hyper-activation of coagulation that is seen in sepsis results in a widespread microvascular thrombosis and intravascular deposition of fibrin

which contributes to multiple organ dysfunction and tissue hypoxia [4]. Accordingly, DIC has been previously described as an independent predictor of organ failure and mortality in septic patients [5] and is increasingly considered as one of the main complications that affect sepsis outcomes together with cardiocirculatory shock [6, 7]. However, it is well known that overt-DIC is mostly a late complication of sepsis and that the internationally validated score for overt-DIC detection has very strict criteria. Moreover, the timing of diagnosis utilizing the standard "DIC score" might be too late to allow for potential therapeutic interventions [6].

In recent years, a new diagnostic tool for sepsis-induced coagulopathy, the "SIC score", was established by the International Society on Thrombosis and Hemostasis (ISTH) [8] to allow early and relatively simple recognition of coagulopathy in patients with sepsis. The SIC score seems to detect early derangements in coagulation before the development of clinically significant complications, such as seen in overt-DIC [9, 10], and it could be easily calculated at the patients' bedside with little data. Subtle sepsis-related coagulopathy detected by SIC can both be seen as part of a continuum between normal coagulation and the development of overt-DIC, but also as an independent factor that contributes to the development of multiple organ dysfunction through a mechanism of diffuse microvascular thrombosis [11]. At present, however, the clinical significance and the predictive role of the SIC score for sepsis-induced coagulopathy obtained immediately upon ED admission are still unknown.

2. Methods

This is a single-center, retrospective, observational cohort study conducted in an urban teaching hospital with a catchment area of about 1.8 M inhabitants and an average ED access of 75,000/year. Patient data were collected from the electronic clinical records from January to December 2021. The study enrolled all the consecutive adult patients evaluated in the ED and diagnosed with sepsis based on the SEPSIS-3 criteria [12] (presence of infection with an increase of Sequntial Organ Failure Assessment (SOFA) score $\geq$2 from baseline), and who were subsequently admitted to the hospital (either general ward or intensive-care unit).

Inclusion criteria were a sepsis diagnosis as the main cause of the ED visit followed by hospital admission, complete clinical data, together with an available full laboratory panel (within 6 hours of ED admission).

Exclusion criteria were known cancer or hematologic disease, major trauma, and pregnancy.

After the patient's selection, clinical records were reviewed to extract study variables, including symptoms and timing at ED admission, vital parameters and laboratory values. Laboratory values which were considered were complete blood count, inflammation markers (C-reactive protein and procalcitonin), renal and hepatic function, and coagulation study. Based on the vital parameters at admission, the National Early Warning Score (NEWS) score was calculated for all the patients. All the study variables were reassessed at 48 hours and seven days after admission. The research follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.1 Study endpoints

Our primary endpoint was the predictive value of a positive SIC score calculated at ED admission for all-cause in-hospital death. As secondary outcomes, we considered the predictive value of the SIC score for the development of clinically significant complications related to septic coagulopathy, including the development of overt-DIC, clinically significant bleeding and/or major thrombotic event, need for blood component transfusion, and development of new organ injuries.

2.2 Outcome measures

The SIC score was calculated according to the previously published criteria by Iba *et al.* [13] (Fig. 1). Three parameters are considered for the calculation of the SIC score: international normalized ratio (INR), platelet count, and SOFA four-item score (hepatic, renal, respiratory and cardiovascular). SIC score was considered positive with a total of 4 points or more, provided that the sum of platelet and INR sub-scores exceeds 2. In our cohort of patients, we considered a positive SIC score if the sum of the platelet and INR sub-scores was $\geq$2 and the four-item SOFA baseline score was $\geq$2 (Table 1).

The development of overt-DIC was diagnosed according to the ISTH overt-DIC criteria, with a total score $\geq$5 positive for overt-DIC [14].

All the study variables and the primary and secondary outcomes were assessed according to the electronic health records of our institution. The patients' records were thoroughly examined by three different authors (GT, FLD, GC) to ensure consistency and data reproducibility.

Extracted data included the occurrence during the hospital stay of:

- Clinically evident bleeding (gastrointestinal hemorrhage, intracranial hemorrhage, bleeding from a catheter, or percutaneous drainage skin insertion with the need of compression or surgical control).
- Major thrombotic events (deep venous thrombosis, pulmonary embolism, arterial thrombotic events of non-cardioembolic origin).
- Need for blood component transfusion (red cells, platelet pools and fresh frozen plasma).
- New onset or worsening of renal, hepatic, respiratory, cardiovascular or neurological injury. Organ injuries were assessed according to the most recent definitions and guidelines [15–19].

2.3 Statistical analysis

Continuous variables are reported as median (interquartile range). Categorical variables are reported as absolute numbers (%). Statistical univariate comparison for primary and secondary outcomes was assessed by the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables (with Fisher test if appropriate). Significant factors in the univariate analysis were entered into a multivariate logistic regression model to identify independent predictors of the defined outcomes. Multivariate

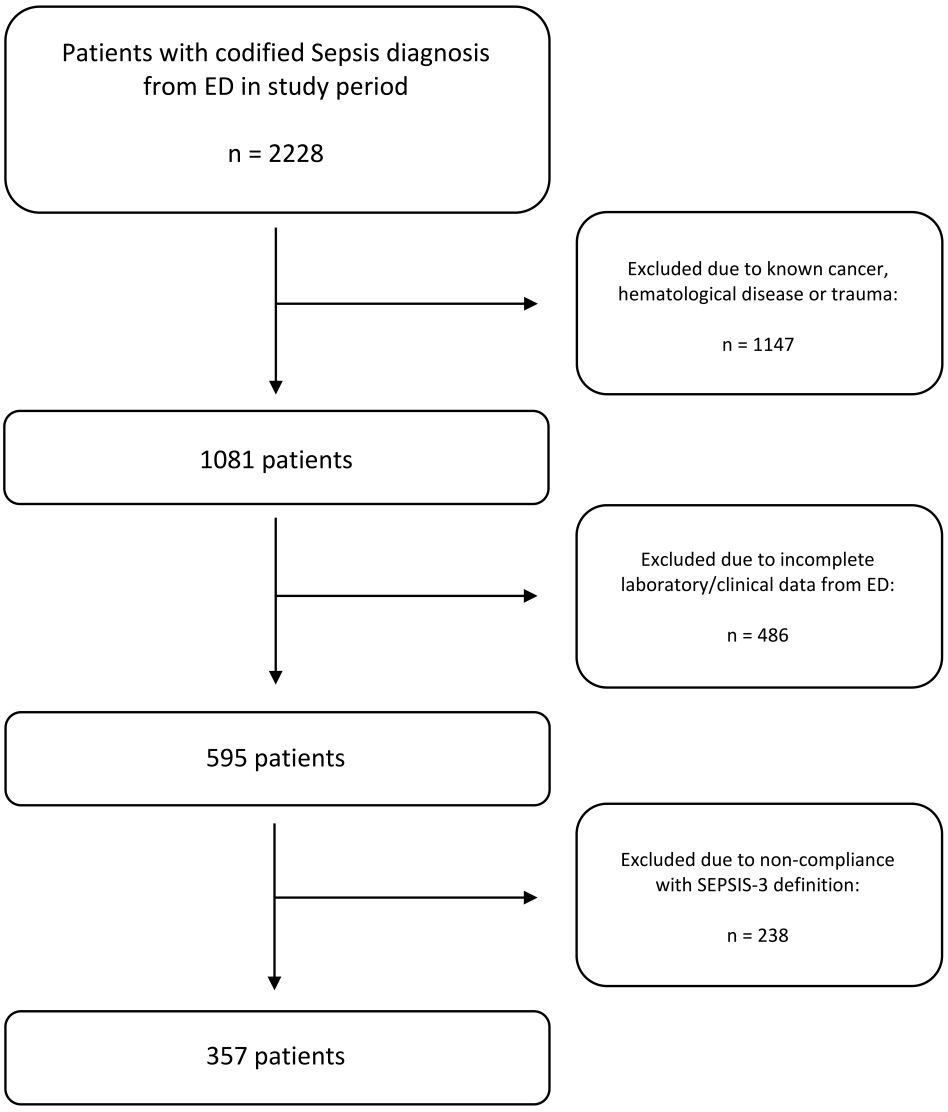

FIGURE 1. Study cohort enrollment flowchart. ED: emergency department.

TABLE 1. Sepsis-induced coagulopathy score. SIC score is considered positive with a total score of 4 or more, provided that the sum of PT-INR and platelet count sub-score exceeds 2. Total SOFA score is the sum of four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, renal SOFA).

Parameter	0 point	1 point	2 points
PT-INR	≤1.2	>1.2	≥1.4
Platelet count ($\times 10^9$/L)	≥150	<150	<100
Total SOFA score	0	1	≥2

INR: international normalized ratio; PT: prothrombin time; SOFA: sequential organ failure assessment.

models excluded the single items composing any derived or composed variable, both to avoid model overfitting and parameter overestimation.

The significance was established for a two-sided p-value < 0.05. Only one decimal digit was reported and rounded up. Data were analyzed by SPSS v25® (IBM, Armonk, NY, USA).

3. Results

Overall 2228 patients with suspected sepsis were assessed for inclusion in our study. Among them, 357 patients with confirmed sepsis fulfilling the study criteria were included in the study cohort (Fig. 1). Their median age was 79 years (interquartile range (IQR) 69–84), and 185 (51.8%) were male.

The majority of patients in the study cohort had a NEWS score <5 ad admission (NEWS >5: 19.0%; NEWS 3–5: 32.3%; NEWS <3: 48.7%), and the most commonly identified septic focus was urinary tract (48.7%) followed by respiratory tract (13.7%). In 55 patients (15.4%), the septic focus remained unknown upon ward admission. Two hundred thirty-seven patients (66.4%) had a positive result in the blood culture obtained in the ED.

The prevalence of a positive SIC score at ED admission was 15.4% (55 patients).

Overall, 82 patients (23.0%) died, and 27 (7.6%) developed an overt-DIC during the hospital stay.

Patients positive for SIC score had a significantly different NEWS score at admission (Table 2), had a lower rate of chronic antiplatelet medication use (9.1% *vs.* 21.5%, $p = 0.033$), and more often had a coexistent COVID-19 infection (9.1% *vs.* 2.3%, $p = 0.010$). Similarly, serum creatinine (2.0 (IQR, 1.5–2.8) *vs.* 1.3 (IQR, 0.9–2.0), $p < 0.001$), C-reactive protein (200 (IQR, 134–241) *vs.* 151 (IQR, 81–232), $p < 0.026$) and procalcitonin (18.8 (IQR, 4.0–61.8) *vs.* 4.5 (IQR, 0.7–22.8), $p < 0.001$) significantly differed between the two groups (Table 2).

3.1 Association between SIC score and study endpoints

At univariate analysis, a positive SIC score at admission was significantly associated with in-hospital death (26.8% *vs.* 12.0%, $p < 0.001$). Deceased patients were also older (83 years (IQR, 78–87) *vs.* 77 (IQR, 66–84), $p = 0.001$), had a worse NEWS score at admission (NEWS >5: 37.8% *vs.* 13.5%; NEWS 3–5: 37.8% *vs.* 30.5%; NEWS <3: 20.4% *vs.* 56.0%, $p < 0.001$), were more frequently on chronic anticoagulant therapy (39.0% *vs.* 24.9%, $p = 0.013$), had coexistent COVID-19 infection (8.5% *vs.* 1.8%, $p = 0.003$), and higher white-blood-cell count (16.01 (IQR, 10.8–21.5) *vs.* 12.97 (IQR, 8.2–18.7), $p = 0.010$) (Table 3). The multivariate analysis confirmed the SIC score as an independent predictor for poor outcome (OR 2.28 (95% CI, 1.16–4.48), $p = 0.017$) along with NEWS >5 at admission (OR 4.36 (95% CI, 2.14–8.90), $p < 0.001$), and older age (OR 1.04, (95% CI, 1.01–1.07), $p = 0.001$) (Table 3).

3.2 Association of SIC score with secondary endpoints

Overall, 27 patients developed an overt disseminated intravascular coagulation (7.6%). At the ED evaluation, these patients had a higher prevalence of positive SIC score (63.0% *vs.* 11.5%, $p < 0.001$) along with higher NEWS, a higher prevalence of COVID-19 infection, and a higher value of procalcitonin and creatinine. At multivariate, logistic regression analysis, only positive SIC score (OR 10.39 (95% CI, 4.08–26.46), $p < 0.001$) and COVID-19 infection (OR 9.11 (95% CI, 2.14–38.78), $p = 0.003$) showed a significant independent predictive association with overt-DIC during hospitalization (Table 4). Similar results were observed with other sepsis-induced coagulopathy-related outcomes developed during the hospital stay. A positive SIC score in the ED was an independent predictor of new organ injury (OR 6.33, (95% CI, 2.90–13.83), $p < 0.001$), significant thrombotic complications (OR 9.48, (95% CI, 2.95–30.40), $p < 0.001$), major bleeding events (OR 4.83, (95% CI, 2.22–10.50), $p < 0.001$), as well as of the need for blood component transfusion (OR 5.28, (95% CI, 2.35–11.83), $p < 0.001$) (Fig. 2). We also observed that a NEWS score >5 at ED admission was predictive of organ injury (OR 3.58, (95% CI, 1.88–6.82), $p < 0.001$), as well as the procalcitonin value (OR 1.01, (95% CI, 1.00–1.02), $p = 0.014$). Similarly, a history of heart failure was an independent predictor for the development of major thrombotic events (OR 5.63, (95% CI, 1.70–18.68), $p = 0.005$), while COVID-19 infection (OR 7.74 (95% CI, 1.71–35.02), $p = 0.008$) and lower baseline hemoglobin (OR 0.58, (95% CI, 0.48–0.70), $p < 0.001$) were independently associated with the need of blood component transfusion during hospital stay. Finally, higher creatinine (OR 1.26, (95% CI, 1.10–1.44), $p = 0.001$) and lower fibrinogen levels (OR 0.99, (95% CI, 0.99–1.00), $p = 0.022$) were independently predictive for clinically significant bleeding events (**Supplementary Tables 1,2,3,4**).

4. Discussion

The major finding of the present study is that the easy-to-calculate SIC score could be predictive of a poor outcome for septic patients since ED admission. A positive SIC score is an independent predictor of most of the relevant clinical outcomes evaluated, including all-cause in-hospital death, development of DIC, development of organ injuries, major bleeding, and major thrombotic events.

The prevalence of positive SIC in the study cohort was 15.4%, a value similar to previous reports on early septic coagulopathy diagnosed using the SIC score in Europe [20]. It has been shown by previous studies that, in the majority of patients, a positive SIC score develops early from sepsis onset, and that only a minority of patients (around 6%) will present with a new positive score at later stages [20]. It should be noted that a significantly higher incidence of positive SIC score is observed in patients admitted to the ICU or in patients with septic shock (40–60%) [21], probably reflecting a higher severity of disease in these cohorts of patients. Nonetheless, it has been noted that at advanced stages of disease (patients with septic shock or admitted to ICU), the SIC score does not perform better than other traditional scores (*i.e.*, ISTH-DIC score) as a predictor of sepsis-associated coagulopathy or DIC [22]. Therefore, we suggest that the optimal timing of SIC score calculation should be early upon disease onset, and the ED might be the right setting for the utilization of this score. In fact, in our cohort, a positive SIC score calculated upon ED admission resulted in being independently predictive of in-hospital mortality, similar to the NEWS score [23, 24]. More relevant, a positive SIC score was independently predictive of the development of new organ injury (with a better performance compared to the NEWS score) and progression to advanced stages of septic-coagulopathy, including the development of serious clinical complications such as bleeding, thrombosis, and overt DIC (Fig. 2). Interestingly, a higher procalcitonin value was an independent predictor for the development of new organ injury in our cohort of patients. It has been previously reported that procalcitonin level in septic patients significantly correlates with adverse outcomes such as organ failure and death, so our observations are in line with previous research [25–28]. Furthermore, we observed that mean values of procalcitonin measured in the ED were significantly higher in those patients who later developed overt-DIC compared to patients who did not, even if this finding was not statistically significant in multivariate analysis. It has been previously reported that procalcitonin level is an independent predictor of DIC in pa-

TABLE 2. Baseline characteristics and clinical outcomes of the patients included in the study cohort.

	All patients (n. 357)	SIC positive in ED (n. 55)	SIC negative in ED (n. 302)	*p*
Anamnestic data:				
Age (yr)	79 (69–84)	80 (72–86)	79 (69–84)	0.335
Sex (male)	185 (51.8%)	35 (63.6%)	150 (49.7%)	0.057
NEWS score				
>5	68 (19.0%)	16 (29.1%)	52 (17.2%)	
3–5	115 (32.3%)	22 (40.0%)	93 (30.8%)	0.012
<3	174 (48.7%)	17 (30.9%)	157 (52.0%)	
Symptom duration (d)	2 (1–3)	2 (1–3)	2 (1–3)	0.863
Symptom duration >7 days (yes)	25 (7.0%)	3 (5.5%)	22 (7.3%)	0.625
Length of stay (d)	11.6 (6.6–19.4)	12.1 (5.6–20.0)	11.5 (7.0–19.0)	0.840
Chronic immunosuppressive therapy (yes)	38 (10.6%)	6 (10.9%)	32 (10.6%)	0.945
Chronic anticoagulant therapy (yes)	100 (28.2%)	16 (29.1%)	84 (28.0%)	0.869
Chronic antiplatelet therapy (yes)	70 (19.6%)	5 (9.1%)	65 (21.5%)	0.033
COVID-19 (yes)	12 (3.4%)	5 (9.1%)	7 (2.3%)	0.010
Comorbidities:				
Ischemic cardiomyopathy	74 (20.7%)	8 (14.5%)	66 (21.9%)	0.219
Heart failure	107 (30.0%)	17 (30.9%)	90 (29.8%)	0.869
TIA/stroke	69 (19.3%)	12 (21.8%)	57 (18.9%)	0.611
Dementia	139 (38.9%)	21 (38.2%)	118 (39.1%)	0.901
COPD	35 (9.8%)	4 (7.3%)	31 (10.3%)	0.492
Cirrhosis	9 (2.5%)	4 (7.3%)	5 (1.7%)	0.015
Diabetes	88 (24.6%)	10 (18.2%)	78 (25.8%)	0.226
CKD	71 (19.9%)	16 (29.1%)	55 (18.2%)	0.063
Sepsis focus:				
Unknown	55 (15.4%)	15 (27.3%)	40 (13.2%)	
Pulmonary	49 (13.7%)	7 (12.7%)	42 (13.9%)	
Urinary	174 (48.7%)	23 (41.8%)	151 (50.0%)	0.120
Abdomen	31 (8.7%)	5 (9.1%)	26 (8.6%)	
Bloodstream infection	11 (3.1%)	0 (0.0%)	11 (3.6%)	
Other	37 (10.4%)	5 (9.1%)	32 (10.6%)	
Positive cultural exam	237 (66.4%)	34 (61.8%)	203 (67.2%)	0.053
Laboratory parameters:				
Hemoglobin (g/dL)	11.2 (9.8–12.8)	11.6 (9.7–13.8)	11.2 (9.8–12.6)	0.208
WBC ($\times 10^9$/L)	13.4 (8.6–19.1)	14.1 (6.5–20.4)	13.3 (8.8–18.9)	0.947
Platelets ($\times 10^9$/L)	205 (137–298)	98 (72–127)	232 (168–324)	<0.001
Creatinine (mg/dL)	1.5 (0.9–2.2)	2.0 (1.5–2.8)	1.3 (0.9–2.0)	<0.001
PT (sec)	12.3 (11.4–13.7)	15.1 (13.7–19.4)	11.9 (11.3–13.0)	<0.001
aPTT (sec)	35.5 (32.2–41.0)	42.2 (37.0–56.2)	34.5 (31.5–38.8)	<0.001
INR	1.2 (1.0–1.3)	1.4 (1.3–1.9)	1.1 (1.0–1.2)	<0.001
Fibrinogen (mg/dL)	566 (425–734)	571 (397–695)	566 (427–747)	0.510
D-Dimer (ng/mL)	3739 (2038–11,029)	3387 (2454–16,197)	4053 (1998–11,002)	0.804
CRP (mg/dL)	160 (88–234)	200 (134–241)	151 (81–232)	0.026
Procalcitonin (ng/mL)	5.8 (1.0–26.1)	18.8 (4.0–61.8)	4.5 (0.7–22.8)	<0.001

TABLE 2. Continued.

	All patients (n. 357)	SIC positive in ED (n. 55)	SIC negative in ED (n. 302)	*p*
Endpoints:				
In-hospital death	82 (23.0%)	22 (40.0%)	60 (19.9%)	0.001
Development of DIC	27 (7.6%)	17 (30.9%)	10 (3.3%)	<0.001
New Organ Damage	166 (46.5%)	46 (83.6%)	120 (39.7%)	<0.001
Bleeding	36 (10.1%)	16 (29.1%)	20 (6.6%)	<0.001
Thrombosis	14 (3.9%)	8 (14.5%)	6 (2.0%)	<0.001
New anticoagulant therapy	118 (33.1%)	21 (38.2%)	97 (32.1%)	0.379
Need for blood component transfusion	57 (15.9%)	20 (36.4%)	37 (12.2%)	<0.001
Need for coagulation complex	5 (1.4%)	1 (1.8%)	4 (1.3%)	0.774
ICU admission	35 (9.8%)	15 (27.3%)	20 (6.6%)	<0.001

aPTT: activated partial thromboplastin time; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CRP: c-reactive protein; DIC: disseminated intravascular coagulation; ED: emergency department; ICU: intensive care unit; INR: international normalized ratio; NEWS: national early warning score; SIC: sepsis induced coagulopathy; PT: prothrombin time; WBC: white blood cell.

TABLE 3. Statistical comparison of the clinical characteristics of the patients deceased for all-cause during the hospital stay, compared to controls. Univariate and multivariate logistic regression analysis results are shown in the table. Logistic model had a log-likelihood^{-2} value = 322.16 and a Nagelkerke R^2 = 0.241.

	In-hospital death (n. 82)	Alive at discharge (n. 275)	*p*	Odds Ratio (95% CI)	*p*
Anamnestic data:					
Age (yr)	83 (78–87)	77 (66–84)	<0.001	1.04 (1.01–1.07)	0.001
Sex (male)	48 (58.5%)	137 (49.8%)	0.166		
NEWS score					
>5	31 (37.8%)	37 (13.5%)			
3–5	31 (37.8%)	84 (30.5%)		4.36 (2.14–8.90)	<0.001
<3	20 (20.4%)	154 (56.0%)	<0.001	2.20 (1.14–4.29)	0.018
Symptom duration (days)	1.5 (1–3)	2 (1–3)	0.099		
Symptom duration >7 days (yes)	4 (4.9%)	21 (7.6%)	0.390		
Length of stay (days)	7.73 (3–19)	12.29 (7–20)	<0.001		
Chronic immunosuppressive therapy (yes)	8 (9.8%)	30 (10.9%)	0.766		
Chronic anticoagulant therapy (yes)	32 (39.0%)	68 (24.9%)	0.013		
Chronic antiplatelet therapy (yes)	17 (20.7%)	53 (19.3%)	0.770		
COVID-19 (yes)	7 (8.5%)	5 (1.8%)	0.003		
Comorbidities:					
Ischemic cardiomyopathy	18 (22.0%)	56 (20.4%)	0.756		
Heart failure	27 (32.9%)	80 (29.1%)	0.506		
TIA/stroke	18 (22.0%)	51 (18.5%)	0.493		
Dementia	38 (46.3%)	101 (36.7%)	0.117		
COPD	13 (15.9%)	22 (8.0%)	0.036	1.90 (0.83–4.32)	0.124
Cirrhosis	3 (3.7%)	6 (2.2%)	0.454		
Diabetes	21 (25.6%)	67 (24.4%)	0.818		
CKD	19 (23.2%)	52 (18.9%)	0.396		

TABLE 3. Continued.

	In-hospital death (n. 82)	Alive at discharge (n. 275)	*p*	Odds Ratio (95% CI)	*p*
Sepsis focus:					
Known focus	15 (18.3%)	40 (14.5%)	0.409	1.05 (0.50–2.21)	0.880
Unknown	15 (18.3%)	40 (14.5%)			
Pulmonary	21 (25.6%)	28 (10.2%)			
Urinary	31 (37.8%)	143 (52.0%)	0.010		
Abdomen	5 (6.1%)	26 (9.5%)			
Bloodstream infection	2 (2.4%)	9 (3.3%)			
Other	8 (9.8%)	29 (10.5%)			
Positive cultural exam	49 (59.8%)	188 (68.4%)	0.078		
Laboratory parameters:					
Hemoglobin (g/dL)	11.25 (9.4–12.8)	11.20 (9.8–12.8)	0.887		
WBC ($\times 10^9$/L)	16.01 (10.8–21.5)	12.97 (8.2–18.7)	0.010	1.01 (0.99–1.03)	0.105
Platelets ($\times 10^9$/L)	195 (121–344)	207 (140–292)	0.739		
Creatinine (mg/dL)	1.60 (1.01–2.32)	1.42 (0.95–2.18)	0.283		
PT (sec)	13.4 (12.0–15.1)	12 (11.4–13.3)	<0.001		
aPTT (sec)	37.9 (33.3–44.0)	34.5 (31.4–39.6)	<0.001		
INR	1.28 (1.13–1.46)	1.14 (1.07–1.27)	<0.001		
Fibrinogen (mg/dL)	582 (438–697)	563 (418–748)	0.875		
D-Dimer (ng/mL)	4109 (2621–7520)	3700 (2011–12,645)	0.800		
CRP (mg/dL)	169.75 (98–248)	159.35 (83–234)	0.406		
Procalcitonin (ng/mL)	3.67 (0.59–14.42)	7.27 (1.18–28.32)	0.040		
SCORE					
Positive SIC score at ED admission	22 (26.8%)	33 (12.0%)	<0.001	2.28 (1.16–4.48)	0.017

aPTT: activated partial thromboplastin time; CI: confidence interval; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CRP: c-reactive protein; ED: emergency department; INR: international normalized ratio; NEWS: national early warning score; SIC: sepsis induced coagulopathy; PT: prothrombin time; WBC: white blood cell.

TABLE 4. Statistical comparison of the clinical characteristics of the patients who developed disseminated intravascular coagulation (DIC) during the hospital stay, compared to controls. Univariate and multivariate logistic regression analysis results are shown in the table. Logistic model had a log-likelihood^{-2} value = 409.99 and a Nagelkerke R^2 = 0.248.

	Development of DIC (n. 27)	No DIC (n. 330)	*p*	Odds Ratio (95% CI)	*p*
Anamnestic data:					
Age (yr)	79 (74–85)	79 (69–84)	0.596		
Sex (male)	14 (51.9%)	171 (51.8%)	0.997		
NEWS score					
>5	10 (37.0%)	58 (17.6%)		2.76 (0.90–8.49)	0.075
3–5	9 (33.3%)	106 (32.1%)	0.028	1.11 (0.35–3.55)	0.849
<3	8 (29.6%)	166 (50.3%)			
Symptom duration (d)	2 (1–4)	2 (1–3)	0.944		
Symptom duration >7 days (yes)	2 (7.4%)	23 (7.0%)	1.000		
Length of stay (d)	13.3 (8.4–25.9)	11.4 (6.5–19.2)	0.216		
Chronic immunosuppressive therapy (yes)	2 (7.4%)	36 (10.9%)	0.753		

TABLE 4. Continued.

	Development of DIC (n. 27)	No DIC (n. 330)	*p*	Odds Ratio (95% CI)	*p*
Chronic anticoagulant therapy (yes)	6 (22.2%)	94 (28.7%)	0.475		
Chronic antiplatelet therapy (yes)	3 (11.1%)	67 (20.3%)	0.319		
COVID-19 (yes)	5 (18.5%)	7 (2.1%)	0.001	9.11 (2.14–38.78)	0.003
Comorbidities:					
Ischemic cardiomyopathy	4 (14.8%)	70 (21.2%)	0.621		
Heart failure	6 (22.2%)	101 (30.6%)	0.361		
TIA/stroke	7 (25.9%)	62 (18.8%)	0.366		
Dementia	12 (44.4%)	127 (38.5%)	0.541		
COPD	3 (11.1%)	32 (9.7%)	0.738		
Cirrhosis	2 (7.4%)	7 (2.1%)	0.143		
Diabetes	6 (22.2%)	82 (24.8%)	0.761		
CKD	4 (14.8%)	67 (20.3%)	0.492		
Sepsis focus:					
Unknown	6 (22.2%)	49 (14.8%)	0.235		
Pulmonary	7 (25.9%)	42 (12.7%)			
Urinary	9 (33.3%)	165 (50.0%)			
Abdomen	3 (11.1%)	28 (8.5%)			
Bloodstream infection	0 (0.0%)	11 (3.3%)			
Other	2 (7.4%)	35 (10.6%)			
Positive cultural exam	16 (59.3%)	221 (67.0%)	0.002	0.71 (0.27–1.83)	0.483
Laboratory parameters:					
Hemoglobin (g/dL)	11.3 (9.2–13.5)	11.2 (9.8–12.7)	0.906		
WBC ($\times 10^9$/L)	15.71 (11.23–21.93)	13.33 (8.50–18.95)	0.187		
Platelets ($\times 10^9$/L)	116 (65–159)	212 (145–308)	<0.001		
Creatinine (mg/dL)	1.89 (1.27–3.53)	1.42 (0.94–2.18)	0.014	1.07 (0.87–1.31)	0.512
PT (sec)	15 (12.3–19.3)	12.2 (11.4–13.4)	<0.001		
aPTT (sec)	41.8 (36.8–53.2)	34.8 (31.8–40.1)	<0.001		
INR	1.45 (1.19–1.92)	1.16 (1.08–1.30)	<0.001		
Fibrinogen (mg/dL)	526 (424–700)	566 (425–743)	0.492		
D-Dimer (ng/mL)	7138 (3153–20,947)	3700 (1997–10,853)	0.071		
CRP (mg/dL)	182.3 (118.8–242.9)	158.7 (84.3–234.2)	0.166		
Procalcitonin (ng/mL)	14.29 (2.41–75.00)	5.38 (0.80–24.01)	0.012	1.01 (0.99–1.02)	0.114
SCORE					
Positive SIC score at ED admission	17 (63.0%)	38 (11.5%)	<0.001	10.39 (4.08–26.46)	<0.001

aPTT: activated partial thromboplastin time; CI: confidence interval; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CRP: c-reactive protein; DIC: disseminated intravascular coagulation; ED: emergency department; INR: international normalized ratio; NEWS: national early warning score; SIC: sepsis induced coagulopathy; PT: prothrombin time; WBC: white blood cell.

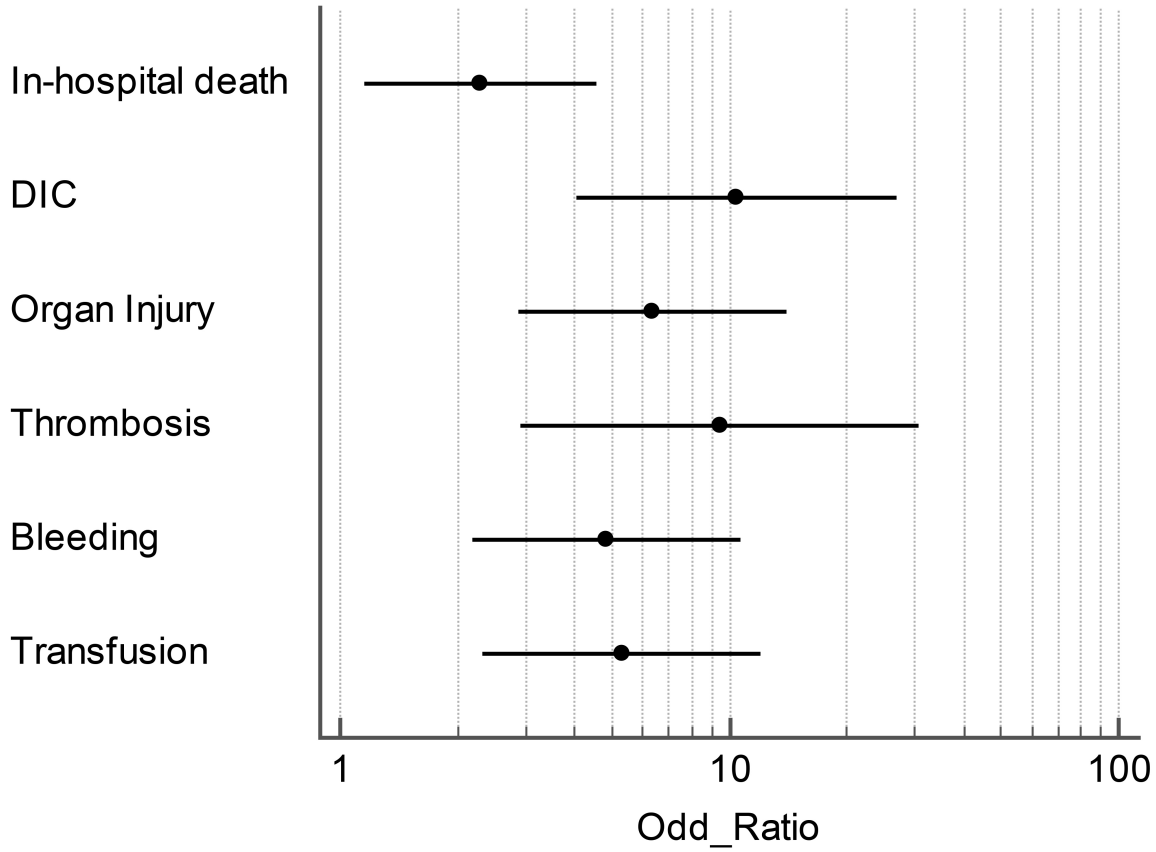

FIGURE 2. Forrest plot represents the multivariate-adjusted odds ratio for primary and secondary study endpoints in patients with a positive SIC score in the ED. DIC: disseminated intravascular coagulation.

tients with severe COVID-19 infection [29] but, at present, it has never been described as an independent predictor of DIC in septic patients. Conversely, the association between COVID-19 infection and coagulopathy has been noted since the early phases of the pandemic and thoroughly described in the literature [30–32]. Indeed, in our cohort of patients, COVID-19 co-infection was independently predictive of the development of overt-DIC and the need for blood component transfusion. Coagulopathy in COVID-19 can present with a wide range of clinical manifestations, ranging from the coexistence of micro- and macrovascular thrombotic events [33] to overt organ failure, especially pulmonary, due to thrombotic microangiopathy-like mechanisms and severe endothelial injury [34, 35]. In such a clinical scenario, the SIC score could be used as a screening tool for COVID-19 patients [36]. However, the prevalence of COVID-19 patients in our cohort is too low to draw a definitive conclusion on this point.

According to our results, the SIC score is capable of predicting in-hospital mortality, organ injury, and severe coagulopathy from a much earlier stage than previously described, that is immediately upon ED admission and sepsis diagnosis. The possibility of calculating this relatively easy score at the patient's bedside upon ED arrival might provide the clinician with an invaluable tool for risk stratification. Furthermore, this early individuation of coagulopathic septic patients might contribute to the complex decision-making in terms of possible therapeutic intervention [37]. It is nowadays clear how coagulation activation in sepsis significantly contributes to multiple organ dysfunction and death [38]. Nonetheless, at present, the evidence on the beneficial effects of coagulopathy-targeted therapies in patients with sepsis as a possible therapeutic intervention for aberrant hypercoagulation is scarce and debated [39, 40]. Potential strategies have been proposed, including the identification of clinical phenotypes of patients with sepsis and DIC as the subgroup of patients who might benefit more from targeted therapies such as antithrombin concentrate administration [41–43], or recombinant human soluble thrombomodulin [44, 45]. In these subgroups of patients, the risk of bleeding complications could be outweighed by the benefits in terms of reduced organ failure and progression to death [46–48]. In this perspective, the early calculation of SIC score in ED patients with sepsis might be explored as a potential indicator of a subgroup of patients at higher risk of DIC and organ failure and who might benefit from early targeted treatment.

5. Study limitations

Our study has several limitations. Firstly, it has a retrospective design that introduces a certain degree of bias. Secondly, the prevalence of SIC in our cohort of septic patients is lower compared to most of the recent literature on the issue, even though the only paper to our knowledge that addressed early septic coagulopathy in European patients had similar results. Similarly, the incidence of DIC is lower than previously reported. Thirdly, the determination of pre-specified secondary

outcomes was performed by manual extraction of information from patient records and possible unknown concomitant factors that might have caused the event could not have been taken into consideration. For this reason, a prospective cohort study should be performed to confirm our observations.

6. Conclusions

Sepsis-induced coagulopathy score in ED patients with sepsis is an independent, early predictor of in-hospital mortality, development of disseminated intravascular coagulation, and organ dysfunction. Its role as a potential indicator of a subgroup of patients who might benefit from targeted therapies should be addressed in future research.

ABBREVIATIONS

aPTT, activated partial thromboplastin time; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, c-reactive protein; DIC, disseminated intravascular coagulation; ED, emergency department; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; ISTH, international society for thrombosis and hemostasis; OR, odds ratio; SOFA, sequential organ failure assessment; NEWS, national early warning score; SIC, sepsis induced coagulopathy; PT, prothrombin time; WBC, white blood cell.

AVAILABILITY OF DATA AND MATERIALS

The data analyzed during the study are not publicly available but may be available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

GT and MC—were involved in conceptualization and drafting of the original manuscript. GT, FLD and GC—were involved in data extraction and database work. GT, MC, AP, DDP and MP—were involved in data analysis. MC, LC, AG, CS and FF—assisted in drafting, reviewing and editing the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

We conducted this study following the ethical standards established in the 1964 Declaration of Helsinki and its later amendments. The study was approved by the local institutional review board (Fondazione Policlinico Universitario A. Gemelli, IRCCS #0025817/22) and waived the need for informed consent based on the study's observational design and use of anonymized patient data.

The research follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Marcello Covino is serving as one of the Editorial Board members of this journal. We declare that Marcello Covino had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to OK.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1798886839032922112/attachment/Supplementary%20material.docx.

REFERENCES

[1] Lupu F, Keshari RS, Lambris JD, Mark Coggeshall K. Crosstalk between the coagulation and complement systems in sepsis. Thrombosis Research. 2014; 133: S28–S31.

[2] Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood. 2019; 133: 906–918.

[3] Levi M, Schultz M, Van Der Poll T. Sepsis and thrombosis. Seminars in Thrombosis and Hemostasis. 2013; 39: 559–566.

[4] Levi M. Infection and inflammation and the coagulation system. Cardiovascular Research. 2003; 60: 26–39.

[5] Semeraro N, Ammollo CT, Semeraro F, Colucci M. Sepsis, thrombosis and organ dysfunction. Thrombosis Research. 2012; 129: 290–295.

[6] Iba T, Umemura Y, Watanabe E, Wada T, Hayashida K, Kushimoto S. Diagnosis of sepsis-induced disseminated intravascular coagulation and coagulopathy. Acute Medicine & Surgery. 2019; 6: 223–232.

[7] Hayakawa M, Saito S, Uchino S, Yamakawa K, Kudo D, Iizuka Y, *et al*. Characteristics, treatments, and outcomes of severe sepsis of 3195 ICU-treated adult patients throughout Japan during 2011–2013. Journal of Intensive Care. 2016; 4: 44.

[8] Yamakawa K, Yoshimura J, Ito T, Hayakawa M, Hamasaki T, Fujimi S. External validation of the two newly proposed criteria for assessing coagulopathy in sepsis. Thrombosis and Haemostasis. 2019; 119: 203–212.

[9] Iba T, Levi M, Thachil J, Helms J, Scarlatescu E, Levy JH. Communication from the scientific and standardization committee of the international society on thrombosis and haemostasis on sepsis-induced coagulopathy in the management of sepsis. Journal of Thrombosis and Haemostasis. 2023; 21: 145–153.

[10] Iba T, Arakawa M, Di Nisio M, Gando S, Anan H, Sato K, *et al*. Newly proposed sepsis-induced coagulopathy precedes international society on thrombosis and haemostasis overt-disseminated intravascular coagulation and predicts high mortality. Journal of Intensive Care Medicine. 2020; 35: 643–649.

[11] Iba T, Umemura Y, Wada H, Levy JH. Roles of coagulation abnormalities and microthrombosis in sepsis: pathophysiology, diagnosis, and treatment. Archives of Medical Research. 2021; 52: 788–797.

[12] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016; 315: 801.

[13] 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: e017046.

[14] Taylor F, Toh C, Hoots K, Wada H, Levi M. Towards definition,

clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thrombosis and Haemostasis. 2001; 86: 1327–1330.
[15] Wendon J, Cordoba J, Dhawan A, Larsen FS, Manns M, Nevens F, *et al*. EASL clinical practical guidelines on the management of acute (fulminant) liver failure. Journal of Hepatology. 2017; 66: 1047–1081.
[16] ARDS Definition Task Force; Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, *et al*. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012; 307: 2526–2533.
[17] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clinical Practice. 2012; 120: c179–c184.
[18] Chaudhry N, Duggal AK. Sepsis associated encephalopathy. Advances in Medicine. 2014; 2014: 1–16.
[19] Lee HJ, Ko BS, Ryoo SM, Han E, Suh GJ, Choi SH, *et al*. Modified cardiovascular SOFA score in sepsis: development and internal and external validation. BMC Medicine. 2022; 20: 263.
[20] Schmoch T, Möhnle P, Weigand MA, Briege J, Bauer M, Bloos F, *et al*. The prevalence of sepsis-induced coagulopathy in patients with sepsis - a secondary analysis of two German multicenter randomized controlled trials. Annals of Intensive Care. 2023; 13: 3.
[21] Tanaka C, Tagami T, Kudo S, Takehara A, Fukuda R, Nakayama F, *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. International Journal of Hematology. 2021; 114: 164–171.
[22] Ding R, Wang Z, Lin Y, Liu B, Zhang Z, Ma X. Comparison of a new criteria for sepsis-induced coagulopathy and International Society on Thrombosis and Haemostasis disseminated intravascular coagulation score in critically ill patients with sepsis 3.0. Blood Coagulation & Fibrinolysis. 2018; 29: 551–558.
[23] Brink A, Alsma J, Verdonschot RJCG, Rood PPM, Zietse R, Lingsma HF, *et al*. Predicting mortality in patients with suspected sepsis at the emergency department; a retrospective cohort study comparing qSOFA, SIRS and National Early Warning Score. PLOS ONE. 2019; 14: e0211133.
[24] Oduncu AF, Kıyan GS, Yalçınlı S. Comparison of qSOFA, SIRS, and NEWS scoring systems for diagnosis, mortality, and morbidity of sepsis in emergency department. The American Journal of Emergency Medicine. 2021; 48: 54–59.
[25] Mustafić S, Brkić S, Prnjavorac B, Sinanović A, Porobić Jahić H, Salkić S. Diagnostic and prognostic value of procalcitonin in patients with sepsis. Medicinski Glasnik. 2018; 15: 93–100.
[26] Anand D, Das S, Ray S, Bhargava S, Srivastava LM. Interrelationship between procalcitonin and organ failure in sepsis. Indian Journal of Clinical Biochemistry. 2014; 29: 93–96.
[27] Covino M, Gallo A, Montalto M, De Matteis G, Burzo ML, Simeoni B, *et al*. The role of early procalcitonin determination in the emergency department in adults hospitalized with fever. Medicina. 2021; 57: 179.
[28] Jekarl DW, Lee S, Kim M, Kim Y, Woo SH, Lee WJ. Procalcitonin as a prognostic marker for sepsis based on SEPSIS-3. Journal of Clinical Laboratory Analysis. 2019; 33: e22996.
[29] Asoğlu R, Tibilli H, Afşin A, Türkmen S, Barman HA, Asoğlu E. Procalcitonin is a predictor of disseminated intravascular coagulation in patients with fatal COVID-19. European Review for Medical and Pharmacological Sciences. 2020; 24: 11953–11959.
[30] Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, *et al*. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020; 136: 489–500.
[31] Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. International Journal of Hematology. 2021; 113: 45–57.
[32] Kovačević M, Rizvanović N, Šabanović Adilović A, Čaušević S. COVID-19 associated coagulopathy in septic critically ill patients—a retrospective cohort study. Medicinski Glasnik. 2023; 20: 142–147.
[33] De Vita A, De Matteis G, d'Aiello A, Ravenna SE, Liuzzo G, Lanza GA, *et al*. Incidence and predictors of thrombotic complications in 4742 patients with COVID-19 or other acute infectious respiratory diseases: a propensity score-matched study. Journal of Clinical Medicine. 2021; 10: 4973.
[34] Levi M, Iba T. COVID-19 coagulopathy: is it disseminated intravascular coagulation? Internal and Emergency Medicine. 2021; 16: 309–312.
[35] Wool G, Miller J. The impact of COVID-19 disease on platelets and coagulation. Pathobiology. 2021; 88: 15–27.
[36] Shafiee M, Hosseini S, Behnam- Roudsari S, Alavinia G, Emami A, Toghyani A, *et al*. Diagnostic and prognostic value of sepsis-induced coagulopathy and international society on thrombosis and hemostasis scoring systems in COVID-19-associated disseminated intravascular coagulopathy. Journal of Research in Medical Sciences. 2021; 26: 102.
[37] Umemura Y, Nishida T, Yamakawa K, Ogura H, Oda J, Fujimi S. Anticoagulant therapies against sepsis-induced disseminated intravascular coagulation. Acute Medicine & Surgery. 2023; 10: e884.
[38] Iba T, Levi M, Levy JH. Sepsis-induced coagulopathy and disseminated intravascular coagulation. Seminars in Thrombosis and Hemostasis. 2020; 46: 089–095.
[39] Yamakawa K, Umemura Y, Hayakawa M, Kudo D, Sanui M, Takahashi H, *et al*. Benefit profile of anticoagulant therapy in sepsis: a nationwide multicentre registry in Japan. Critical Care. 2016; 20: 229.
[40] Zhang Z, Yan T, Ren D, Zhou J, Liu L, Li J, *et al*. Low-molecular-weight heparin therapy reduces 28-day mortality in patients with sepsis-3 by improving inflammation and coagulopathy. Frontiers in Medicine. 2023; 10: 1157775.
[41] Kienast J, Juers M, Wiedermann CJ, Hoffmann JN, Ostermann H, Strauss R, *et al*. Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation. Journal of Thrombosis and Haemostasis. 2006; 4: 90–97.
[42] Tagami T, Matsui H, Horiguchi H, Fushimi K, Yasunaga H. Antithrombin and mortality in severe pneumonia patients with sepsis-associated disseminated intravascular coagulation: an observational nationwide study. Journal of Thrombosis and Haemostasis. 2014; 12: 1470–1479.
[43] Wiedermann CJ. Antithrombin concentrate use in disseminated intravascular coagulation of sepsis: meta-analyses revisited. Journal of Thrombosis and Haemostasis. 2018; 16: 455–457.
[44] Vincent J, Francois B, Zabolotskikh I, Daga MK, Lascarrou J, Kirov MY, *et al*. Effect of a recombinant human soluble thrombomodulin on mortality in patients with sepsis-associated coagulopathy. JAMA. 2019; 321: 1993.
[45] Imaura M, Katagiri F, Nagase S, Hatoyama-Tanaka S, Takahashi H, Takayanagi R, *et al*. Optimal plasma concentration of thrombomodulin alfa to treat sepsis-induced disseminated intravascular coagulation. Shock. 2023; 60: 221–226.
[46] Umemura Y, Yamakawa K. Optimal patient selection for anticoagulant therapy in sepsis: an evidence-based proposal from Japan. Journal of Thrombosis and Haemostasis. 2018; 16: 462–464.
[47] Yu S, Ma X, Li X. Phenotype-oriented anticoagulant therapy for sepsis: still a work in progress. International Journal of Hematology. 2022; 116: 48–54.
[48] Umemura Y, Yamakawa K, Ogura H, Yuhara H, Fujimi S. Efficacy and safety of anticoagulant therapy in three specific populations with sepsis: a meta-analysis of randomized controlled trials. Journal of Thrombosis and Haemostasis. 2016; 14: 518–530.

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