Sepsis-Associated Coagulopathy Severity Predicts Hospital Mortality*

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Objectives: To assess whether sepsis-associated coagulopathy predicts hospital mortality.

Design: Retrospective cohort study.

Setting: One-thousand three-hundred beds urban academic medical center.

Patients: Six-thousand one-hundred forty-eight consecutive patients hospitalized between January 1, 2010, and December 31, 2015.

Interventions: Mild sepsis-associated coagulopathy was defined as an international normalized ratio greater than or equal to 1.2 and less than 1.4 plus platelet count less than or equal to 150,000/µL but greater than 100,000/µL; moderate sepsis-associated coagulopathy was defined with either an international normalized ratio greater than or equal to 1.4 but less than 1.6 or platelets less than or equal to 100,000/µL but greater than 80,000/µL; severe sepsis-associated coagulopathy was defined as an international normalized ratio greater than or equal to 1.6 and platelets less than or equal to 80,000/µL.

Measurements and Main Results: Hospital mortality increased progressively from 25.4% in patients without sepsis-associated coagulopathy to 56.1% in patients with severe sepsis-associated coagulopathy. Similarly, duration of hospitalization and ICU care increased progressively as sepsis-associated coagulopathy severity increased. Multivariable analyses showed that the presence of sepsis-associated coagulopathy, as well as sepsis-associated coagulopathy severity, was independently associated with hospital mortality regardless of adjustments made for baseline patient characteristics, hospitalization variables, and the sepsis-associated coagulopathy-cancer interaction. Odds ratios ranged from 1.33 to 2.14 for the presence of sepsis-associated coagulopathy and from 1.18 to 1.51 for sepsis-associated coagulopathy severity for predicting hospital mortality ($p < 0.001$ for all comparisons).

Conclusions: The presence of sepsis-associated coagulopathy identifies a group of patients with sepsis at higher risk for mortality. Furthermore, there is an incremental risk of mortality as the severity of sepsis-associated coagulopathy increases. (*Crit Care Med* 2018; 46:736–742)

Key Words: coagulopathy; hospital mortality; outcome; sepsis

Sepsis is a common and important medical condition for which increased awareness and early recognition are paramount concerns so that rapid administration of appropriate antibiotics and other urgent treatments can be applied in a timely manner to improve outcomes (1, 2). Sepsis often presents as, or progresses to, a recognized syndrome with dysfunction of multiple organs (3). It is also well known that the development of coagulopathy is common in sepsis and is associated with worse outcomes (4). Initiation of coagulation activation and consequent thrombin generation is due to expression of tissue factor on activated monocytes and endothelial cells and is inefficiently counterbalanced by tissue factor pathway inhibition in sepsis (5). Furthermore, endothelial-associated anticoagulant pathways like the protein C system are impaired by proinflammatory cytokines present in septic patients and up-regulation of plasminogen activator inhibitor type 1 leads to increased fibrin generation and impaired breakdown (5). These coagulation pathway changes result in microvascular clot formation that contributes to tissue ischemia and subsequent organ dysfunction during sepsis. Unfortunately, to date no specific therapies aimed at the coagulation abnormalities associated with sepsis have been definitively demonstrated to improve outcomes (2, 5–7).

Disseminated intravascular coagulation (DIC) is the development of a widespread state of dyscoagulopathy that can lead to both microvascular and macrovascular clotting and compromised blood flow, ultimately resulting in multiple organ dysfunction (8). No single history, physical examination, or

*See also p. 818.

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laboratory component can lead to a diagnosis of, or rule out, DIC; therefore, a combination of both subjective, objective, and laboratory findings must be used to make a diagnosis of DIC (5, 9). Due to the complexity in establishing the diagnosis of DIC, several systems have been developed for defining the presence of DIC using clinical and laboratory criteria (10, 11).

Sepsis-associated coagulopathy (SAC) represents the coagulation abnormalities associated with severe infections (12). Several interventions aimed at modifying SAC have shown potential benefit in the subgroups of patients with the greatest severity of illness (13, 14). However, the past inability to target novel sepsis therapies to specific, previously unrecognized, subgroups of septic patients most likely to benefit from those treatments has been raised as a potential explanation for failed prior investigations (15, 16). Similar arguments have been raised for other disease processes in critically ill patients such as the acute respiratory distress syndrome (17). Therefore, we carried out a cohort study of patients with sepsis and septic shock to determine whether the presence of SAC, using simplified criteria relative to DIC, and SAC severity predict clinical outcomes such as mortality and length of stay (LOS).

METHODS

Setting and Study Population

This observational cohort study was performed at Barnes-Jewish Hospital (1,300 beds) between January 1, 2010, and December 31, 2015. Data were obtained from all consecutive adult patients hospitalized during the study dates who had *International Classification of Disease*, 9th revision, Clinical Modification (ICD-9-CM) codes for either severe sepsis (995.92) or septic shock (785.52). The study analyzed deidentified data from the hospital's Healthcare Informatics group, which is maintained by the Center for Clinical Excellence at BJC HealthCare. The study protocol was approved by Washington University (institutional review board [IRB] number 201503035) and St. Louis College of Pharmacy (IRB number 2016–31) IRBs.

Data Collection and Definitions

Patient age, gender, and race were collected from the electronic health record (EHR), as were ICD-9-CM codes corresponding to patient comorbidities, including congestive heart failure, chronic obstructive pulmonary disease (COPD), chronic kidney disease and end-stage renal disease, cirrhosis, complicated and uncomplicated diabetes mellitus (DM), HIV virus infection, cancer, and the Charlson Comorbidity Index (18). The use of vasopressors, mechanical ventilation, renal replacement therapy, and antibiotics during hospitalization was also identified. All routinely collected vital signs and laboratory values were extracted from the EHR, as were sites and results of all microbiology cultures. For severity of illness, we calculated the Acute Physiology and Chronic Health Evaluation (APACHE) II score (19).

In those patients carrying a diagnosis of severe sepsis or septic shock, sepsis onset was defined as the first day in which a patient had a recorded systolic blood pressure less than 100 mm Hg and received treatment with antibiotics targeting Gram-negative bacteria (cefepime, meropenem, or piperacillin/tazobactam). Only the first occurrence of sepsis for each hospital admission was considered. Patients with SAC were identified as having an international normalized ratio (INR) greater than or equal to 1.2 and a platelet count of less than or equal to 150,000/μL within 3 days of meeting the sepsis criteria.

We a priori stratified all patients with SAC into three levels of severity based on INR and platelet values: mild SAC was defined as INR greater than or equal to 1.2 and less than 1.4 plus platelet count less than or equal to 150,000/μL but greater than 100,000/μL; moderate SAC was defined with either an INR greater than or equal to 1.4 but less than 1.6 or platelets less than or equal to 100,000/μL but greater than 80,000/μL; severe SAC was defined as an INR greater than or equal to 1.6 and platelets less than or equal to 80,000/μL. Patients with an INR greater than 1.2 but no recorded platelet counts, as well as those with platelet counts less than 150,000/μL but no recorded INR, were considered to have indeterminate SAC and were treated as not having SAC in the analysis. Whenever multiple values were available, the most abnormal values were selected for determining SAC severity.

We also a priori defined preexisting coagulopathy as meeting the SAC criteria (INR and platelet cutoffs) on the first resulted values for INR and platelets, if both were drawn within the first 2 hospital days. Patients with preexisting coagulopathy were excluded from the analysis. All other coagulopathy was considered to be acquired.

Outcomes

The primary outcome of the study was inpatient mortality. Secondary outcomes included hospital and ICU LOS.

Statistics

Continuous variables were expressed as means and SDs or medians and interquartile range. The *t* and one-way analysis of variance tests were used to analyze normally distributed continuous variables, whereas the Mann-Whitney *U* and Kruskal-Wallis tests were used to analyze nonnormally distributed continuous variables. Categorical data were reported as frequency distributions and analyzed using chi-square or McNemar tests. Unadjusted logistic regression models were fit to estimate the change in odds of inpatient mortality for patients with SAC compared with those without SAC. Adjusted logistic regression models were then fit for each outcome to control for patient characteristics (age, sex, race, comorbidities, and year of hospitalization within the first or second half of the study period) and hospitalization variables (severity of illness as measured by APACHE II score, ICU admission, shock, mechanical ventilation, bacteremia, fungemia, acute renal failure, and source of infection—lung, genitourinary, abdominal, skin or soft tissue, indwelling line, or unknown). All tests of significance used a two-sided *p* value of less than 0.05. Statistical analyses were completed using Stata Version 15 (College Station, TX).

RESULTS

The final cohort included 6,148 consecutive patients (mean age 60.5 ± 15.6 yr; 55.1% men) with significant comorbidities (mean Charlson Comorbidity Index, 6.4 ± 3.2) and severity of illness (mean APACHE II, 20.3 ± 6.4). There were 4,549 patients (74.0%) who did not have SAC based on our criteria, 244 (4.0%) with mild SAC, 984 (16.0%) with moderate SAC, and 371 (6.0%) with severe SAC (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D277). Of the total cohort, 1,326 patients (21.6%) were categorized as having sepsis on hospital day 1 based on ICD-9 codes for sepsis without meeting the systolic blood pressure- or antibiotic-based sepsis criteria previously described. Most of these patients (1,220; 92.0%) did not meet SAC criteria, whereas 25 patients (1.9%) had mild SAC, 73 patients (5.5%) had moderate SAC, and eight patients (0.6%) had severe SAC.

Table 1 indicates that there were statistically significant differences in baseline characteristics according to the severity of SAC. Patients with mild SAC were older, whereas those with severe SAC were more likely to be Caucasian and less likely to be African-American. Rates of all comorbidities except HIV infection varied by SAC severity. For example, patients with severe SAC were significantly more likely to have an underlying malignancy but less likely to have DM and COPD compared with less severe SAC or patients without SAC. Severity of illness as assessed by incremental APACHE II scores, use of vasopressors, mechanical ventilation, occurrence of acute kidney injury, and need for renal replacement therapy correlated with increasing severity of SAC. Frequency of positive blood cultures irrespective of the pathogen type (Gram-positive bacteria, Gram-negative bacteria, mixed bacteria, fungi, and mixed infection with bacteria and fungi) was also associated with increasing severity of SAC.

Table 2 demonstrates that hospital mortality increased progressively from 25.4% in patients without SAC to 56.1% in patients with severe SAC. Similarly, duration of hospitalization and ICU care increased progressively from no SAC to severe SAC. Kaplan-Meier curves confirmed the greater mortality among patients with SAC compared with those without SAC (**Fig. 1**). Furthermore, Kaplan-Meier curves show that there was a progressive increase in mortality from mild SAC to moderate SAC and severe SAC (**Fig. 2**). However, there was no difference seen in the curves comparing patients without SAC and those with mild SAC.

Multivariable analyses are shown in **Table 3** and **Supplemental Table 1** (Supplemental Digital Content 2, http://links.lww.com/CCM/D278) and include an interaction term between SAC and the presence of an underlying malignancy. The presence or absence of SAC, as well as the severity of SAC, was independently associated with hospital mortality regardless of adjustments made for baseline patient characteristics, hospitalization variables, and the SAC-cancer interaction. Odds ratios (ORs) varied from 1.33 to 2.14 for the presence of SAC and from 1.18 to 1.51 for SAC severity for predicting hospital mortality. Additionally, linear regression showed that after adjustment for patient and hospitalization characteristics, the presence of SAC was associated with increased hospital LOS (2.23 d; 95% CI, 0.56–3.96; $p = 0.009$) and ICU LOS (61.5 hr; 95% CI, 31.7–91.3; $p < 0.001$). Similar findings were demonstrated for increasing SAC severity.

A sensitivity analysis examining the study cohort based on study entry year (2010–2012 vs 2013–2015) showed similar relationships between SAC severity and mortality after adjustment for patient- and hospitalization-related confounders (first half—SAC final adjusted OR, 1.14 [95% CI, 0.86–1.50] and SAC severity final adjusted OR, 1.54 [95% CI, 1.15–2.06], $p = 0.004$; second half—SAC final adjusted OR, 1.67 [95% CI, 1.31–2.13], $p < 0.001$ and SAC severity final adjusted OR, 1.47 [95% CI, 1.14–1.91], $p = 0.003$). An additional sensitivity analysis including the 2,821 patients with preexisting coagulopathy who were excluded from the primary analysis also demonstrated similar relationships between the presence of SAC and SAC severity with mortality (SAC final adjusted OR, 1.65 [95% CI, 1.43–1.90]; $p < 0.001$ and SAC severity final adjusted OR, 1.85 [95% CI, 1.64–2.10]; $p < 0.001$).

DISCUSSION

We found that the presence of SAC as defined by elevated INR and decreased platelet count correlates with a group of patients with sepsis at elevated risk for mortality. Furthermore, there is an increasing risk of mortality as the severity of SAC increases, especially from mild SAC to moderate and severe forms of SAC. Incremental increases in SAC severity also correlated with greater lengths of stay in the ICU and hospital. Interestingly, among the 6,148 patients in our cohort, 16% had moderate SAC and only 6% had severe SAC. We also found that both the presence of SAC and SAC severity independently correlated with hospital mortality after controlling for patient characteristics, hospitalization variables, and severity of illness. Finally, rates of bacterial, fungal, and mixed bloodstream infections increased as SAC severity did.

These data have several potential implications for the management of patients with sepsis. First, as with other markers of sepsis severity such as the Sequential Organ Failure Assessment score and increasing lactate levels, SAC severity could be used as another relatively simple way for comparing populations of patients with sepsis to each another. This could have important implications for comparing the outcomes of patients with sepsis from different hospitals, especially with increasing requirements for public reporting of such data through systems such as the Severe Sepsis/Septic Shock Early Management Bundle-1 and New York State's Rory's Regulations (20, 21).

Potentially more important are the implications of our data for the conduct and interpretation of clinical trials for novel sepsis therapies. For example, the Protein C Worldwide Evaluation in Severe Sepsis study was stopped early for efficacy after the enrollment of 1,690 patients with severe sepsis (22). Absolute mortality in the intention-to-treat population was reduced by 6.1 percentage points, a relative risk reduction of 19.4%. Subsequent subgroup analysis suggested that the mortality benefit was limited to patients with high illness severity (i.e., those with more than one sepsis-related dysfunctional

TABLE 1. Patient Characteristics

Characteristics	No SAC (*n* = 4,549)	Mild SAC (*n* = 244)	Moderate SAC (*n* = 984)	Severe SAC (*n* = 371)	*p*
Age, yr, median (IQR)	61 (52–72)	64 (52–75)	62 (53–71)	60 (50–67)	< 0.001
Female, *n* (%)	2,073 (45.6)	95 (38.9)	427 (43.4)	168 (45.3)	0.150
Race, *n* (%)					
Caucasian	2,859 (62.8)	161 (66.0)	674 (68.5)	260 (70.1)	< 0.001
African-American	1,362 (29.9)	67 (27.5)	256 (26.0)	75 (20.2)	
Asian	31 (0.7)	1 (0.4)	2 (0.2)	0 (0.0)	
Other	58 (1.3)	2 (0.8)	14 (1.4)	7 (1.9)	
Unknown	239 (5.3)	13 (5.3)	38 (3.9)	29 (7.8)	
Comorbidities, *n* (%)					
Diabetes mellitus	1,702 (37.4)	101 (41.4)	342 (34.8)	100 (27.0)	< 0.001
Congestive heart failure	1,368 (30.0)	97 (39.8)	368 (37.4)	141 (38.0)	< 0.001
Underlying malignancy	1,430 (31.4)	60 (24.6)	382 (38.8)	147 (39.6)	< 0.001
Chronic obstructive pulmonary disease	903 (19.9)	48 (19.7)	215 (21.8)	51 (13.7)	0.011
Chronic kidney disease	1,013 (22.3)	68 (27.9)	250 (25.4)	72 (19.4)	0.015
End-stage renal disease	381 (8.4)	25 (10.2)	114 (11.6)	35 (9.4)	0.013
Cirrhosis	191 (4.2)	16 (6.6)	81 (8.2)	29 (7.8)	< 0.001
HIV	50 (1.1)	3 (1.2)	18 (1.8)	4 (1.1)	0.300
Charlson Comorbidity Index, median (IQR)	6 (4–8)	6 (4–9)	6 (5–9)	6 (4–8)	0.004
Time period of hospitalization, *n* (%)					
2010–2012	1,552 (34.1)	103 (42.2)	451 (45.8)	181 (48.8)	< 0.001
2013–2015	2,997 (65.9)	141 (57.8)	533 (54.2)	190 (51.2)	< 0.001
Maximum Acute Physiology and Chronic Health Evaluation II score, median (IQR)	19 (15–23)	21 (16–24)	22 (18–26)	24 (19–29)	< 0.001
ICU admission, *n* (%)	2,699 (59.3)	198 (81.1)	782 (79.5)	304 (81.9)	< 0.001
Vasopressors, *n* (%)	2,621 (57.6)	148 (60.7)	713 (72.5)	280 (75.5)	< 0.001
Mechanical ventilation, *n* (%)	1,930 (41.8)	137 (56.1)	626 (63.6)	273 (73.6)	< 0.001
Acute kidney injury, *n* (%)	2,636 (58.0)	154 (63.1)	656 (66.7)	278 (74.9)	< 0.001
Renal replacement therapy, *n* (%)	297 (6.5)	22 (9.0)	176 (17.9)	101 (27.2)	< 0.001
Metabolic acidosis, *n* (%)	1,456 (32.0)	80 (32.8)	440 (44.7)	220 (59.3)	< 0.001
Positive blood culture, *n* (%)	932 (20.5)	54 (22.1)	280 (28.5)	132 (35.6)	< 0.001
Gram-negative bacteremia	451 (9.9)	28 (11.5)	137 (13.9)	90 (24.3)	< 0.001
Gram-positive bacteremia	469 (10.3)	25 (10.2)	144 (14.6)	55 (14.8)	< 0.001
Mixed bacteremia	80 (1.8)	4 (1.6)	30 (3.0)	22 (5.9)	< 0.001
Fungemia	110 (2.4)	7 (2.9)	43 (4.4)	20 (5.4)	< 0.001
Bacteremia and fungemia	27 (0.6)	3 (1.2)	16 (1.6)	11 (3.0)	< 0.001
Source of Infection, *n* (%)[a]					
Pulmonary	1,479 (32.5)	98 (40.1)	413 (42.0)	164 (44.2)	< 0.001
Genitourinary	944 (20.8)	57 (23.4)	243 (24.7)	81 (21.8)	0.047
Abdominal	567 (12.5)	25 (10.3)	178 (18.1)	80 (21.6)	< 0.001
Skin or soft tissue	371 (8.2)	21 (8.6)	89 (9.0)	42 (11.3)	0.182
Indwelling line	160 (3.5)	10 (4.1)	41 (4.2)	17 (4.6)	0.585
CNS	8 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	0.765
Unknown	1,953 (42.9)	87 (35.7)	300 (30.5)	101 (27.2)	< 0.001

IQR = interquartile range, SAC = sepsis-associated coagulopathy.

[a]Some patients had positive cultures from > 1 site.

Analysis of variance was used to analyze normally distributed continuous variables, whereas the Kruskal-Wallis test was used to analyze nonnormally distributed continuous variables.

TABLE 2. Outcomes stratified by Sepsis-Associated Coagulopathy Severity

Outcomes	No SAC (*n* = 4,549)	Mild SAC (*n* = 244)	Moderate SAC (*n* = 984)	Severe SAC (*n* = 371)	*p*
Hospital mortality, *n* (%)	1,155 (25.4)	66 (27.0)	400 (40.7)	208 (56.1)	< 0.001
Hospital days, median (IQR)	10.5 (5.4–20.8)	12.3 (6.8–24.3)	17.0 (8.7–29.3)	19.5 (10.3–36.6)	< 0.001
ICU days, median (IQR)	5 (2.5–12.8)	5.9 (2.7–14.8)	7.9 (3.7–16.0)	8.8 (4.0–20.8)	< 0.001

IQR = interquartile range, SAC = sepsis-associated coagulopathy.

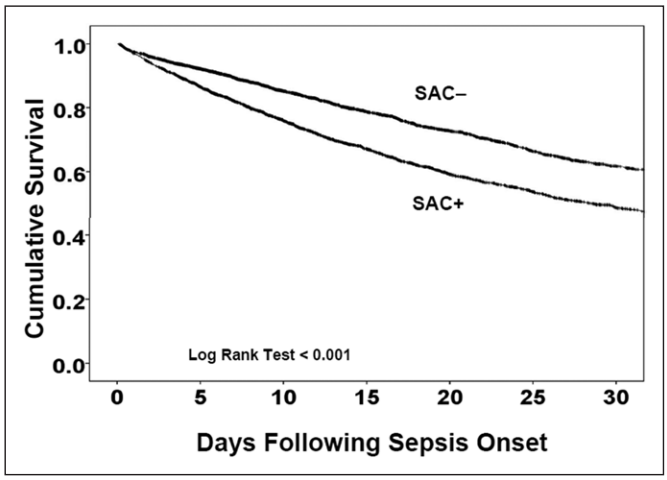

Figure 1. Kaplan-Meier curves for cumulative survival according to presence or absence of sepsis-associated coagulopathy (SAC).

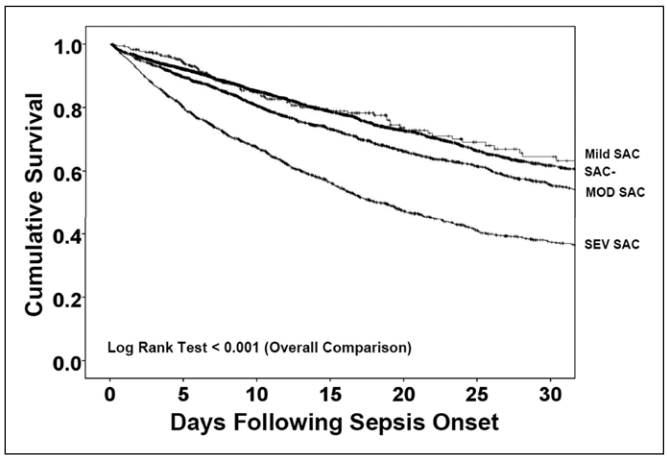

Figure 2. Kaplan-Meier curves for cumulative survival according to sepsis-associated coagulopathy (SAC) severity. Statistical comparisons by log-rank test: overall comparison, $p < 0.001$; SAC negative (SAC–) versus mild SAC, $p = 0.153$; SAC– versus moderate (MOD) SAC, $p < 0.001$; SAC– versus severe (SEV) SAC, $p < 0.001$; mild SAC versus MOD SAC, $p = 0.002$; mild SAC versus SEV SAC, $p < 0.001$; MOD SAC versus SEV SAC, $p < 0.001$.

TABLE 3. Multivariable Analyses

Model for the Association Between SAC and Mortality	OR	95% CI	*p*
SAC alone	2.14	1.90–2.41	< 0.001
SAC + patient characteristics	1.90	1.67–2.17	< 0.001
SAC + patient characteristics + hospitalization variables	1.33	1.15–1.53	< 0.001
SAC + patient characteristics + hospitalization variables + SAC-cancer interaction	1.42	1.18–1.70	< 0.001
Model for the Association Between SAC Severity and Mortality	OR	95% CI	*p*
SAC severity[a] alone	1.48	1.40–1.56	< 0.001
SAC severity[a] + patient characteristics	1.40	1.32–1.49	< 0.001
SAC severity[a] + patient characteristics + hospitalization variables	1.18	1.11–1.26	< 0.001
SAC severity[a] + patient characteristics + hospitalization variables + SAC-cancer interaction	1.51	1.24–1.83	< 0.001

OR = odds ratio, SAC = sepsis-associated coagulopathy.

[a]Absence of SAC, mild SAC, moderate SAC, severe SAC.

Patient characteristics: age, gender, race, Charlson Comorbidity Index, all individual comorbidities, year of hospitalization. Hospitalization variables: Acute Physiology and Chronic Health Evaluation II, ICU admission, shock, mechanical ventilation, bacteremia, fungemia, acute renal failure, source of infection.

organ or with an APACHE II score of > 24). However, a subsequent trial of human activated protein C in adults with septic shock failed to show any mortality benefit, ultimately resulting in the medication's removal from the marketplace (6, 23). Interestingly, within that trial more than 75% of the enrollees had platelet counts greater than 100,000/μL and the mean prothrombin time was approximately 20.7 seconds corresponding to an INR value of approximately 1.5. These results would suggest that only the minority of patients in that trial had moderate or severe SAC. A potential implication for human activated protein C as a sepsis therapeutic may be that prior trials contained too few patients with moderate or severe SAC, to demonstrate a therapeutic effect form this drug given its proposed mechanism of action (24).

The future investigation of other sepsis therapies affecting the coagulation cascade such as antithrombin or human recombinant thrombomodulin could also potentially be influenced by our findings (4). Septic patients with severe enough coagulation abnormalities to allow appropriate investigation of these agents may be difficult to identify and enroll into clinical trials. A panel of experts in sepsis trials recommended improved methods to

define appropriate molecular targets for preclinical development and development of superior techniques to determine the clinical value of novel sepsis agents (25). This panel has also suggested that biomarker-driven studies should be considered to categorize specific "at risk" populations most likely to benefit from a new treatment. Our results would suggest that patients with moderate to severe SAC might be the best targets for agents influencing the coagulation cascade in sepsis. Further support for this premise comes from a recent cohort study from Japan involving 2,663 consecutive patients with sepsis; in this study, 1,247 patients received anticoagulants and 1,416 received none (26). After adjustment for imbalances, these investigators found that anticoagulant administration was significantly associated with reduced mortality only in subsets of patients diagnosed with DIC, but not in non-DIC subsets, in which mortality between the anticoagulated and non-anticoagulated groups was similar. This same group of investigators conducted a meta-analysis of randomized controlled trials of anticoagulant therapies in sepsis within three specific patient categories: the overall population with sepsis, the population with sepsis-induced coagulopathy, and the population with sepsis-induced DIC (27). A survival benefit with anticoagulation was only identified within the subgroup of patients with sepsis-induced DIC.

Strengths of our study include its large and diverse sample, as well as the fact that our observed rates of coagulopathy appear relatively similar to rates described elsewhere (6), which may increase the generalizability of our results. Additionally, we were able to control for a large number of potential confounders including patient comorbidities, severity of illness, and culture data. In particular, our exclusion of patients with preexisting coagulopathy and our ability to adjust for the interaction between active malignancy and coagulopathy lends additional strength to our analysis.

There are several important limitations of our study. First, these data are from a single center and may not be representative of other institutions or regions. Being a regional referral center likely influences the case mix of patients with sepsis at our hospital to include individuals with more severe disease compared with community-based hospitals. Therefore, larger databases of sepsis severity are required to estimate the true prevalence of SAC and its severity in the community setting. The results of a recent patient-level meta-analysis of goal-directed therapy for sepsis did not provide data to determine the presence of SAC, nor its severity, in this large international population (28). Second, our cohort was composed of patients with more severe sepsis, as manifested by the higher APACHE II scores and mortality compared with septic patients enrolled in recent sepsis trials (28). Therefore, our findings may not pertain to patients with less severe sepsis. Third, we selected arbitrary cutoffs for establishing the severity of SAC. It is possible that the selection of different cutoff values for INR and platelet count could have resulted in different findings. Likewise, we did not determine whether INR or platelet values alone would have been adequate for determining SAC severity. Finally, we did not specifically identify patients as having DIC, nor did we attempt to assess the relationship between DIC and outcomes. This was purposely done as we aimed to identify a simplified assessment of coagulopathy that could be easily used to stratify patients into severity categories for prognostic determinations and for potential future therapeutic interventions. Additionally, the INR and platelet thresholds were selected based on our clinical experience. It is possible that future use of more evidence-based thresholds, using our findings as a reference point, could improve upon the diagnostic accuracy of these criteria. Furthermore, our simplified criteria for defining SAC limit any generalizability to patients with DIC.

In conclusion, septic patients with SAC, as defined by elevated INR and platelet count, appear to have a greater risk of death compared with those without coagulopathy. Our results also suggest that the mortality risk with SAC can be quantified according to the severity of the coagulation abnormalities. Future studies are needed to confirm these findings in larger populations. More importantly, future trials of sepsis therapies targeting the coagulation cascade should take into account the presence or absence of SAC, as well as the severity of SAC, when formulating potential trial designs.

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