Dielectric Blood Coagulometry for the Early Detection of Sepsis-Induced Disseminated Intravascular Coagulation: A Prospective Observational Study

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OBJECTIVES: To evaluate the utility of dielectric blood coagulometry for early sepsis–induced disseminated intravascular coagulation diagnosis.

DESIGN: Single-center, prospective observational study.

SETTING: Patients with sepsis or septic shock at the Tokyo Medical and Dental University Hospital of Medicine between September 2019 and September 2020.

PATIENTS: The patients were divided into three groups according to the timing of disseminated intravascular coagulation diagnosis based on the Disseminated Intravascular Coagulation score by the Japanese Association for Acute Medicine: 1) no disseminated intravascular coagulation group, 2) late-diagnosed disseminated intravascular coagulation group: not diagnosed with disseminated intravascular coagulation on day 1 but diagnosed within 48 hours after admission, and 3) disseminated intravascular coagulation group: diagnosed with disseminated intravascular coagulation on day 1. The study evaluated 80 patients (no disseminated intravascular coagulation, 31 [38.8%]; late-diagnosed disseminated intravascular coagulation, 34 (42.5%); disseminated intravascular coagulation, 15 [18.8%]).

MEASUREMENTS AND MAIN RESULTS: We compared the clinical severity scores and mortality of the groups and assessed the correlation between the dielectric blood coagulometry–derived coagulation marker, thrombin levels, and Disseminated Intravascular Coagulation score using Spearman rank correlation. The mortality rate was 0% (0/31) in the no disseminated intravascular coagulation group, 35.3% (12/34) in the late-diagnosed disseminated intravascular coagulation group, and 33.3% (5/15) in the disseminated intravascular coagulation group. Although the Disseminated Intravascular Coagulation score on day 1 did not reflect disseminated intravascular coagulation in approximately 70% of patients who developed disseminated intravascular coagulation by day 2, dielectric clot strength measured by dielectric blood coagulometry on day 1 strongly correlated with disseminated intravascular coagulation development by day 2 (Spearman $\rho = 0.824$; $p < 0.05$) and with thrombin level on day 1 (Spearman $\rho = 0.844$; $p < 0.05$).

CONCLUSIONS: Dielectric blood coagulometry can be used to detect early-phase disseminated intravascular coagulation in patients with sepsis and is strongly correlated with thrombin levels. Larger studies are needed to verify our results for developing clinical applications.

KEY WORDS: dielectric blood coagulometry; disseminated dysfunction of blood coagulation; sepsis; thrombin

Sepsis, defined as organ dysfunction caused by a dysregulated host response to infection, is a life-threatening condition (1). Disseminated intravascular coagulation (DIC) is often considered one of such organ dysfunctions,

and it is common in sepsis and strongly associated with mortality (2, 3). In DIC, the activation of coagulation via the elevation of thrombin levels is initiated by the expression of tissue factors on activated monocytes and endothelial cells, which results in microvascular thrombosis leading to tissue ischemia and multiple organ dysfunctions (4). The early recognition and treatment of DIC would prevent significant complications (2).

Thrombin is a protein involved in the early regulation of coagulation and hemostatic processes (5), and excessive thrombin production is one of the major characteristics of DIC. Although thrombin levels increase 3–5 hours after the occurrence of bacteremia or endotoxemia, it is inhibited rapidly by antithrombin as a biological defense reaction against the DIC (6, 7). Therefore, although measuring pure soluble thrombin levels is ideal for real-time coagulation monitoring, it is not practical in clinical settings because most measuring assays are costly, highly complex, and time consuming (8). Clinically, DIC is diagnosed using scoring systems proposed by several organizations (9, 10). However, early detection is often challenging because of the time lag between DIC development and the elevation of the scores. Furthermore, the relationship between these scoring systems and thrombin level has not been fully elucidated.

Recently, dielectric blood coagulometry (DBCM) was developed to evaluate blood coagulability by measuring the change in the dielectric permittivity of the whole blood sample. To date, there have been several reports about DBCM in various fields, including the prediction of thrombosis (11) and stroke (12). We hypothesized that coagulation measurements by DBCM would enable the detection of the early phase of DIC and reflect thrombin levels more accurately than existing diagnostic scores. The purpose of this study was to assess the utility of DBCM in recognizing the early phase of DIC and predict thrombin levels.

MATERIALS AND METHODS

Design, Setting, and Ethics Approval

This study was a prospective observational study and included patients with sepsis or septic shock admitted at the Tokyo Medical and Dental University Hospital of Medicine, a Japanese tertiary critical care center, between September 2019 and September 2020. This study complied with the principles of the 1964 Declaration of Helsinki and its later amendments. The study was approved by the institutional review board of Tokyo Medical and Dental University (number 2018-320). Written informed consent was obtained from the patients or their relatives at the time of hospital admission.

Study Population

Patients diagnosed with sepsis or septic shock based on the Sepsis-3 criteria upon admission at the emergency department (ED) were prospectively enrolled (13). Patients who met at least one of the following criteria were excluded from the analysis: 1) age less than 18 years, 2) had do-not-attempt-resuscitation orders, 3) received cardiopulmonary resuscitation before admission, 4) transferred from another hospital, 5) transferred to another hospital within 24 hours after admission, 6) history of malignancy, and 7) missing or insufficient data regarding the study variables. In addition, patients were excluded if they had a history of anticoagulant or antiplatelet medication because these agents could significantly affect clotting function. All included patients received treatments according to the Surviving Sepsis Campaign guideline 2016 (14).

Data Collection

The following information was collected prospectively: age; sex; Charlson Comorbidity Index (15); the primary source of infection; concomitant therapies; the Acute Physiology and Chronic Health Evaluation II score and the Sequential Organ Failure Assessment score on days 1, 2, and 3; ventilator-free days (VFDs) (16); ICU-free days (IFDs) at 28 days (17); and status at hospital discharge (i.e., dead or alive).

Blood Collection and Laboratory Analysis

The first blood sampling was performed as soon as possible upon arrival at the ED (day 1) to eliminate the effect of any therapeutic interventions. Blood samples were also collected on days 2 and 3. Whole blood was analyzed using DBCM immediately after the blood collection. In addition, platelet-poor plasma (PPP) was immediately processed from the remaining whole blood by consecutive centrifugations (2,500g for 15 min at 4°C) and stored at –80°C. The soluble thrombin level in the PPP was measured by enzyme-linked immunosorbent assay (ELISA) immediately after thawing the

frozen sample at room temperature to minimize the in vitro effect of proteases converting prothrombin to thrombin, using antibodies against human thrombin (Human Thrombin ELISA Kit [Factor II], ab108909; Abcam, Cambridge, United Kingdom). This antibody was designed for the quantitative measurement of the pure soluble thrombin concentrations (i.e., independent from thrombin-antithrombin complex), and the measurable range was 0.31–20.0 ng/mL. Regarding standard laboratory data, complete blood count was measured using an XN-9000 auto-analyzer (Sysmex Corporation, Kobe, Japan), and prothrombin time and fibrin/fibrinogen degradation product were measured by a CS-5100 auto-analyzer (Sysmex Corporation).

DBCM Analysis

To measure the coagulation status, DBCM analyses were performed on days 1–3 with a dielectric coagulometer (Sony Corp., Tokyo, Japan) (18), approved for clinical use in Japan in September 2019 (**Supplementary Fig. 1**, http://links.lww.com/CCM/G629; **legend**, http://links.lww.com/CCM/G634). The main response to DBCM is produced by the aggregation and shape transformation of erythrocytes during coagulation (18). The DBCM uses dielectric spectroscopy to measure blood rheology. Each cell in the whole blood, including the erythrocytes, could be considered as a component of an electrical circuit. When whole blood is applied to the reagent cartridge and placed into the alternating current electric field, the dielectric constant spectrum changes according to the aggregation and shape transformation of erythrocytes during coagulation (18). During this process, the dielectric clot strength (DCS), a variable of fibrin formation, can be estimated by measuring and analyzing changes in permittivity associated with blood coagulation with high sensitivity. The reference range of the DCS calculated by DBCM is 17–29. The DCS is not significantly affected by the blood cell counts, coagulation factors, electrolytes, or blood temperature. However, severe polycythemia and/or anemia could affect the result; DCS can be measured appropriately when the hematocrit is in the range of 20–60%.

Score-Based DIC Diagnosis

The DIC score was calculated on days 1–3 based on the Japanese Association for Acute Medicine (JAAM) criteria (10) (**Supplementary Table 1**, http://links.lww.com/CCM/G630), which is widely used in Japan (19). The diagnosis of DIC was confirmed if the JAAM score was 4 points or higher.

Based on the timing of DIC diagnosis, the patients were divided into three groups: 1) no-DIC; 2) late-diagnosed DIC, which included patients who were not diagnosed with DIC upon ED admission but were diagnosed with DIC during the first 48 hours after admission using the JAAM criteria; and 3) DIC, which comprised patients who were diagnosed with DIC upon ED admission using the JAAM criteria.

Statistical Analysis

We evaluated the differences between the aforementioned three groups with regard to the clinical scores and laboratory results. In the univariate analysis, continuous variables were compared using the Student t test or Mann-Whitney U test. Categorical variables were compared using the chi-square test or Fisher exact test, depending on the distribution. First, we used a one-way analysis of variance (ANOVA) to assess the differences between the three groups. Thereafter, we performed a post hoc residual analysis to identify the divergent group when a significant difference was observed in the one-way ANOVA. The residual was the difference between the observed value and the mean of all the expected values within each group. A significant adjusted standardized residual indicated a significant difference in the corresponding variable. In this analysis, Bonferroni correction was used to address multiple comparisons. The correlation between DCS calculated by DBCM, the JAAM DIC score, and thrombin levels in PPP was evaluated using a Spearman rank correlation test. Furthermore, we explored the correlation between each variable in the JAAM DIC score and the DCS on each day. All statistical analyses were conducted using R software (Version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria). Two-sided p values less than 0.05 were considered statistically significant.

RESULTS

Figure 1 shows the patient selection diagram. Among 101 potentially eligible patients, we analyzed 80; among them, 31 patients (38.8%), 34 patients (42.5%), and 15 patients (18.8%) were assigned to the no-DIC,
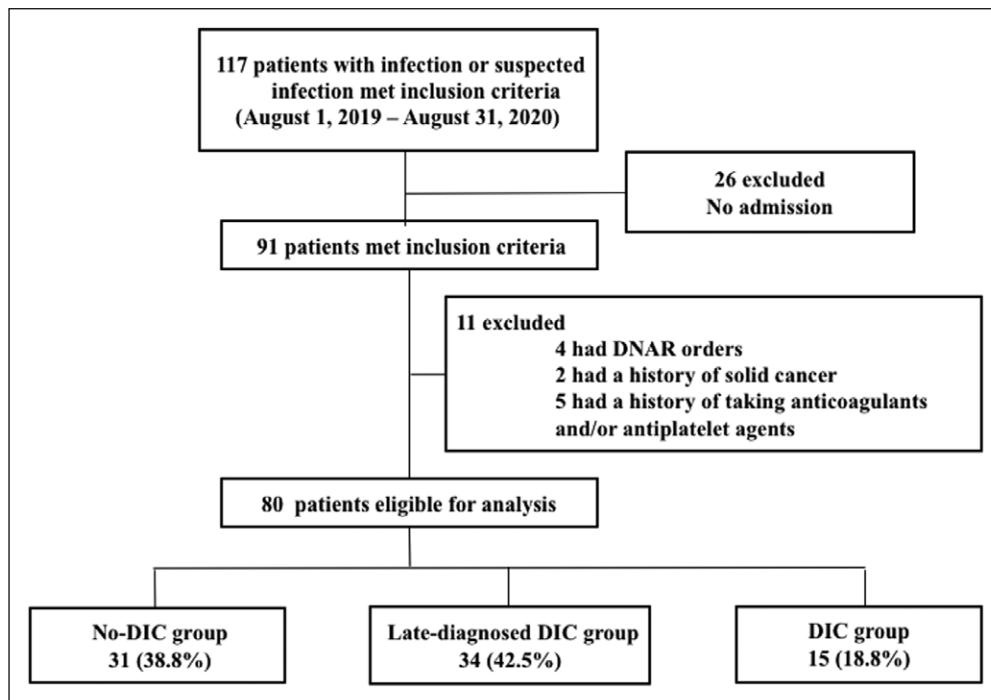
Figure 1. Flow diagram of patient selection. DIC = disseminated intravascular coagulation, DNAR = do-not-attempt-resuscitation.

late-diagnosed DIC, and DIC groups, respectively. **Table 1** presents the characteristics of the groups. All patients in the late-diagnosed DIC group were diagnosed with DIC within 2 days after admission. No significant differences were observed regarding the patient demographics and primary source of infection. Compared with the no-DIC group, the late-diagnosed DIC and DIC groups had higher severity scores on all the days. Patients who developed DIC, including late-diagnosed DIC, were likely to undergo invasive treatments and received larger amounts of fluid and anticoagulation therapy.

Table 2 shows a comparison of the outcomes. The mortality rate in the no-DIC group was 0% (0/31), 35.3% (12/34) in the late-diagnosed DIC group, and 33.3% (5/15) in the DIC group. **Supplementary Table 2** (http://links.lww.com/CCM/G631) shows the results of the residual analysis of the outcomes in each group. The adjusted standardized residual of the DIC and late-diagnosed DIC groups for in-hospital mortality was significantly larger, indicating a stronger association between the two groups and in-hospital mortality compared with the no-DIC group. In addition, compared with the late-diagnosed DIC and DIC groups, the no-DIC group had significantly greater VFD and IFD.

The JAAM DIC score, DBCM-derived DCS level, and thrombin level in the three groups are summarized in **Table 3**. The late-diagnosed DIC and DIC groups had significantly higher DCS levels on day 1 than the no-DIC group (median [interquartile range], 22.8 [18.2–28.4] in the no-DIC group vs 51.9 [43.3–56.1] in the late-diagnosed DIC group vs 53.3 [47.4–57.5] in the DIC group; $p < 0.001$). Similarly, the thrombin levels in the late-diagnosed DIC and DIC groups were significantly higher on day 1 than in the no-DIC group (median [interquartile range], 2.3 [1.8–2.9] vs 5.8 [4.3–6.9] vs 6.6 [5.5–7.4]; $p < 0.001$). The correlation between the JAAM DIC score, DCS level, and thrombin level is shown in **Table 4**. The DCS level on day 1 was strongly correlated with thrombin level on day 1 ($\rho = 0.844$; $p < 0.05$) and DIC score on day 2 ($\rho = 0.824$; $p < 0.05$). However, we did not observe a correlation between the DCS level on day 1 and the DIC score on day 1 ($\rho = 0.384$; $p = 0.081$). Similarly, thrombin level on day 1 was strongly correlated with the DIC score on day 2 ($\rho = 0.801$; $p < 0.05$) and weakly correlated with the DIC score on day 1 ($\rho = 0.364$; $p < 0.05$). The individual variables of the JAAM DIC score according to group are summarized in **Supplementary Table 3** (http://links.lww.com/CCM/G632). We did not observe strong correlations between individual variables of the JAAM DIC score and DCS level (**Supplementary Table 4**, http://links.lww.com/CCM/G633).

DISCUSSION

In this prospective observational study, we evaluated the utility of DBCM for the early detection of DIC and thrombin level in 80 patients with sepsis. The main findings were as follows: 1) the severity and mortality of patients with a delayed diagnosis were similar to those of patients who were diagnosed with DIC upon ED admission and higher than those of patients who

TABLE 1.
Comparison of the Characteristics of Patients

Variable	No-DIC Group (*N* = 31)	Late-Diagnosed DIC Group (*N* = 34)	DIC Group (*N* = 15)	*p*
Baseline characteristic				
Age (yr), median (interquartile range)	71 (63–88)	74 (50–89)	77 (74–86)	0.466
Male, *n* (%)	23 (74.2)	21 (62.0)	11 (73.3)	0.878
Charlson Comorbidity Index score, median (interquartile range)	3 (3–4)	3 (2–4)	3 (2–4)	0.453
Site of infection, *n* (%)				
Lung	8 (25.8)	6 (17.6)	3 (20.0)	0.224
Abdominal	5 (16.1)	9 (26.5)	5 (33.3)	0.142
Urinary	6 (19.3)	11 (32.4)	5 (33.3)	0.129
Soft tissue	8 (25.8)	4 (11.8)	1 (6.7)	0.078
Other or unknown	4 (12.9)	4 (11.8)	1 (6.7)	0.243
Severity scores				
Sequential Organ Failure Assessment score, median (interquartile range)				
Day 1	3 (2–6)	7 (3–15)	11 (8–16)	< 0.001
Day 2	4 (2–8)	15 (10–16)	16 (9–19)	< 0.001
Day 3	2 (1–4)	15 (8–19)	12 (8–16)	< 0.001
Acute Physiology and Chronic Health Evaluation II score, median (interquartile range)				
Day 1	3 (2–8)	11 (3–16)	13 (6–19)	< 0.001
Day 2	5 (3–8)	17 (10–21)	15 (7–18)	< 0.001
Day 3	5 (4–7)	15 (7–19)	14 (8–18)	< 0.001
Therapy				
Total infusion volume within first 3 d (mL/kg), median (interquartile range)	72 (66–79)	88 (78–95)	91 (80–96)	< 0.001
Platelet concentrates, *n* (%)	0 (0.0)	9 (26.4)	5 (33.3)	< 0.001
Albumin, *n* (%)	1 (3.2)	9 (26.4)	7 (46.7)	< 0.001
Surgery, *n* (%)	0 (0.0)	4 (11.8)	6 (40.0)	< 0.001
Renal replacement therapy, *n* (%)	2 (6.5)	8 (23.5)	7 (46.7)	0.003
Mechanical ventilation, *n* (%)	2 (6.5)	17 (50.0)	8 (53.3)	< 0.001
Extracorporeal life support, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Anticoagulants, *n* (%)				
Recombinant thrombomodulin	0 (0.0)	2 (5.9)	1 (6.7)	0.314
Antithrombin concentrates	1 (3.2)	8 (23.5)	5 (33.3)	0.003
Heparin	2 (6.5)	5 (14.7)	3 (20.0)	0.196

DIC = disseminated intravascular coagulation.
We used one-way analysis of variance to assess the differences between the three groups.

did not develop DIC; 2) the JAAM criteria failed to diagnose the early phase of DIC on day 1, as approximately 70% of patients who developed DIC were not identified; and 3) the DCS level estimated by DBCM on day 1 could detect late-diagnosed DIC and DIC upon hospital admission and was strongly correlated with the thrombin level on day 1. To the best of our knowledge, this is the first study to evaluate the association

TABLE 2.
Comparison of the Outcomes

Outcomes	No-DIC Group (N = 31)	Late-Diagnosed DIC Group (N = 34)	DIC Group (N = 15)	p
In-hospital mortality, n (%)	0 (0)	12 (35.3)	5 (33.3)	< 0.001
Ventilator-free days (d), median (interquartile range)	28 (28–28)	18 (15–25)	19 (17–24)	< 0.001
ICU-free days (d), median (interquartile range)	25 (24–27)	12 (3–17)	14 (5–18)	< 0.001

DIC = disseminated intravascular coagulation.
One-way analysis of variance was used to estimate the p value.

TABLE 3.
Japanese Association for Acute Medicine 2006 Disseminated Intravascular Coagulation Score, Dielectric Clot Strength Level, and Thrombin Level in the Three Groups According to Disseminated Intravascular Coagulation Development

Variable	No-DIC Group (N = 31)	Late-Diagnosed DIC Group (N = 34)	DIC Group (N = 15)	p
Japanese Association for Acute Medicine 2006 DIC score, median (interquartile range)				
Day 1	2.1 (1.7–2.3)	2.2 (1.6–3.0)	5.2 (4.1–6.0)	< 0.001
Day 2	1.9 (1.8–2.2)	5.4 (4.6–6.0)	5.8 (4.1–7.0)	< 0.001
Day 3	2.0 (1.4–2.5)	6.5 (4.9–7.5)	6.2 (4.5–7.1)	< 0.001
Laboratory results, median (interquartile range)				
Dielectric clot strength level measured by dielectric blood coagulometry				
Day 1	22.8 (18.2–28.4)	51.9 (43.3–56.1)	53.3 (47.4–57.5)	< 0.001
Day 2	19.2 (15.8–24.1)	33.0 (24.3–38.3)	31.2 (26.1–40.5)	0.072
Day 3	21.5 (14.8–23.4)	31.0 (27.3–34.3)	29.2 (25.1–34.5)	0.132
Thrombin level				
Day 1 (ng/mL)	2.3 (1.8–2.9)	5.8 (4.3–6.9)	6.6 (5.5–7.4)	< 0.001
Day 2 (ng/mL)	2.2 (1.1–2.8)	3.3 (2.4–3.6)	3.2 (2.3–3.9)	0.103
Day 3 (ng/mL)	1.8 (1.0–2.8)	2.8 (1.9–3.3)	2.9 (2.3–3.5)	0.214

DIC = disseminated intravascular coagulation.
One-way analysis of variance was used to estimate the p value.

among a DBCM-derived variable, thrombin level, and DIC score.

Several guidelines for the diagnosis and treatment of DIC have been reported (20–22). The JAAM criteria were published in 2006 for DIC diagnosis (23), and they have shown higher sensitivity and predictive accuracy compared with other DIC criteria (10, 24). However, the present study showed that the JAAM criteria were not sensitive enough to diagnose the early phase of DIC. Recent studies have shown that early

anticoagulation therapy might be beneficial in a specific subpopulation with sepsis-induced DIC (25, 26), suggesting that the delay of diagnosis could worsen patient outcomes. Our results indicate that DBCM could help clinicians detecting the early phase of DIC in patients with sepsis at a high risk of death.

It has been reported that elevated or reduced thrombin levels are associated with hypercoagulable or hypocoagulable states, respectively (27, 28). Compared with other tests, such as the viscoelastic test, which

TABLE 4.
Comparison of Spearman Rank Correlation Coefficient (ρ)

		DCS Level			DIC Score			Thrombin Level		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
DCS level	Day 1	–	–	–	0.384	0.824[a]	0.614[a]	0.844[a]	−0.343	0.132
	Day 2	–	–	–	−0.061	−0.324	0.213	−0.055	0.543[a]	0.155
	Day 3	–	–	–	0.054	0.121	0.167	0.253	−0.032	0.485[a]
DIC score	Day 1	0.384	−0.061	0.054	–	–	–	0.364[a]	0.405[a]	0.210
	Day 2	0.824[a]	−0.324	0.121	–	–	–	0.801[a]	0.441[a]	0.109
	Day 3	0.614[a]	0.213	0.167	–	–	–	0.621[a]	0.487[a]	0.034
Thrombin level	Day 1	0.844[a]	−0.343	0.132	0.364[a]	0.801[a]	0.621[a]	–	–	–
	Day 2	−0.055	0.543[a]	0.155	0.405[a]	0.441[a]	0.487[a]	–	–	–
	Day 3	0.253	−0.032	0.485[a]	−0.125	0.109	0.034	–	–	–

DCS = dielectric clot strength, DIC = disseminated intravascular coagulation.
[a]$p < 0.05$.
Dashes indicate the comparison of same variables.

assesses fibrin clot formation in general, the measurement of thrombin generation could provide more information on the total coagulation capacity (29). However, because thrombin has a short half-life and is rapidly bound by naturally occurring inhibitors, the real-time measurement of thrombin level is difficult in clinical settings (30, 31). Our results indicate that DCS estimated by DBCM could be an alternative to measure thrombin level in patients with sepsis.

Most coagulation markers, to calculate DIC scores, do not use whole blood but plasma. Thus, information on blood cells, which play a critical role in the coagulation process, is lacking in these conventional measurement methods (32). DBCM can evaluate whole blood dielectric permittivity by detecting the aggregation and deformation of RBCs associated with early fibrin formation (19). Excessive thrombin generation, which can cause impaired fibrin degradation leading to intravascular fibrin deposition, is characteristic of DIC (33, 34). These interactions between plasma factors and blood cells would partially explain why DBCM could detect coagulation abnormalities related to thrombin generation and fibrin formation in the early phase of DIC. However, detailed interactions in the process of clotting have not been elucidated when DBCM is used to estimate coagulation status. Further investigation is required to clarify the mechanism underlying the abnormal coagulation function that affects DBCM variables.

Several limitations should be considered when interpreting the results of our study. First, this was an observational study conducted at a single center, which prevented us from performing statistical adjustments for potential confounders due to the limited sample size. Additional research is necessary to provide more definitive data, including large-scale studies adjusted by covariates. Second, we did not consider the effects of treatment, including anticoagulation and fluid therapy, which could influence the coagulation state and DIC score on days 2 and 3. Although there were no patients with severe polycythemia and/or anemia at hospital admission, fluid therapy could cause blood dilution and may affect the results. Third, in the thrombin assay, any protease inhibitors were not used to stop conversion from prothrombin to thrombin. Furthermore, although an ideal PPP processing protocol had not been established, cold activation of Factor VII (35) remained in the centrifugation process to prepare the PPP at low temperatures. These factors could have affected the thrombin concentrations. Fourth, a comparison between DBCM and specific modalities for monitoring global blood coagulability, such as thromboelastography or rotational thromboelastometry (ROTEM), was not performed in this study (36–38). Further research is needed to compare DBCM and thromboelastography/ROTEM results and assess their utility for predicting DIC development. Despite these limitations,

our study highlights the utility of DBCM in the early recognition of DIC and thrombin levels in patients with sepsis. These findings provide relevant insight into the diagnosis and treatment strategies for sepsis-induced DIC.

CONCLUSIONS

DCS measured by DBCM was used to detect the early phase of sepsis-induced DIC and was correlated with thrombin levels. This procedure could lead to the accurate and swift diagnosis and timely treatment of early sepsis–induced DIC. Larger studies are necessary to investigate the generalizability of our results and the feasibility of a clinical application.

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