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■ Original Article ■

The Prevalence and Significance of Overt Disseminated Intravascular Coagulation in Patients with Septic Shock in the Emergency Department According to the Third International Consensus Definition

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Background: The prevalence and prognostic value of overt disseminated intravascular coagulation (DIC) in patients with septic shock presenting to emergency departments (EDs) is poorly understood, particularly following the release of a new definition of septic shock. The purpose of this study was to investigate the prevalence and prognostic value of DIC in septic shock.
Methods: We performed retrospective review of 391 consecutive patients with septic shock admitting to the ED of tertiary care, university-affiliated hospital during a 16-month. Septic shock was defined as fluid-unresponsive hypotension requiring vasopressor to maintain a mean arterial pressure of 65 mmHg or greater, and serum lactate level ≥ 2 mmol/L. Overt DIC was defined as an International Society on Thrombosis and Hemostasis (ISTH) score ≥ 5 points. The primary endpoint was 28-day mortality.
Results: Of 391 patients with septic shock, 290 were included in the present study. The mean age was 65.6 years, the 28-day mortality rate was 26.9%, and the prevalence of overt DIC was 17.6% (n = 51) according to the ISTH score. The median DIC score was higher in non-survivors than in survivors (5.0 vs. 2.0, p = 0.001). Significant higher risk of mortality was observed in overt DIC patients compared to those without (28.2% vs. 13.7%, p = 0.005). Multivariable logistic regression analysis identified DIC to be independently associated with 28-day mortality (odds ratio, 2.689 [95% confidence interval, 1.390-5.201]).
Conclusions: Using the ISTH criteria of DIC, overt DIC in septic shock was found to be common among patients admitting to the ED and to be associated with higher mortality when it is accompanied with septic shock. Efforts are required to identify presence of overt DIC during the initial treatment of septic shock in patients presenting the the ED.

Key Words: disseminated intravascular coagulation; prevalence; shock, septic.

Introduction

Sepsis and septic shock are grave consequences of infection. Despite the significant improvement in intensive management, sepsis still has shown high morbidity and mortality. [1-4] Definition of sepsis was recently published as life-threatening organ dysfunction with infection. And organ dysfunction can be identified by an acute increase of ≥ 2 points in the sequential organ failure assessment (SOFA) score.[5] The new criteria for septic shock include fluid-unresponsive hypotension requiring vasopressors to main-

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tain mean arterial pressure of ≥ 65 mmHg with serum lactate level ≥ 2 mmol/L. Disseminated intravascular coagulation (DIC), which leads to fibrin thrombosis, microvascular obstruction, and decreased oxygen delivery resulting in organ failure.[6,7] Although previous studies have reported an association between DIC and mortality of sepsis patients in intensive care units, few studies have evaluated patients with septic shock attending emergency department (ED).[8,9] Furthermore, there is no study about the prevalence and prognostic value of DIC in septic shock patients following the new definition of septic shock.

Therefore, the purpose of present study was to evaluate the prevalence of DIC according to the definition of the International Society on Thrombosis and Hemostasis (ISTH) and determine the predictive value of overt DIC in septic shock patients.

Materials and Methods

1) Study design

The present retrospective cohort study was conducted in the academic ED of a tertiary care, university-affiliated hospital in Seoul, Korea that cares for approximately 110,000 patients per year. Intensive care physicians are available 24 h a day, 7 days a week, for patients who require treatment for sepsis. Because of the retrospective nature of the study, our institutional review board approved the review of patient data before its commencement and waived the requirement for informed consent.

2) Data collection and patient management

The electronic medical records of all consecutive adult (age, > 18 years) patients with septic shock admitted to the ED of our hospital between November 2014 and March 2016 were examined. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[5] Organ dysfunction was defined as an acute change in the total SOFA score by ≥ 2 points due to infection.[5,10] Septic shock was defined as a clinical evidence of sepsis with persistent hypotension requiring vasopressor to maintain a mean arterial pressure of ≥ 65 mmHg and serum lactate level > 2 mmol/L (> 18 mg/dL) despite adequate volume resuscitation.[5] The exclusion criteria utilized were as follows: known coagulation disorder, use of anticoagulation medications, do-not-resuscitate order, absence of outcome data, and lack of blood coagulation testing while in ED. Patients with recognized septic shock after 6 h since ED admission were also excluded. The primary outcome of the present study was 28-day mortality.

Clinical and demographic characteristics of all patients, including age, sex, comorbidities, initial vital signs, laboratory findings, site of infection, and clinical outcomes, were retrieved from electronic hospital records. We used initial laboratory findings, including coagulation testing, from ED. Platelet count, prothrombin time, fibrinogen, and fibrinogen degradation products (FDP) were used to calculate ISTH scores (Table 1). No increase, moderate

Table 1. Scoring system for overt DIC proposed by ISTH

Score	
Platelet count (× 10^3/μL)	
< 50	2
≥ 50 and < 100	1
≥ 100	0
Fibrin-related markers	
Strong increase	3
Moderate increase	2
No increase	0
Prothrombin time (s)	
≥ 6	2
3-6	1
< 3	0
Fibrinogen level (g/mL)	
< 100	1
≥ 100	0
Calculate score	
If ≥ 5, compatible with overt DIC; repeat scoring daily	
If < 5, suggestive (not affirmative) for non-overt DIC; repeat next 1 to 2 days	

DIC: disseminated intravascular coagulation; ISTH: international society of thrombosis and hemostasis.

increase, and strong increase in fibrin-related markers were defined as FDP < 10, 10 ≤ FDP < 25, and FDP ≥ 25 mg/L, respectively.[11] DIC was defined as an ISTH score of ≥ 5. Blood sampling was conducted within 10 min of presentation to ED. Septic shock treatment was administered according to the recommendations of the international guidelines of Surviving Sepsis Campaign.[12] Rapid administration of sufficient amounts of fluids and antibiotics was performed as soon as possible. Other therapies, such as vasopressors and glucocorticoids, were administered as required. Transfusions of fresh frozen plasma or platelets were not performed for the treatment of DIC unless there was an evidence of significant bleeding. Decisions to perform continuous renal replacement therapy, mechanical ventilation, or other interventions were at the discretion of the attending intensive care physician.

3) Statistical analysis

All data are presented as the mean ± standard deviation or median with the interquartile range for continuous variables, and as absolute or relative frequencies for categorical variables. Patients who survived to day 28 were compared with patients who did not. Student's *t* test and Mann–Whitney *U* test were used to compare continuous variables. The chi-square test was used to compare categorical variables. The results of logistic regression analysis for 28-day mortality adjusted for significant factors identified by univariate analysis ($p < 0.2$) are presented as odds ratios (ORs) and 95% confidence intervals (CIs). P-values of ≤ 0.05 were considered statistically significant. All statistical analyses were performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 391 septic shock patients meeting the new definition of septic shock presented to our ED. Of these, we excluded 56 patients with previously known coagulopathy, 9 with do-not-resuscitate orders, 21 whose initial DIC blood tests were not obtained, 11 currently receiving anticoagulation medications, and 4 in whom 28-day mortality data were unavailable. Accordingly, a number of finally included patients with septic shock was 290 (Fig. 1). The mean age of the patients included in the study was 65.6 ± 12.7 years, 60.3% of which were male. Of the 290 patients, 78 (26.9%) did not survive to day 28 after admission to the ED. Base-

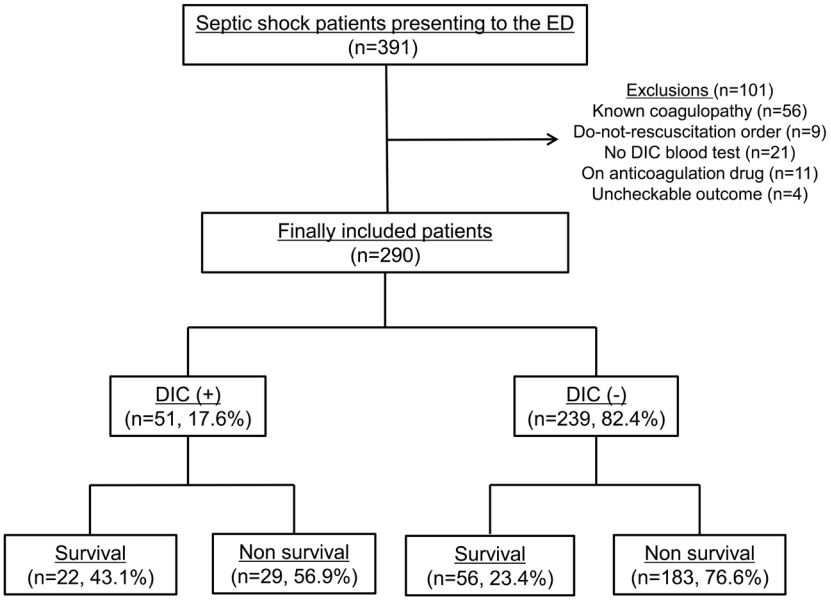

Fig. 1. Patient flow diagram. ED: emergency department; DIC: disseminated intravascular coagulation.

Table 2. Baseline characteristics and vital signs of septic shock patients according to presence of DIC

Variables	No DIC (n = 239)	DIC (n = 51)	p-value
Demographic factor			
Age (years)	66.0 ± 12.9	63.4 ± 11.4	0.173
Male sex	145 (60.7)	30 (58.8)	0.875
Comorbidity			
Hypertension	75 (31.4)	14 (27.5)	0.620
Diabetes mellitus	62 (25.9)	8 (15.7)	0.150
Cardiac disease	37 (15.5)	4 (7.8)	0.188
Liver disease	14 (8.4)	7 (20.0)	0.062
Neoplasm	105 (43.9)	27 (52.9)	0.279
CKD	12 (5.0)	1 (2.0)	0.477
COPD	18 (7.5)	0 (0.0)	0.050
Immunosuppressed	120 (50.2)	29 (56.9)	0.442
Sites of infection			
Lung	65 (27.2)	2 (3.9)	0.000
Urinary tract	34 (14.2)	2 (3.9)	0.058
Intraabdominal	41 (17.2)	11 (21.6)	0.546
Soft tissue	4 (1.7)	2 (3.9)	0.285
CNS	2 (0.8)	0 (0.0)	1.000
Others	93 (38.9)	34 (66.7)	0.000
Initial vital signs			
Systolic blood pressure (mmHg)	100.6 ± 30.3	89.0 ± 20.4	0.001
Diastolic blood pressure (mmHg)	63.9 ± 20.8	57.3 ± 16.0	0.014
Heart rate (beats/min)	109.0 ± 27.3	105.7 ± 26.5	0.431
Respiration rate (breaths/min)	23.4 ± 6.4	22.0 ± 4.0	0.056
Body temperature	37.4 ± 1.4	36.9 ± 1.1	0.002

Values are expressed as mean ± SD, median and interquartile range, or n (%).
DIC: disseminated intravascular coagulation; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CNS: central nervous system.

line characteristics and vital signs of patients with septic shock, according to the presence of DIC, are summarized in Table 2. No significant differences in age or sex were observed according to 28-day survival (Table 3). Further, no significant differences in the presence of comorbidities or infection site were observed between the two groups. No initial vital signs, except body temperature, differed significantly between the two groups.

Demographic characteristics, initial vital signs, and infection site are presented in Table 3, according to survival at day 28. The overall prevalence of DIC according to ISTH criteria was 17.6%. The prevalence of DIC was higher in patients who did not survive to day 28 compared to those who did (28.2% vs. 13.7%, p = 0.005). A significant difference in median ISTH score was observed between the 28 day survival and non-survival groups (2.0 vs. 5.0, p = 0.001; Table 3).

Cardiac disease, chronic kidney disease, chronic obstructive lung disease, urinary tract infection, body temperature, DIC frequency, and DIC score were identified to be significantly associated with 28-day mortality using univariate analysis. Stepwise logistic regression analysis

Table 3. Baseline characteristics and vital signs of septic shock patients according to 28-day mortality

Variables	Survival (n = 212)	Non survival (n = 78)	p-value
Demographic factor			
Age (years)	65.4 ± 11.8	66.1 ± 15.1	0.720
Male sex	126 (59.4)	49 (62.8)	0.685
Comorbidity			
Hypertension	65 (30.7)	24 (30.8)	1.000
Diabetes mellitus	51 (24.1)	19 (24.4)	1.000
Cardiac disease	26 (12.3)	15 (19.2)	0.182
Liver disease	16 (10.5)	5 (10.2)	1.000
Neoplasm	99 (46.7)	33 (42.3)	0.510
CKD	7 (3.3)	6 (7.7)	0.119
COPD	10 (4.7)	8 (10.3)	0.100
Immunosuppressed	110 (51.9)	39 (50.0)	0.792
Sites of infection			
Lung	45 (21.2)	22 (28.2)	0.271
Urinary tract	30 (14.2)	6 (7.7)	0.163
Intraabdominal	35 (16.5)	17 (21.8)	0.304
Soft tissue	4 (1.9)	2 (2.6)	0.662
CNS	1 (0.5)	1 (1.3)	0.466
Others	97 (45.8)	30 (38.5)	0.288
Initial vital signs			
Systolic blood pressure (mmHg)	98.7 ± 29.1	98.1 ± 29.3	0.865
Diastolic blood pressure (mmHg)	62.5 ± 19.2	63.3 ± 22.7	0.772
Heart rate (beats/min)	107.7 ± 27.5	110.3 ± 26.2	0.469
Respiration rate (breaths/min)	23.0 ± 6.5	23.4 ± 4.5	0.631
Body temperature	37.4 ± 1.3	37.0 ± 1.3	0.021
DIC score	2.0 (2.0-3.0)	5.0 (5.0-5.0)	0.001
DIC frequency	29 (13.7)	22 (28.2)	0.005

Values are expressed as mean ± SD, median and interquartile range, or n (%).
CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CNS: central nervous system; DIC: disseminated intravascular coagulation.

was conducted to find independent variables able to predict 28-day mortality. DIC scores were not entered into the logistic regression analysis because of multicollinearity with DIC frequency. The presence of DIC was revealed to be independently associated with higher risk of mortality (OR, 2.689; [95% CI, 1.390-5.201], p = 0.003; Table 4).

The ORs of prothrombin time and fibrinogen were 1.033 and 0.772, respectively (p = 0.054 and p = 0.003, respectively). Platelet count and fibrin-related markers were not significantly associated with higher risk of death (Table 5). Increasing ISTH scores was found to be an association with higher risk of death (Fig. 2).

Discussion

The prevalence of overt DIC by ISTH criteria, was

Table 4. Multivariate logistic regression analysis for 28-day mortality

Variables	Non-survival	
	p-value	OR (95% CI)
DIC	0.003	2.689 (1.390-5.201)

Adjusted for age, sex, cardiac disease, CKD, COPD, UTI origin infection, body temperature, and DIC.
DIC: disseminated intravascular coagulation; CI: confidence interval; OR: odds ratio.

Table 5. OR of each components of ISTH score for 28-day mortality

Variables	Non survival	
	p-value	OR (95% CI)
Platelet count	0.805	1.000 (0.997-1.002)
Fibrin-related marker	0.089	1.007 (0.999-1.015)
Prothrombin time	0.054	1.033 (0.999-1.068)
Fibrinogen	0.003	0.772 (0.650-0.917)

OR: odds ratio; ISTH: international society of thrombosis and hemostasis; CI: confidence interval.

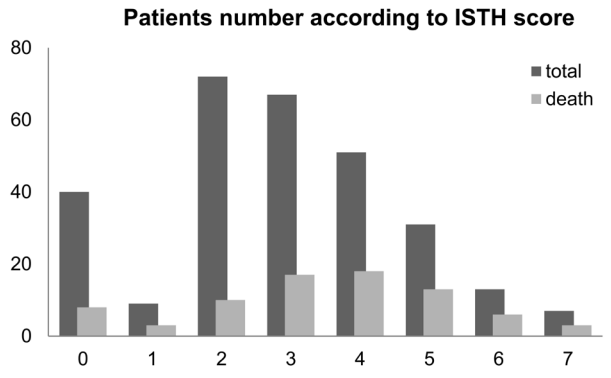

Fig. 2. Patient number according to ISTH score. ISTH: international society of thrombosis and hemostasis.

common among patients attending ED with septic shock diagnosed by new definition (17.6%). Higher DIC scores were observed in the non-survival group than in survival group at 28 days after ED admission. Furthermore, the presence of DIC in septic shock patients has shown independent association with 28-day mortality.

A new septic shock definition was recently published. Compared with the previous septic shock definition, the new clinical criteria includes a vasopressor requirement and serum lactate > 2 mmol/L despite volume administration to maintain a mean arterial pressure ≥ 65 mmHg.[12] In that report, risk-adjusted hospital mortality for this group was significantly higher than fluid resistant hypotension requiring vasopressor but with a serum lactate of ≤ 2 mmol/L (42.3% vs. 30.1%). These results indicate that the new septic shock definition identifies patients with more severe septic shock than the previous definition. Accordingly, the prevalence of DIC and prognostic value of DIC in terms of outcomes should be reevaluated according to the new definition of septic shock. We evaluated the prevalence and prognostic value of DIC using a relatively large sample and strict diagnostic criteria with uniform treatment at a single institution. Our results indicate DIC scores have utility in identifying patients at a high risk of septic shock. Although there has been a controversy regarding the efficacy of treating DIC in patients with sepsis, therapies aimed at DIC may improve outcomes if the presence of DIC is confirmed early.[13-15]

The prevalence of DIC in severe sepsis and septic shock were reported as 18.1% and 27.5%, respectively, in a previous study by Gando et al.[11] The apparent difference in the prevalence of DIC observed in the present study may be attributable to Gando et al.[11] performing DIC blood tests on days 1 and 4, whereas DIC-related blood sample were drawn on the first day of ED admission in the present study. Although our results indicate a lower prevalence of DIC, the actual prevalence of DIC may be higher if serial evaluations for DIC had been performed. A previous ED-based study reported that overt DIC according to ISTH criteria was found in 13.4% of patients with sepsis; but, the prevalence overt DIC in septic shock may have been underestimated in this study because all patients of sepsis, severe sepsis, and septic shock patients were included in that study.[6]

The ISTH DIC score is commonly used in clinical setting and associated with adverse outcomes in sepsis patients.[16-20] The result of our study also demonstrate the prognostic value of DIC to identify high risk patients in septic shock. The frequency of patients who had developed DIC in the 28-day mortality group was higher than that of survival group. Further, DIC has shown independent association with 28-day mortality in multivari-

ate logistic regression analysis, corroborating the results of pre-existing studies. The result of this present study indicate that DIC still has predictive value of identifying high risk patients of sepsis when applied to a new definition of septic shock. Previous studies have reported the areas under the receiver operating characteristic curve of the ISTH criteria in predicting 30-day mortality as 0.819, which is higher than in the present study (0.629). This difference may be attributable to differences in the study population and the lower mortality despite we only included septic shock patients in our study.[6]

The major limitation of the present study was the single center retrospective study design that reduced the broader generalization of our results. Furthermore, we did not adjust for disease severity during logistic regression analysis and were, therefore, unable to accurately evaluate DIC unable to accurately assume that DIC can predict 28-day mortality. Moreover, differences in individual treatment may have affected the outcomes observed in the present study as the treatment for septic shock was not protocolized, although the management of septic shock was followed by the surviving sepsis campaign. However, the overall 28-day mortality was 26.9%, which was lower than the > 40% mortality previously reported when utilizing the previous consensus definition of septic shock.[5] Accordingly, inconsistent treatment did not have a significant effect on patient outcomes. In addition, the proportion of immunosuppressed patient is quite high, so it might be difficult to generalize our result. Lastly, we are unable to exclude the possibility of underestimating the true prevalence of DIC as we used initial DIC laboratory results only. Serial evaluations of the DIC score may increase the accurate evaluation of DIC prevalence and prognostic value observed in our study.

In conclusion, the prevalence of DIC in patients meeting the new definition of septic shock was 17.6%, according to the overt DIC criteria of ISTH. DIC independently associated with 28-day mortality and may have utility in identifying patients at a high risk of death due to septic shock. Efforts are required to identify presence of overt DIC during the early treatment of septic shock in patients attending ED.

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