A Proposal of the Modification of Japanese Society on Thrombosis and Hemostasis (JSTH) Disseminated Intravascular Coagulation (DIC) Diagnostic Criteria for Sepsis-Associated DIC

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Abstract

Sepsis-associated disseminated intravascular coagulation (DIC) carries a high risk of death. Thus, a simple tool to quickly establish DIC diagnosis is required. The purpose of this study was to introduce the simple and reliable tool for the prediction of outcome in patients with sepsis complicated by coagulopathy. We investigated the performance of simplified Japanese Society on Thrombosis and Hemostasis (JSTH) DIC diagnostic criteria. In this study, we conducted a retrospective, multicenter survey in 107 general emergency and critical care centers in secondary and tertiary care hospitals. A total of 918 patients with sepsis-associated coagulopathy who underwent antithrombin supplementation were examined. The relationships between patient mortality and each of the baseline (ie, before treatment) JSTH-DIC diagnostic criteria were examined. A reduced platelet count, increased prothrombin time (PT) ratio, and lower antithrombin activity were correlated with 28-day mortality, while fibrinogen and fibrin degradation product (FDP) level were not. Thus, the number of points assigned to FDP levels was reduced from 3 to 1 (above 20 µg/mL). The simplified JSTH diagnostic criteria combining platelet count, PT ratio, antithrombin activity, and FDP level (reduction in the maximum score) strongly predicted 28-day mortality and allowed us to diagnose a larger/similar number of patients with DIC as compared to the original JSTH-DIC. The simplified JSTH-DIC diagnostic criteria show a similar performance to JSTH-DIC criteria in patients with septic coagulopathy. The lower number of laboratory markers used in the simplified JSTH-DIC score may increase its applicability and routine use in emergency and critical care setting.

Keywords

disseminated intravascular coagulation, sepsis, diagnostic criteria, fibrinogen and fibrin degradation products, antithrombin activity

Introduction

Disseminated intravascular coagulation (DIC) and shock independently predict a poor outcome in severe sepsis,¹ which makes a rapid and accurate diagnosis of these conditions of extreme importance. There are 3 well-accepted diagnostic criteria for DIC: the Japanese Ministry of Health, Labour and Welfare (JMHW) criteria,² the International Society on Thrombosis and Haemostasis (ISTH) criteria,³ and the Japanese Association of Acute Medicine (JAAM) criteria.⁴ A comparison of the performances of these criteria is hampered by the lack of a reference test as well as the absence of a standard and objective definition of DIC. However, it is important to understand the prognostic value of each criterion and a set of criteria to enable the prompt identification of patients who may benefit from specific treatments for coagulopathy. The JAAM criteria are most commonly used for the diagnosis of acute-phase DIC in

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Japan because they are easy to calculate,⁵ seem to own a higher prognostic value compared to other scoring systems,^{4,6,7} and enable the initiation of DIC treatment at earlier stages.^{8,9} One of the reasons for this better performance of the JAAM score was considered to be the inclusion of systemic inflammatory response syndrome (SIRS) among the criteria. In the latest Third International Consensus Definitions for Sepsis and Septic Shock, SIRS criteria have not been included. In addition, the severity of coagulation/fibrinolysis abnormalities which are the characteristic features of DIC is not considered in the consensus, making it unhelpful for the diagnosis of sepsis-associated DIC. Recent studies have shown that anticoagulant therapies are only effective in patients with relatively severe coagulation disorders.^{10,11} Thus, diagnostic criteria that reflect the severity of the coagulopathy would be potentially more useful since they would allow an early start of treatment. For this reason, the Japanese Society on Thrombosis and Hemostasis (JSTH) recently proposed new criteria for the diagnosis of DIC where SIRS is replaced by antithrombin activity and additional markers of coagulation activation such as thrombin-antithrombin (TAT) complex, soluble fibrin (SF), and prothrombin fragment₁₊₂ (PF₁₊₂) are considered.¹² However, the current JSTH diagnostic criteria are too complicated for use in emergency and critical care settings. Thus, the purpose of the present study was to derive a simplified JSTH score for patients with septic coagulopathy that would be easier to calculate and would maintain a similar prognostic value to the original JSTH score. Finally, we intended to compare the prognostic values of the original and the simplified scoring systems.

Patients and Methods

Data Collection

Pooled data from postmarketing surveys conducted by Nihon Pharmaceutical (Tokyo, Japan) were utilized for the analysis. Patients with sepsis having coagulopathy who had undergone antithrombin substitution were accumulated between May 2006 and March 2015. From 1746 cases, 918 full data sets were obtained. All the patients were treated with a supplementation dose of antithrombin concentrate (1500-3000 IU/d; Nihon Pharmaceutical). The survey was conducted in accordance with the Declaration of Helsinki, Good Vigilance Practice, and Good Post-Marketing Study Practice. The complete anonymization of personal data was performed upon data collection. Therefore, the board of each hospital and the ethical committees waived the need for informed consent acquisition and approval by the institutional review boards. The prespecified data monitoring committee examined the study methods and approved the use of data.

Laboratory Measurements

In this survey, the platelet count, fibrin degradation product (FDP) level, prothrombin time (PT), and antithrombin activity were measured at local laboratories. The platelet count was calculated using the electric impedance method, PT was

Table 1. Baseline Patient Demographics.

Characteristics	Survivor (n = 604)	Nonsurvivor (n = 314)	P Value
Sex			
Male	340	192	.160
Female	264	122	
Age (years)	72 (62-79)	77 (68-83)	.000
Body weight (kg)	52.8 (45.0-62.0)	50.0 (43.2-60.0)	.003
SIRS score	3.0 (2.0-3.0)	3.0 (2.0-3.0)	.725
Suspected source of infection			
Respiratory tract	185	144	.000
Digestive tract	159	57	.005
Urinary tract biliary tract	66	15	.001
Hepatobiliary tract	63	12	.000
Coagulation/fibrinolysis markers			
Platelet count ($\times 10^9/L$)	6.9 (4.1-10.5)	5.8 (3.0-8.5)	.000
FDP ($\mu g/mL$)	23.9 (12.8-45.7)	22.5 (12.0-44.6)	.501
PT ratio	1.35 (1.20-1.63)	1.42 (1.27-1.81)	.000
AT activity (%)	48.0 (39.0-60.0)	42.0 (34.0-52.0)	.000

Abbreviations: SIRS, systemic inflammatory response syndrome; FDP, fibrin degradation products; PT, prothrombin time; AT, antithrombin.

measured using the scattered light detection method, and FDP was detected using latex immunoassays. For the measurement of antithrombin activity, the plasma anti-factor Xa activity or the antithrombin activity was assessed (chromogenic substrate method, reference intervals: 70%-120%).

Statistical Analysis

The numerical values in the text and tables represent the median and interquartile range. Univariate associations were evaluated using the Fisher exact test or the unpaired Wilcoxon signed rank test. The relationships between 28-day mortality and baseline characteristics (collected before antithrombin supplementation) were analyzed using logistic regression analysis (the enter method). The primary outcome of the analysis was 28-day mortality (survived, 1; died, 0). Age, body weight, SIRS score, platelet count, FDP, PT ratio, antithrombin activity, and suspected infectious sites were considered as explanatory variables. The results were reported as the odds ratio (OR), Wald value, *P* value, and 95% confidence intervals. The sensitivity, specificity, positive predictive value, and negative predictive value of the criteria were calculated. *P* < .05 was considered to denote statistical significance. All analyses were performed using SPSS 22.0 for Windows (IBM SPSS Inc, Chicago, Illinois).

Results

Study Population

Of the 918 patients included, 604 patients survived (65.8%) and 314 patients (34.2%) died at 28 days. Table 1 shows the

Table 2. Relationship Between 28-Day Mortality and Patient Characteristics.

Characteristics	OR	Wald	P Value	95% CI
Age	0.970	23.988	.000	0.959-0.982
Body weight	1.010	2.467	.116	0.997-1.023
SIRS score	0.935	0.756	.385	0.802-1.089
Platelet count	1.048	10.937	.001	1.019-1.078
Fibrinogen and FDP	1.002	1.498	.221	0.999-1.004
PT ratio	0.666	8.595	.003	0.507 - 0.874
AT activity	1.026	20.708	.000	1.015-1.037
Respiratory tract infection	0.751	2.263	.132	0.518-1.09
Digestive tract infection	1.836	7.639	.006	1.193-2.824
Hepatobiliary tract infection	3.329	11.516	.001	1.662-6.667
Urinary tract infection	2.600	7.923	.005	1.337-5.059

Abbreviations: AT, antithrombin; CI, confidence interval; FDP, fibrin degradation products; OR, odds ratio; PT, prothrombin time; SIRS, systemic inflammatory response syndrome.

baseline characteristics of the patients. The gender distribution was similar between the survivor and nonsurvivor groups. The median age of the survivors was 72 (62-79) years compared to 77 (68-83) years of the nonsurvivors ($P < .001$). The causes of sepsis included respiratory tract infections in 329 (40.2%) cases, digestive tract infections in 216 (23.5%) cases, urinary tract infections in 81 (9.9%) cases, and hepatobiliary tract infections in 75 (9.2%) cases. Regarding the coagulation profile, the JSTH-DIC score was higher in the nonsurvivors (survivors: 5 [4-6] vs nonsurvivors: 6 [5-7], $P < .001$). The platelet count was lower ($P < .01$), the PT ratio was higher ($P < .001$), and the antithrombin activity was lower in the non-survivors ($P < .001$). In contrast, the FDP level did not differ significantly between survivors and nonsurvivors.

Relationship Between Markers and Mortality

Logistic regression analysis showed a significant association with mortality for patient age, platelet count, PT ratio, antithrombin activity, and a source of infection originating in the digestive tract, hepatobiliary tract, or urinary tract significantly (Table 2). A better survival was observed in younger patients (OR: 0.970, $P < .001$), patients with a higher platelet count (OR: 1.048, $P = .001$), patients with a lower baseline PT ratio (OR: 0.666, $P = .003$), and patients with a higher baseline antithrombin activity (OR: 1.026, $P < .001$). In contrast, body weight, baseline SIRS score, baseline FDP level, and a source of infection originating in the respiratory tract did not have any influence on survival (Table 2).

The relationship between each baseline JSTH-DIC laboratory criterion and 28-day mortality is shown in Figures 1 to 4. Figure 1 shows the relation between the platelet counts at baseline and the 28-day mortality. The mortality rate increased as the platelet count decreased. The mortality rate increased along with the prolongation of PT (Figure 2). Similar relations were observed between the mortality and antithrombin activity level (Figure 3). In contrast, approximately half of the patients had

Figure 1. Patient counts and mortality rates according to platelet count. The bar graph shows the number of patients in each category, and the line graph represents the mortality rate. Mortality rate increased along with a decrease in the platelet count.

Figure 2. Patient counts and mortality rates according to prothrombin time (PT) ratio. The bar graph shows the number of patients in each category, and the line graph represents the mortality rate. The mortality rate increased with a decrease in PT time ratio.

an FDP level of less than 20 $\mu\text{g/mL}$ and the FDP level was not correlated with the mortality rate (Figure 4).

Comparison of the Original and Simplified JSTH Criteria

When the molecular markers, that is, TAT complex, SF, and PF₁₊₂, were removed from the original JSTH-DIC diagnostic criteria and DIC was diagnosed for a score of 4 or more, neither the DIC diagnostic rate (69.7% vs 70.7%) nor the mortality rate (38.1% vs 38.8%) differed between the original and the simplified JSTH criteria. Figure 5 shows the relationships between the original and simplified JSTH-DIC scores and the mortality rate. The mortality rate was 17% for an original JSTH-DIC

Figure 3. Patient counts and mortality rates according to antithrombin activity. The bar graph shows the number of patients in each category, and the line graph represents the mortality rate. The mortality increased along with a decrease in antithrombin activity.

Figure 4. Patient counts and mortality rates according to fibrinogen and fibrin degradation products. The bar graph shows the number of patients in each category, and the line graph represents the mortality rate. Mortality did not change depending on the fibrinogen and fibrin degradation product (FDP) level.

score of 1, and it gradually increased as the score increased, reaching a maximum of 46% for a score of 8. The mortality rate then decreased to 43% for a score of 9. For the simplified JSTH-DIC scores, the mortality rate ranged between 23% and 24% when the score was 1 to 3 points. For higher simplified JSTH-DIC scores, the mortality rate increased linearly from 34% at 4 points up to a maximum of 53% with 7 points. Table 3 summarizes the diagnostic performance of the original and simplified JSTH-DIC criteria. The sensitivity of the simplified JSTH-DIC criteria was over 80% and higher than that of the original JSTH-DIC. Specificity was almost identical.

Discussion

This study found that a simplified JSTH-DIC score owns a similar/higher prognostic value compared to the original JSTH-DIC score and identifies a similar/larger group of patients with DIC at an earlier stage. The simplified JSTH-DIC score used only 4 readily available laboratory parameters, which increases ease of use and applicability. If confirmed in future studies, the simplified JSTH-DIC score could replace the JAAM and JSTH-DIC scores for the diagnosis of DIC in patients with sepsis and allow the prompt start of anticoagulant treatment.

Disseminated intravascular coagulation is defined as the “activation of intravascular coagulation with a loss of localization.”³ To identify patients with DIC, all of the currently available major diagnostic criteria include the platelet count, PT, and FDP/D-dimer. While the JMW and ISTH criteria use also fibrinogen levels as a fourth category, the JAAM criteria consider the presence of SIRS. At present, the JAAM criteria are the most commonly used criteria for the diagnosis of sepsis-associated DIC in Japan.¹³ However, the SIRS score did not differ significantly between survivors and nonsurvivors in the present study. In addition, we recently reported that the SIRS category was replaceable with the antithrombin activity without changing the sensitivity and specificity to death.¹⁴ Indeed, the number of patients diagnosed as having DIC, the incidence of bleeding, the degree of organ dysfunction, and the mortality rate were similar between the modified and the original JAAM criteria.

Based on the new evidence, the JSTH recently proposed a new scoring system (Table 4)¹² that includes antithrombin activity and other molecular markers, such as TAT complex, SF, and PF₁₊₂. These markers are sensitive to the activation of coagulation and may be useful to detect early stages of the coagulopathy, such as pre-DIC¹⁵⁻¹⁷; however, testing for these markers is not yet widespread and is time-consuming, which make such tests not suitable for routine use in emergency situations. Since the primary purpose of the current study was to identify the patients with the risk of death, we did not measure these molecular markers. However, the value of these markers in the detection of early-stage DIC should be examined in the other study. Another issue of debate is the weight assigned to fibrin-related markers and their relevance, which may differ depending on the underlying disease.¹⁸ While the JSTH-DIC score allocates 3 points for FDP, the current study did not demonstrate higher mortality in parallel with increasing FDP values among patients with sepsis. This allowed us to allocate just 1 point for FDP, thereby simplifying the JSTH criteria. The reason for the peak in FDP can be explained by the suppression of the fibrinolytic system induced by the increased production of plasminogen activator inhibitor 1.^{19,20} In addition, thrombin induces the formation of thrombin-activatable fibrinolysis inhibitor, which further suppresses fibrinolysis.²¹ Inflammation and coagulation have been widely accepted to play pivotal roles in the pathogenesis of sepsis,²²⁻²⁴ and pro-thrombotic and antifibrinolytic

Figure 5. The patient counts and mortality rates according to the categories of the original and simplified versions of Japanese Society on Thrombosis and Hemostasis (JSTH) disseminated intravascular coagulation (DIC) diagnostic criteria. The bar graph shows the number of patients in each category, and the line graph represents the mortality rate. The mortality rate increased linearly for scores of 3 to 7 and exceeded 30% based on the simplified JSTH-DIC score of 4.

Table 3. Comparison of the Diagnostic Performance Between Original and Simplified JSTH-DIC Criteria.

Variables	JSTH-DIC Diagnostic Criteria	Simplified JSTH-DIC Diagnostic Criteria	
Sensitivity (%)	77.7	80.3	NS
Specificity (%)	34.4	34.3	NS
PPV (%)	38.1	38.8	NS
NPV (%)	74.8	77.0	NS

Abbreviations: DIC, disseminated intravascular coagulation; JSTH, Japanese Society on Thrombosis and Hemostasis; NPV, negative predictive value; NS, not significant; PPV, positive predictive value.

reactions are both induced as part of the host defense scheme.²⁵⁻²⁷ The other possible reason is the different reference value between the reagents. Since FDP was measured in the local laboratories, this might affect the result.

One of the unique aspects of the JSTH-DIC is the inclusion of antithrombin activity among the criteria. The measurement of plasma levels of physiological coagulation inhibitors, such as antithrombin and protein C, has been repeatedly reported to be useful.²⁸⁻³⁰ Gando et al³¹ found decreased levels of these coagulation inhibitors in 40% to 60% of critically ill patients and in 90% of patients with DIC. In a previous study, we showed that antithrombin activity decreases along with an increase in DIC severity and a cutoff value of 70% might be appropriate for the diagnosis of DIC since the mortality exceeds 30% when the level decreased to less than 70%.¹⁴ Similarly, JSTH adopted this cutoff since the supplementation of antithrombin is initiated with this value.

Table 4. Comparison of the Original and Simplified JSTH-DIC Criteria.

	JSTH Criteria	Score	Simplified DIC Criteria	Score
Platelet count ($\times 10^9/L$)	$\geq 120, <80$	1	$\geq 120, <80$	1
	$\leq 80, <50$	2	$\geq 80, <50$	2
	≥ 50	3	≥ 50	3
FDP ($\mu g/mL$)	$\geq 10, <20$	1	≥ 20	1
	$\geq 20, <40$	2		
	≥ 40	3		
PT ratio	$\geq 1.25, <1.67$	1	$\geq 1.25, <1.67$	1
	≥ 1.67	2	≥ 1.67	2
AT activity (%)	≤ 70	1	≤ 70	1
TAT complex, SF, PFI +2	≥ 2 -fold of upper limit in normal range	1	NA	–
Hepatic failure	If present	–3	NA	–
Diagnosis of DIC		≥ 6		≥ 4

Abbreviations: AT, antithrombin; DIC, disseminated intravascular coagulation; FDP, fibrin degradation products; JSTH, Japanese Society on Thrombosis and Hemostasis; NA, not assessed; PFI+2, prothrombin fragment 1+2; PT, prothrombin time; SF, soluble fibrin; TAT, thrombin–antithrombin.

Currently, antithrombin and recombinant thrombomodulin are the primary anticoagulants recommended by the Japanese guidelines.^{32,33} Previous studies have suggested that these anticoagulant therapies might only be effective in patients with sepsis having severe coagulation disorders and predicted mortality of over 30%.^{34,35} Since mortality rates higher than 30% are predicted by a simplified JSTH-DIC of 4 points or more, we suggest that a score of 4 might be the optimal cutoff

and should be validated in future prospective and standardized studies.

Limitations

The present study has some limitations. First, the database was consisted of postmarketing survey data. Although only the data before the treatment were utilized, selection bias can exist. For example, the antithrombin activity in most of the participants was less than 70% at baseline because the use of antithrombin concentrate is permitted when the antithrombin activity is 70% or less and this could be a strong bias. We have previously reported that approximately one-fourth of patients with sepsis having DIC showed baseline antithrombin activity of 70% or more and the mortality of these patients were significantly lower than the others.¹⁴ Thus, the generalization of the study findings should be made with caution. Patients with antithrombin activity levels of more than 70% should be included in future studies to examine the diagnostic value of TAT complex, SF, PF₁₊₂, and antithrombin activity. Furthermore, the data were collected for 9 years, and the advances of the treatment during this period should influence the patients' outcome.

Second, because data on the fibrinogen and D-dimer levels were not available, we could not compare the simplified JSTH criteria with the ISTH criteria. This interesting subject should be addressed in a future study.

Third, since the median age was higher in the nonsurvivors, it would be a significant confounding factor in this study. Thus, a future analysis should be performed in age-matched groups. Finally, the performance of the simplified JSTH-DIC score outside sepsis-associated DIC remains to be determined, and it should also be validated in a future prospective study.

Conclusion

Simplified JSTH-DIC diagnostic criteria predict 28-day mortality rate in patients with septic coagulopathy with an accuracy similar to the original JSTH-DIC criteria. The lower number of laboratory markers used in the simplified JSTH-DIC may increase their applicability and generalizability in emergency and critical care settings. Therapeutic strategies for DIC are time sensitive and should target patients with hypercoagulability and a high risk of death. Thus, the impact of these criteria on decisions to initiate anticoagulant therapy should be examined in a future prospective study.

Authors' Note

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