

# Natural history of disseminated intravascular coagulation diagnosed based on the newly established diagnostic criteria for critically ill patients: Results of a multicenter, prospective survey\*

Satoshi Gando, MD, FCCM; Daizoh Saitoh, MD; Hiroshi Ogura, MD; Toshihiko Mayumi, MD; Kazuhide Koseki, MD; Toshiaki Ikeda, MD; Hiroyasu Ishikura, MD; Toshiaki Iba, MD; Masashi Ueyama, MD; Yutaka Eguchi, MD; Yasuhiro Ohtomo, MD; Kohji Okamoto, MD; Shigeki Kushimoto, MD; Shigeatsu Endo, MD; Shuji Shimazaki, MD; Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) Study Group

**Objective:** To survey the natural history of disseminated intravascular coagulation (DIC) in patients diagnosed according to the Japanese Association for Acute Medicine (JAAM) DIC scoring system in a critical care setting.

**Design:** Prospective, multicenter study during a 4-month period.

**Setting:** General critical care center in a tertiary care hospital.

**Patients:** All patients were enrolled when they were diagnosed as DIC by the JAAM DIC scoring system.

**Interventions:** None.

**Measurements and Main Results:** Platelet counts, prothrombin time ratio, fibrinogen, and fibrin/fibrinogen degradation products were measured, and the systemic inflammatory response syndrome criteria met by the patients were determined following admission. Of 3,864 patients, 329 (8.5%) were diagnosed with DIC and the 28-day mortality rate was 21.9%, which was significantly different from that of the non-DIC patients (11.2%) ( $p < .0001$ ). The progression of systemic inflammation, deterioration of organ function, and stepwise increase in incidence of the International Society on Thrombosis and Haemostasis (ISTH) DIC and its scores

all correlated with an increase in the JAAM DIC score as demonstrated by the patients on day 0. There were significant differences in the JAAM DIC score and the variables adopted in the scoring system between survivors and nonsurvivors. The logistic regression analyses showed the JAAM DIC score and prothrombin time ratio on the day of DIC diagnosis to be predictors of patient outcome. The patients who simultaneously met the ISTH DIC criteria demonstrated twice the incidence of multiple organ dysfunction (61.1 vs. 30.5%,  $p < .0001$ ) and mortality rate (34.4 vs. 17.2%,  $p = .0015$ ) compared with those without the ISTH DIC diagnosis.

**Conclusions:** This prospective survey demonstrated the natural history of DIC patients diagnosed by the JAAM DIC diagnostic criteria in a critical care setting. The study provides further evidence of a progression from the JAAM DIC to the ISTH overt DIC. (Crit Care Med 2008; 36:145–150)

**KEY WORDS:** critical illness; diagnosis; disseminated intravascular coagulation; International Society on Thrombosis and Haemostasis; natural history; systemic inflammatory response syndrome

**D**isseminated intravascular coagulation (DIC) is a serious and frequent complication in critically ill patients that is associated with a high mortality rate (1). However, a diagnosis of DIC is hampered

by the limited availability of reliable diagnostic criteria with sufficient accuracy. Based on the previously developed criteria for DIC diagnosis from the Japanese Ministry of Health and Welfare, the subcommittee of the International Society

on Thrombosis and Haemostasis (ISTH) proposed an overt and a nonovert DIC scoring system (2, 3). Both the overt and nonovert scoring systems have been prospectively validated, and this demonstrated the overt DIC scoring system to

## \*See also p. 348.

From the Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine (SG); Division of Traumatology, National Defense Medical College Research Institute, National Defense Medical College (DS); Department of Traumatology and Acute Critical Care Medicine, Osaka University Medical School (HO); Department of Emergency and Critical Care Medicine, Nagoya University Graduate School of Medicine (TM); Emergency and Critical Care Medicine, Kawaguchi Municipal Medical Center (KK); Department of Critical Care and Emergency Medicine, Tokyo Medical University Hachioji Medical Center (TIK); Department of Emergency and Critical Care Medicine,

National Hospital Organization, Kyoto Medical Center (HI); Department of Emergency Medicine, Juntendo University (Tib); Department of Traumatology, Critical Care Medicine and Burn Center, Social Insurance Chukyo Hospital (MU); Critical and Intensive Care Medicine, Shiga University of Medical Science (YE); Department of Acute Critical Care and Disaster Medicine, Tokyo Medical and Dental University (YO); Department of Surgery 1, School of Medicine, University of Occupational and Environmental Health (KO); Department of Emergency and Critical Care Medicine, Nippon Medical School (SK); Department of Critical Care Medicine, School of Medicine, Iwate Medical University (SE); and Department of Trauma and Critical Care Medicine, Kyorin University School of Medicine (SS).

Supported, in part, by the Japanese Association for Acute Medicine, Tokyo, Japan.

The authors have not disclosed any potential conflicts of interest.

Address requests for reprints to: Satoshi Gando, MD, FCCM, Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine, N17 W5, Kita-ku, Sapporo 060–8638 Japan. E-mail: gando@med.hokudai.ac.jp

Copyright © 2007 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/01.CCM.0000295317.97245.2D

**Table 1** Scoring system for disseminated intravascular coagulation (DIC) by the Japanese Association for Acute Medicine

I. Clinical conditions that may be associated with DIC	
A. Sepsis/severe infection (any microorganism)	
B. Trauma/burn/surgery	
C. Vascular abnormalities	
Large vascular aneurysms	
Giant hemangioma	
Vasculitis	
D. Severe toxic or immunological reactions	
Snakebite	
Recreational drugs	
Transfusion reactions	
Transplant rejection	
E. Malignancy (except bone marrow suppression)	
F. Obstetric calamities	
G. Conditions that may be associated with systemic inflammatory response syndrome	
Organ destruction (e.g., severe pancreatitis)	
Severe hepatic failure	
Ischemia/hypoxia/shock	
Heat stroke/malignant syndrome	
Fat embolism	
Rhabdomyolysis	
Other	
H. Other	
II. Clinical conditions that should be carefully ruled out	
A. Thrombocytopenia	
1. Dilution and abnormal distribution	
Massive blood loss and transfusion, massive infusion	
2. Increased platelet destruction	
ITP, TTP/HUS, HIT, drugs, viral infection, alloimmune destruction, APS, HELLP, extracorporeal circulation	
3. Decreased platelet production	
Viral infection, drugs, radiation, nutritional deficiency (vitamin B <sub>12</sub> , folic acid), disorders of hematopoiesis, liver disease, HPS	
4. Spurious decrease	
EDTA-dependent agglutinins, insufficient anticoagulation of blood samples	
5. Other	
Hypothermia, artificial devices in the vessel	
B. Prolonged prothrombin time	
Anticoagulation therapy, anticoagulant in blood samples, vitamin K deficiency, liver cirrhosis, massive blood loss and transfusion	
C. Elevated FDP	
Thrombosis, hemostasis and wound healing, hematoma, pleural effusion, ascites, anticoagulant in blood samples, antifibrinolytic therapy	
D. Other	
III. Diagnostic algorithm for systemic inflammatory response syndrome	
A. Temperature >38°C or <36°C	
B. Heart rate >90 beats/min	
C. Respiratory rate >20 breaths/min or Paco <sub>2</sub> <32 torr (<4.3 kPa)	
D. White blood cell >12,000 cells/mm <sup>3</sup> , <4,000 cells/mm <sup>3</sup> , or 10% immature (band) forms	
IV. Diagnostic algorithm	
	score
Systemic inflammatory response syndrome criteria	
≥3	1
0–2	0
Platelet counts (10 <sup>9</sup> /L)	
<80 or >50% decrease within 24 hrs	3
≥80 and <120 or >30% decrease within 24 hrs	1
≥120	0
Prothrombin time (value of patient/normal value)	
≥1.2	1
<1.2	0
Fibrin/fibrinogen degradation products (mg/L)	
≥25	3
≥10 and <25	1
<10	0
Diagnosis	
≥4 points	DIC

ITP, idiopathic thrombocytopenic purpura; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; HIT, heparin-induced thrombocytopenia; APS, antiphospholipid syndrome; HELLP, hemolysis, elevated liver enzymes, and low platelet; HPS, hemophagocytic syndrome; EDTA, ethylenediaminetetraacetic acid; FDP, fibrin/fibrinogen degradation products.

be sufficiently accurate to diagnose DIC in intensive care unit (ICU) patients (4). However, the nonovert DIC algorithm could not clearly distinguish nonovert DIC patients from the patients with overt DIC (5).

The Japanese Association for Acute Medicine (JAAM) DIC Study Group recently announced new DIC diagnostic criteria for critically ill patients (6). The scoring system was prospectively validated, thus revealing the algorithm to be able to diagnose DIC early, at a high diagnostic rate, with the use of global coagulation markers. The scoring system precisely evaluates the DIC process and its severity and can predict organ dysfunction and outcome associated with DIC for critically ill patients. In addition, almost all the patients who developed DIC based on the ISTH scoring system can be identified by the JAAM DIC criteria in the early stage.

Both the JAAM and the ISTH scoring systems for DIC have been prospectively validated for their feasibility and DIC diagnostic property; however, the clinical epidemiology of the critically ill patients diagnosed using these scoring systems has not been prospectively evaluated. The aim of this study was to address the characteristics and natural history of the DIC patients diagnosed by the JAAM DIC scoring system in a critical care setting.

## MATERIALS AND METHODS

**Patients.** This study enrolled 329 patients in this prospective trial conducted at 14 critical care centers in tertiary care hospitals during 4-month period in 2005.

**Selection Criteria.** All patients diagnosed with DIC using the JAAM DIC scoring system were eligible for this study. The patients who met the following criteria were excluded: 1) <15 yrs of age; 2) hematopoietic malignancy; 3) liver cirrhosis classified as Child-Pugh grade C; 4) concomitant treatment with carcinostatics or irradiation; and 5) known clotting disorders or receiving anticoagulant therapy.

**Surveillance and Data Sampling.** Prospective surveillance and blood sampling were performed on admission to critical care centers and daily thereafter as part of the routine clinical and laboratory workup. Platelet count, prothrombin time, fibrinogen, and fibrin/fibrinogen degradation products (FDP) or D-dimer were measured using established standard laboratory techniques. For the measurement of FDP, both serum and plasma samples were used (3 and 11 centers, respectively). In our country, all the companies providing the plasma FDP measuring kits confirm a significant linear regression between plasma

and serum samples and guarantee their quality, which means that the difference in the measuring samples did not affect the results of FDP.

Daily systemic inflammatory response syndrome (SIRS) criteria met by the patients were also determined (7). Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score were assessed at the time of enrollment (8, 9). If the patients met the criteria of the JAAM DIC and were included in the study (day 0), then blood sampling for DIC diagnosis and evaluation of SIRS criteria, APACHE II score, and SOFA score on day 3 was mandatory. Multiple organ dysfunction syndrome (MODS) (severe organ dysfunction with high mortality) was defined as having a SOFA score >11 (10). All patients were followed for 28 days after enrollment in the study and were assessed for 28-day all-cause mortality.

The surveillance was performed as a routine clinical workup, the collection of clinical and paraclinical data did not modify the patients' management, no interventions were conducted on the patients, and statistical analyses were processed anonymously. Based on these reasons, informed consent for participation in the study was waived by the JAAM.

**DIC Diagnosis and Treatment.** We used the JAAM DIC and ISTH overt DIC (ISTH DIC) diagnostic algorithm for scoring DIC. Scoring systems for the JAAM DIC definitions are presented in Table 1 and the other criteria are found elsewhere (3). FDP was used for fibrin-related marker in the ISTH criteria. No increase, moderate increase, and strong increase were defined as FDP <10, >10 <25, >25, respectively. All laboratory tests to confirm or reject the diagnosis of DIC were consecutively measured when DIC was clinically suspected based on the patients' symptoms or laboratory data. The differential diagnosis of the disorders presented in Table 1 from DIC was systematically applied to all the patients suspected of having DIC. Management of DIC included a combination of anticoagulants, plasma and platelet substitution therapy, and coagulation inhibitor concentrate based on the Japanese Ministry of Health and Welfare guideline. The standard treatments for the underlining disorders of DIC were applied simultaneously to the patients.

**Statistical Analysis.** If not otherwise noted, the data are reported as the mean  $\pm$  sd. The Mann-Whitney U test or Wilcoxon's signed ranks test was applied for two-group unpaired and paired comparisons. The unpaired Student's *t*-test was used for the parametric data. Proportions were compared using the chi-square test or Fisher's exact test when necessary. The relationships between the outcome and the following various factors were analyzed by two logistic regression analyses (common method and backward elimination method based on the likelihood ratio). The common method of logistic analysis used the

outcome (survived, 0; dead, 1) as a criterion variate and used the criteria of the JAAM DIC diagnostic algorithm as explanatory variates. The stepwise method (backward elimination method based on the likelihood ratio) used the outcome (survived, 0; dead, 1) as a criterion variate, and used age, gender (male, 0; female, 1), the JAAM DIC score, and the ISTH DIC score as explanatory variates. The results are reported as odds ratios, *p* values, and 95% confidence intervals.

For all reported results, *p* < .05 was considered statistically significant.

## RESULTS

**Baseline Characteristics of the Patients.** During a 4-month survey period, 3,864 patients were admitted to the 14 centers participating in the study. Of the 3,864 patients, 329 (8.5%) were diagnosed as having DIC, and the 28-day mortality of the patients was 21.9% (72 of 329), which was significantly different from that of the non-DIC patients (11.2%, 396 of 3,535) (*p* < .0001). The underlying diseases for patient admission consisted of 135 surgical and 194 medical conditions. The clinical manifestations of the patients who caused the DIC and

their mortality rates are presented in Table 2. Characteristics of the patients for inclusion in this study are summarized in Table 3.

**DIC-Related Markers and Clinical Outcome.** Higher APACHE II score, SOFA score, and SIRS criteria were observed in the nonsurvivors than in survivors (Table 3 and Fig. 1). Figure 1 also shows the DIC scores and measured variables on days 0 and 3 in the survivors and nonsurvivors. Significantly different changes were observed over this time course in the platelet count, FDP, and D-dimer between the survivors and nonsurvivors. The nonsurvivors showed a significant reduction in their platelet count, but FDP and D-dimer remained at high levels until day 3. In contrast, the platelet count on day 3 remained the same as values from day 0, and the levels of FDP and D-dimer in survivors significantly decreased on day 3. Although there was no difference in the time course of the prothrombin time ratio, significant differences were found in this ratio between the survivors and nonsurvivors on days 0 and 3. A logistic regression analysis showed a high pro-

Table 2 Clinical manifestations of the patients that caused disseminated intravascular coagulation

Condition	No. of Patients	
	Total	Died (%)
Trauma/burn/surgery	149	19 (12.8)
Sepsis/severe infection	98	34 (34.7)
Ischemia/hypoxia/shock	16	2 (12.5)
Severe pancreatitis	9	0 (0)
Malignant syndrome/rhabdomyolysis	7	0 (0)
Malignancy	5	2 (40.0)
Vascular abnormalities	4	2 (50.0)
Severe hepatic failure	4	0 (0)
Obstetrical calamities	4	0 (0)
Severe toxic or immunological reactions	2	0 (0)
Other	31	13 (41.9)
Total	329	72 (21.9)

Table 3 Characteristics of the patients at the time of inclusion

	Total (n = 329)	Survivors (n = 257)	Nonsurvivors (n = 72)	<i>p</i> Value <sup>a</sup>
Age, yrs	58.4 $\pm$ 18.5	57.7 $\pm$ 18.4	60.8 $\pm$ 19.0	.2104
Gender, male/female	222/107	166/91	56/16	.0457
APACHE II score	19.2 $\pm$ 9.2	17.4 $\pm$ 8.2	25.7 $\pm$ 9.9	<.0001
SOFA score	8.7 $\pm$ 4.1	8.0 $\pm$ 3.9	11.4 $\pm$ 4.0	<.0001
ISTH DIC score	3.4 $\pm$ 1.4	3.4 $\pm$ 1.3	3.6 $\pm$ 1.6	.3479
ISTH DIC, yes/no	65/264	44/213	21/51	.0293

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; DIC, disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis.

<sup>a</sup>Survivors vs. nonsurvivors.

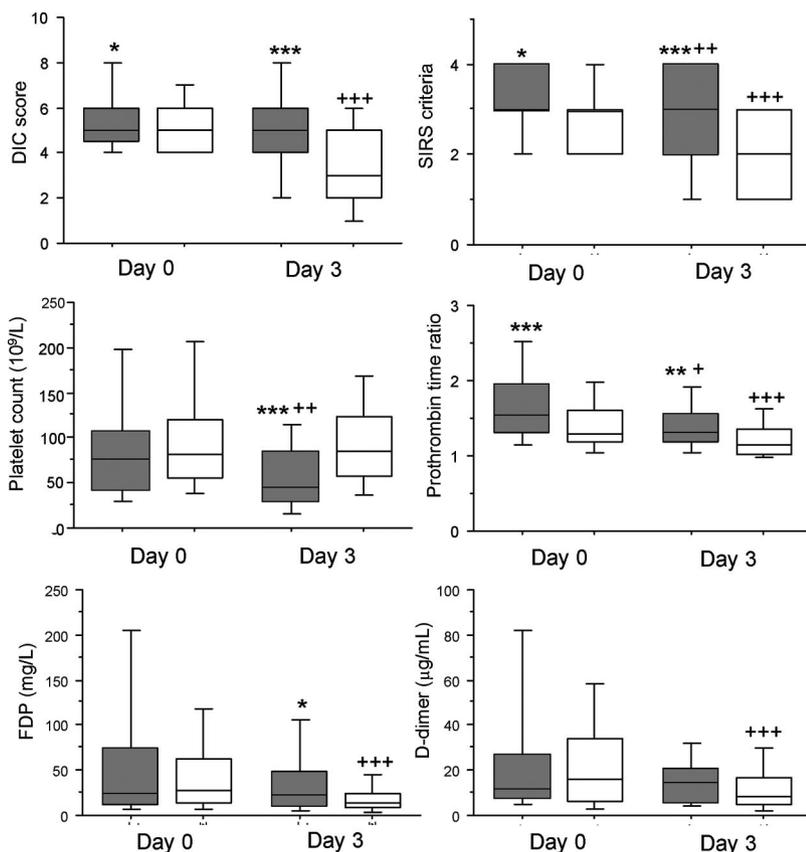


Figure 1. Box plots showing the changes in the disseminated intravascular coagulation (DIC) score and the criteria of the DIC diagnostic algorithm. The central horizontal bars, columns, and peripheral horizontal bars indicate the median, the 25th–75th percentiles, and the 10th–90th percentiles, respectively. The gray and the white columns represent the nonsurvivors and the survivors, respectively. \* $p < .05$ , \*\* $p < .001$ , \*\*\* $p < .0001$  vs. survivors; + $p < .05$ , ++ $p < .001$ , +++ $p < .0001$  vs. day 0. FDP, fibrin/fibrinogen degradation products; SIRS, systemic inflammatory response syndrome.

Table 4 Logistic regression analyses of the various factors at the time of inclusion for the prediction of outcome

Factors	Odds Ratio	$p$ Value	95% Confidence Interval
A.			
SIRS criteria	2.289	.060	0.964–5.434
Platelet counts	0.973	.214	0.931–1.016
Prothrombin time ratio	2.143	.004	1.277–3.595
FDP	1.002	.207	0.999–1.006
B.			
Gender	0.508	.031	0.274–0.941
JAAM DIC score	1.223	.046	1.004–1.489

A, multivariate logistic regression analysis; SIRS, systemic inflammatory response syndrome; FDP, fibrin/fibrinogen degradation products; B, stepwise method (backward elimination method based on likelihood ratio) of logistic regression analysis; JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation.

thrombin time ratio at the time of diagnosis of DIC to independently predict the 28-day mortality of the DIC patients (odds ratio 2.143,  $p = .004$ , 95% confidence interval 1.277–3.595) (Table 4).

An increase in the APACHE II score, progression of systemic inflammation, deterioration of multiple organ function, and a trend in increased mortality rate

were observed with an increase in the JAAM DIC score assigned to the patients on day 0. The results are shown in Table 5. There was a significant difference in the JAAM DIC score at the time of inclusion between the survivors and nonsurvivors ( $p < .05$ ) (Fig. 1). However, there were no significant differences in the ISTH scores between the two groups (Table 3). The

logistic regression analysis also suggests that the JAAM DIC score at the time of DIC diagnosis is a predictor of mortality (odds ratio 1.223,  $p = .046$ , 95% confidence interval 1.004–1.489) (Table 4).

*Relationship Between the Patients Diagnosed by the JAAM and ISTH DIC Criteria.* Table 5 demonstrates that the JAAM DIC score at the time of inclusion had a significant correlation with the ISTH DIC score and the incidence of the ISTH DIC. Table 6 shows that 90 patients (27%, 90 of 329) simultaneously met the JAAM and ISTH DIC diagnostic criteria. The patients who fulfilled both JAAM and ISTH DIC criteria showed higher APACHE II scores, SOFA scores, and SIRS criteria than those who met only the JAAM DIC criteria. The patients who met the ISTH DIC criteria demonstrated higher incidence of MODS and poorer outcome than those without ISTH DIC diagnosis ( $p < .0001$  and  $p = .0015$ , respectively). The results clearly show that the risks for MODS and mortality were approximately doubled if the JAAM DIC patients were also diagnosed by the ISTH DIC criteria.

On day 0, 264 patients did not meet the ISTH criteria. By day 3, 14 patients had died. Finally, 25 patients (10%, 25 of 250) progressed to ISTH overt DIC on day 3.

## DISCUSSION

According to the ISTH definition, the ISTH scoring system should be used only in patients with specific underlying diseases, which thus makes the system highly specific for the DIC diagnosis (3). As discussed in previous studies, the JAAM criteria consist of clinical conditions that may be associated with DIC, clinical conditions that should be carefully ruled out, and scoring algorithms for SIRS and DIC (6, 9, 11). The present study provides the entire JAAM scoring system in Table 1. We carefully excluded any patients who had had false-positive high DIC scores, such as those with hematologic malignancies, bone marrow suppression according to chemotherapy, and irradiation in the present study. These exclusion criteria, the confirmation of an explicit etiology, and the lists of conditions to be ruled out in our scoring system give specificity in the DIC diagnosis and support the validity of the results in our study.

The present study demonstrated an 8.5% incidence of DIC diagnosed by the JAAM criteria in heterogeneous critically

**Table 5** Various scores, multiple organ dysfunction, and mortality for disseminated intravascular coagulation (DIC) score at the time of inclusion

DIC score	4	5	6	7-8
APACHE II score max	18.2 ± 9.3	21.2 ± 9.1 <sup>a</sup>	21.2 ± 10.7	23.6 ± 8.7 <sup>a</sup>
SIRS criteria max	2.6 ± 1.1	3.2 ± 0.9 <sup>a</sup>	3.4 ± 0.6 <sup>a</sup>	3.3 ± 0.6 <sup>a</sup>
SOFA score max	8.2 ± 4.2	9.4 ± 4.2 <sup>a</sup>	10.5 ± 5.3 <sup>a</sup>	11.6 ± 4.4 <sup>a,b</sup>
MODS, % (n)	29.9 (35)	35.2 (38)	45.3 (24)	60.8 (31) <sup>a,b</sup>
ISTH DIC score max	3.0 ± 1.1	3.4 ± 1.1 <sup>a</sup>	4.7 ± 1.1 <sup>ab</sup>	5.3 ± 1.3 <sup>a,b,c</sup>
ISTH DIC, % (n)	6.0 (7)	18.5 (20) <sup>a</sup>	49.1 (26) <sup>ab</sup>	72.5 (37) <sup>a,b,c</sup>
Mortality, % (n)	15.4 (18)	25.0 (27)	24.5 (13)	27.5 (14)

APACHE, Acute Physiology and Chronic Health Evaluation; max, maximum criteria or score that the patients met on day 0 and day 3; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; MODS, multiple organ dysfunction syndrome; ISTH, International Society on Thrombosis and Haemostasis.

<sup>a</sup>*p* < .05 vs. score 4; <sup>b</sup>*p* < .05 vs. score 5; <sup>c</sup>*p* < .05 vs. score 6.

**Table 6** Characteristics of the patients who met the International Society on Thrombosis and Haemostasis (ISTH) disseminated intravascular coagulation (DIC) criteria (+) and those who did not meet the ISTH DIC criteria (-)

	ISTH DIC (+) (n = 90)	ISTH DIC (-) (n = 239)	<i>p</i> Value
Age, yrs	56.7 ± 19.2	59.0 ± 18.3	.3299
Gender, male/female	57/33	165/74	.3562
APACHE II score max	24.4 ± 10.4	19.0 ± 8.8	<.0001
SOFA score max	11.9 ± 4.7	8.6 ± 4.2	<.0001
SIRS criteria max	3.3 ± 0.8	2.9 ± 1.0	.0018
ISTH DIC score max	5.6 ± 0.8	3.1 ± 0.9	<.0001
MODS, % (n)	61.1 (55)	30.5 (73)	<.0001
Mortality, % (n)	34.4 (31)	17.2 (41)	.0015

APACHE, Acute Physiology and Chronic Health Evaluation; max, maximum criteria or score that the patients met on day 0 and day 3; SOFA, Sequential Organ Failure Assessment; SIRS, systemic inflammatory response syndrome; MODS, multiple organ dysfunction syndrome.

ill patients admitted to a general ICU in a tertiary care hospital. The DIC patients showed a 28-day mortality rate of 21.9%, which was higher than that of the non-DIC patients. The prevalence of DIC in the previous study that included the patients when their platelet counts decreased to  $<150 \times 10^9/L$  was 67.4% and the mortality rate was 20.7% (6). The present study, without the selection bias of the platelet count, more precisely reflects the incidence of DIC in a critical care setting. Furthermore, coincidence with mortality rate in the two studies suggests that approximately 20% of the patients diagnosed by the JAAM criteria will die within a month. In other studies, the ISTH overt DIC diagnostic criteria found 9.2% (12), 10.1% (5), 19% (13), and 34% (4) DIC patients among the critically ill, and their mortality rates were unknown, 40%, 77.6%, and 45%, respectively. The heterogeneity of the selected patient population and the disease severity make both the interpretation and comparison of the results between these studies and the results presented herein

difficult. However, it is possible to estimate that the mortality rates (40% and 45%) of the ISTH DIC patients in the studies that enrolled the same patient population as presented here are approximately double that of the JAAM DIC patients (21.9%) in the present study (4, 13).

Significant differences in the JAAM DIC score at inclusion between survivors and nonsurvivors and the results of logistic regression analysis revealed that the JAAM DIC scoring system is a predictor of mortality. In addition to the significant impact of the rate of platelet decrease and the SIRS category to the SOFA score and mortality observed in the previous study (6), the present study further indicates that prothrombin time ratio at the time of diagnosis of DIC is also an independent predictor of mortality. Furthermore, different kinetics of platelet counts and FDP between survivors and nonsurvivors after DIC diagnosis suggest an important role of these variables for the patient prognosis. DIC has been clearly established to be a frequent complication of systemic in-

flammation (14). Dhainaut et al. (15) demonstrated the composite dynamic coagulation score during the first day of severe sepsis to accurately identify patients who would progress to MODS and subsequent death. In addition, Kinasevitz and his colleagues (16) showed that a simple evolving DIC score that consists of the dynamic changes in platelet count and prothrombin time, as well as their absolute values, has a good correlation with MODS and patient prognosis. All of these results suggest that the criteria adopted in the scoring algorithm reported in this study may improve the diagnostic and prognostic power of the DIC diagnostic scoring system (17).

The ISTH defines nonovert DIC as a hemostatic dysfunction that is not yet at the stage of severe decompensation (3). Nonovert DIC serves as a possible harbinger of overt DIC, a stressed but decompensated hemostatic system. Therefore, during this transitional state, therapeutic intervention is thought to be most effective (18, 19). The nonovert DIC algorithm, however, cannot predict overt DIC, thus suggesting that nonovert DIC is independent of overt DIC (5). On the contrary, almost all the patients who developed the ISTH DIC (overt DIC) could be identified based on the JAAM DIC criteria (6). The present study demonstrated the progression of the JAAM DIC to the ISTH DIC by stepwise increases in the incidence of the ISTH DIC and its scores, in accordance with the increase in the JAAM DIC score. In addition, progressively increasing MODS and mortality rates were observed in the patients with the ISTH DIC compared with those without this diagnosis. The JAAM DIC criteria could detect DIC patients developing MODS and poor outcome with approximately one half risk of the ISTH criteria. These results clearly indicate that the JAAM DIC is a hierarchical continuum to the ISTH overt DIC and therefore has the ability to predict full-blown DIC. Specifically, the result suggests that the JAAM DIC criteria can diagnose a stressed but compensated DIC.

The inclusion of the dynamics of the coagulation changes that have a strong predictive power (15-17) and better sensitivity than the ISTH criteria to select DIC patients for early treatment are the two main features of the JAAM DIC diagnostic criteria. In these respects, the JAAM system may have a better performance than the ISTH nonovert system.

This issue will be clarified in a prospective study comparing the JAAM criteria and the ISTH nonovert DIC diagnostic criteria. Therefore, the JAAM DIC diagnostic criteria can be useful for selecting DIC patients for early treatment in a critical care setting.

## CONCLUSIONS

This prospective multicenter survey for DIC demonstrated the natural history of the DIC patients diagnosed by the JAAM DIC diagnostic criteria. All the variables adopted in the JAAM scoring system were significant in diagnosing DIC and predicting prognosis. The risk for MODS and death approximately doubled when the JAAM DIC patients fulfilled the ISTH DIC criteria. Thus, the present study provides evidence that the JAAM DIC is a hierarchal continuum to the ISTH overt DIC that allows the selection of DIC patients, thus enabling them to undergo early treatment, while also predicting MODS as well as poor outcome for critically ill DIC patients.

## ACKNOWLEDGMENT

We thank Takahiro Nakamura, PhD, for reviewing our statistical methods and giving us valuable comments.

## REFERENCES

1. Levi M, ten Cate H: Disseminated intravascular coagulation. *N Engl J Med* 1999; 341: 586–592
2. Kobayashi N, Maekawa T, Takeda M, et al: Criteria for diagnosis of DIC based on the analysis of clinical and laboratory findings in 345 DIC patients collected by the Research Committee on DIC in Japan. *Bibl Haematol* 1987; 49:848–852
3. Taylor FB Jr, Toh CH, Hoots WK, et al: Toward definition, clinical and laboratory criteria, and scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001; 86:1327–1330
4. Bakhtiari K, Meijers JCM, de Jonge E, et al: Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. *Crit Care Med* 2004; 32: 2416–2421
5. Toh CH, Downey C: Performance and prognostic importance of a new clinical and laboratory scoring system for identifying non-overt disseminated intravascular coagulation. *Blood Coagul Fibrinolysis* 2005; 16: 69–74
6. Gando S, Iba T, Eguchi Y, et al: A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: Comparing current criteria. *Crit Care Med* 2006; 34: 625–631
7. Members of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference committee. Definition for sepsis and organ failure and guidelines for the use innovative therapies in sepsis. *Crit Care Med* 1992; 20:864–874
8. Knaus WA, Draper EA, Wanger DP, et al: APACHE II: A severity classification system. *Crit Care Med* 1985; 13:818–829
9. Vincent JL, de Mendonça A, Cantraine F, et al: Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. *Crit Care Med* 1998; 26: 1793–1800
10. Ferreira FL, Bota DP, Bross A, et al: Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001; 286:1754–1758
11. Drews RE, Weinberger SE: Thrombocytopenic disorders in critically ill patients. *Am J Respir Crit Care Med* 2000; 162:347–351
12. Angstwurm MW, Dempfle CE, Spannagl M: New disseminated intravascular coagulation score: A useful tool to predict mortality in comparison with Acute Physiology and Chronic Health Evaluation II and Logistic Organ Dysfunction scores. *Crit Care Med* 2006; 34:314–320
13. Sivula M, Tallgren M, Pettilä V: Modified scores for disseminated intravascular coagulation in the critically ill. *Intensive Care Med* 2005; 31:1209–1214
14. Gando S, Kameue T, Nanzaki S, et al: Disseminated intravascular coagulation is a frequent complication of systemic inflammatory response syndrome. *Thromb Haemost* 1996; 75:224–228
15. Dhainaut JF, Shorr AF, Macias WL, et al: Dynamic evolution of coagulopathy in the first day of severe sepsis: Relationship with mortality and organ failure. *Crit Care Med* 2005; 33:341–348
16. Kinasevitz GT, Zein JG, Lee GL, et al: Prognostic value of a simple evolving disseminated intravascular score in patients with severe sepsis. *Crit Care Med* 2005; 33: 2214–2221
17. Levi M: Settling the score for disseminated intravascular coagulation. *Crit Care Med* 2005; 33:2417–2418
18. Wada H, Wakita Y, Nakase T, et al: Outcome of disseminated intravascular coagulation in relation to the score when the treatment was begun. *Thromb Haemost* 1995; 74:848–852
19. Hoots WK: Non-overt disseminated intravascular coagulation: Definition and pathophysiological implication. *Blood Rev* 2002; 16(Suppl 1):S3–S9