Title

A prospective comparison of new Japanese criteria for disseminated intravascular coagulation. New Japanese criteria vs. ISTH criteria.

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Shortened title

New Japanese DIC vs. ISTH DIC

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Summary: In Japan, early diagnosis and early treatment of disseminated intravascular coagulation (DIC) based on the old Japanese criteria have greatly improved the outcomes of DIC patients with hematopoietic malignancy. However, the prognoses of critically ill patients with DIC have remained poor. To overcome this situation, new Japanese DIC criteria for critically ill patients were established in 2002. The new Japanese DIC criteria adopted a concept of coagulopathy associated with systemic inflammatory response syndrome. In the present study, we prospectively investigated the relationships between the new criteria and organ failure, prognosis, and other sets of DIC criteria. This study included 74 patients whose platelet counts were below 150 x 10^9/L. Daily DIC scores and sequential organ failure assessment scores were recorded from days 0 to 4 once the patient was included in the study. The new Japanese DIC criteria diagnosed DIC earlier than both the non-overt DIC and the old Japanese criteria did (p = 0.0005). The new Japanese criteria diagnosed more DIC patients prior to the establishment of multiple organ failure than the other sets (p = 0.023). The new Japanese criteria tended also to predict prognoses more efficiently than the other two sets. In conclusion, the diagnostic sensitivity of the new Japanese criteria was as high as that of the non-overt DIC criteria. Furthermore, the new Japanese criteria provided the earliest detection and most accurate outcome prediction of DIC among the DIC criteria sets.

Key words: Disseminated intravascular coagulation, Diagnostic criteria, Japan, International Society on Thrombosis and Haemostasis, Hemostatic disorders, Systemic inflammatory response syndrome

Clinical and laboratory criteria and a scoring system for disseminated intravascular coagulation (DIC) were published by the International Society on Thrombosis and Haemostasis (ISTH) in 2001 (1). The ISTH established two sets of criteria: one to diagnose a stressed but compensated hemostatic system (non-overt DIC), and another to diagnose a stressed but decompensated hemostatic system (overt DIC) (1). In Japan, the DIC Diagnostic Standards (the old Japanese criteria) were published in 1988 and have been widely used for more than 10 years. Previously we reported a prospective comparison between the ISTH criteria and the old Japanese criteria (2). We showed that both the non-overt DIC and old Japanese criteria accurately predicted outcomes (2). On the other hand, we found that the non-overt DIC criteria were unable to diagnose DIC earlier than the old Japanese criteria (2). The non-overt DIC criteria are not sufficient for the early diagnosis and treatment of DIC (2).

In Japan, early diagnosis and early treatment of DIC based on the old Japanese criteria have greatly improved the outcomes of DIC patients with hematopoietic malignancy. However, the prognoses of critically ill patients with DIC have remained poor. To overcome this situation, the Japanese Association for Acute Medicine (JAAM) and the Japanese Society on Thrombosis and Hemostasis (JSTH) cooperated in 2002 to establish new DIC criteria for critically ill patients (the new Japanese criteria) (2). This new criteria set adopts the concept of coagulopathy associated systemic inflammatory response syndrome (SIRS-associated coagulopathy) and incorporates SIRS scores. Previous reports showed grounds for the adoption of the SIRS-associated coagulopathy concept (3,4). Esmon CT (3) found that the cross talk between inflammation and

coagulation progresses to microvascular injury and organ dysfunction, creating a vicious cycle. Rangel-Frausto MS et al. (4) demonstrated the first evidence of a clinical hierarchical progression from SIRS to sepsis, severe sepsis, and septic shock. They also pointed out stepwise increases in DIC and other organ dysfunction in this hierarchy in critically ill patients (4).

In the present study, we prospectively compared three sets of DIC diagnostic criteria (the ISTH criteria and the old and new Japanese criteria) and assessed the usefulness of the new Japanese criteria for the diagnosis of DIC.

MATERIALS AND METHODS

Patients

With the approval of our Institutional Review Board and with the informed consent of the patients or their next of kin, we studied 74 consecutive patients who were admitted to our general intensive care unit (ICU) between January and December 2002, who met the inclusion criteria of this study, and for whom sequential data could be collected. The patient population overlapped completely with that of our previous study (2). Only patients whose platelet counts were below 150 x 10^9/L were included in this study. Excluded were patients under 15 or over 89 years of age, patients with any known hemostatic disorder or liver cirrhosis, patients currently receiving or recently having received anticoagulant therapy or chemotherapy, and patients having received liver transplantation within four weeks. Organ dysfunction and failure were evaluated according to sequential organ failure assessment (SOFA) scores (5,6).

Definitions

The old Japanese criteria consist of clinical symptoms and global coagulation tests (TABLE 1). Organ dysfunction in the old Japanese criteria was defined as a SOFA score $\geq$2. A total score $\geq$7 establishes a diagnosis of DIC according to the old Japanese criteria. The new Japanese criteria include scores of SIRS (7) and global coagulation tests (TABLE 2). A total score $\geq$5 or 4 positive points establishes a diagnosis of DIC according to the new Japanese criteria. The overt DIC criteria are composed of global coagulation tests (TABLE 3). We used fibrin/fibrinogen degradation products (FDP) of fibrin-related markers. The cutoff values for “no increase”, “moderate increase”, and “strong increase” were defined as less than 10 mg/L, from 10 to 20 mg/L, and more than 20 mg/L, respectively. If the total score was $\geq$5, overt DIC was diagnosed. The non-overt DIC criteria consist of global coagulation tests and molecular markers (TABLE 4). In the non-overt DIC criteria, “rising” and “falling” of platelet counts were defined as an increase and a decrease, respectively, of more than 10×10^9/L. The “rising” and “falling” of prothrombin times were defined as changes of more than 1 second each. The “normal” amount of FDP was defined as less than 10 mg/L. “Rising” and “falling” of FDP were defined as changes of more than 2 mg/L each. The specific criteria of the non-overt DIC criteria were not used in this study because the ISTH has not strictly established them and because our laboratory could not measure routinely all of the recommended molecular markers. Since the ISTH did not define a cutoff value for diagnosis of the non-overt DIC, we defined that value as $\geq$5 in this study, in accordance with a presentation of the

Scientific Subcommittee for DIC by Toh CH at the ISTH Consensus Meeting in Birmingham, UK, July 2003. Organ failure was defined as a SOFA score ≥3. Patients with failure of two or more organs were defined as having MOF. In calculating the SOFA score, coagulation scores were always excluded.

Measurement and protocol

A blood sample was collected using an arterial catheter within 12 hours after a patient was found to meet the inclusion criteria of this study (day 0). Samples were collected again daily on days 1 through 4. Immediately after each sample was taken, platelet count, white blood cell count, fibrinogen and FDP levels, and prothrombin time were measured for the diagnosis of DIC. Platelets were counted by a Coulter® Gen-S™ Hematology Analyzer (Beckman Coulter, Inc., Fullerton, CA, USA). Fibrinogen levels were measured by the thrombin time method using Thrombocheck-Fib® (Sysmex, Kobe, Japan). Prothrombin time was determined by the Quick method using Thrombocheck-PT (Sysmex, Kobe, Japan). Serum FDP was measured by the latex agglutination method using LPIA-FDP (Dia-Iatron, Tokyo, Japan). Simultaneously, we evaluated the patients for symptoms of bleeding and organ dysfunction. In the diagnoses using the non-overt DIC criteria, the laboratory data at day 0 could not be compared with those obtained the day before. Body core temperature, heart rate, and respiratory rate were continuously monitored for SIRS criteria. Blood gas analysis was carried out as needed.

Statistical analysis

The StatView 5.0 statistical software package (SAS Institute Inc., Cary, NC, USA) was used for all statistical calculation analyses. Comparisons among the several groups were made using the Chi-square test or the Kruskal-Wallis test. A p <0.05 was considered statistically significant.

RESULTS

During the study period, a total of 1205 patients were transferred to our tertiary emergency center, of whom 768 were admitted to the center. Of these 768 inpatients, 329 were admitted to our ICU, of whom 74 (46 males and 28 females) met the inclusion criteria and consented to participate in the study. The mean age of the patients was 61 $\pm$ 16 years. The mean Acute Physiology and Chronic Health Evaluation II score was 22.4 $\pm$ 9.3. The clinical backgrounds of the enrolled patients are shown in TABLE 5. During the study period, DIC was diagnosed in 78.4% (58/74) of the patients based on the new Japanese criteria, in 54.1% (40/74) based on the old Japanese criteria, and in 74.3% (55/74) based on the non-overt DIC criteria.

Comparison between the old and the new Japanese criteria sets

Fifty-eight patients (58/74, 78.4%) were diagnosed with DIC during the study period based on either the old or the new Japanese criteria. Diagnostic agreement between these two criteria sets was obtained for 75.7% (56/74) of the patients. The new criteria diagnosed DIC earlier than the old criteria in 41.4%

(24/58) of the patients. In 5.2% (3/58) of the patients, the new criteria diagnosed DIC later than the old criteria.

Comparison between the old Japanese and the non-overt DIC criteria sets

Based on either the old Japanese or the non-overt DIC criteria set, DIC was diagnosed in 77.0% of patients (57/74). Diagnostic agreement between the sets was obtained for 74.3% (55/74) of the patients. In 26.3% (15/57) of the patients, the old Japanese criteria diagnosed DIC earlier than the non-overt DIC criteria; in 36.8% (21/57) of the patients, the old Japanese criteria diagnosed DIC later. Two cases (Cases 1 and 2) were diagnosed by the old Japanese criteria but not by the non-overt DIC criteria. Case 1 died on admission day (day 0). We diagnosed Case 2 with DIC by the old Japanese criteria on days 0 and 1. The conditions of this case improved daily.

Comparison between the new Japanese and the non-overt DIC criteria sets

Sixty-two patients (62/74, 83.8%) were diagnosed with DIC based on either the new Japanese or the non-overt DIC criteria set. Diagnostic agreement between the sets was 85.1% (63/74). In 51.6% (32/62) of the patients, the new Japanese criteria diagnosed DIC earlier than the non-overt DIC criteria; in 9.7% (6/62) of the patients, the new Japanese criteria diagnosed DIC later.

TABLE 6 reveals statistically significant differences in the diagnostic speeds of the three sets based on the overt DIC criteria ($p = 0.0005$).

TABLE 7 compares the first days on which MOF was established with the first days on which DIC was diagnosed using each set. Forty-two patients

complicated with MOF during the study period. In the MOF patients, 45.2% (19/42) were diagnosed with DIC prior to the establishment of MOF based on the non-overt DIC criteria, 52.4% (22/42) based on the old Japanese criteria, and 73.8% (31/42) based on the new Japanese criteria. Statistical significance was observed among the three criteria sets (p = 0.023).

FIGURE 1 shows the mortality rates of patients with and those without DIC on the 28th day based on each criteria set. The new Japanese criteria tended to predict prognoses more effectively than the other two criteria sets.

DISCUSSION

The DIC subcommittee of the ISTH recently proposed a definition of DIC and stressed that the disease can originate from and cause damage to the microvasculature; given sufficient severity, such damage can produce organ dysfunction (1). These findings suggest that DIC strongly influences the morbidity and mortality of critically ill patients through two serious complications: hemorrhage and organ failure. Recently, the effectiveness of several anticoagulants, such as protein C (8,9), antithrombin (10), and thrombomodulin (8) for sepsis or DIC patients was reported. Those studies noted that early recognition and prompt treatment of DIC are crucial (8-11). Wada et al. (11) investigated the outcomes of DIC patients in relation to their Japanese DIC scores obtained at the beginning of treatment (11). They found that patients with higher DIC scores have poorer outcomes, and they emphasized the importance

of the early diagnosis and treatment of DIC by using sensitive diagnostic criteria (11).

These studies suggest that DIC diagnostic criteria should have high sensitivity, and should enable useful treatment decisions to be made (1,8-11). However, clinically applicable DIC diagnostic criteria are somewhat arbitrary, as there is no “gold standard” against which to calibrate them. The absence of a gold standard makes it difficult to determine the diagnostic test properties of DIC diagnostic criteria. To overcome this weakness, we regarded the overt DIC criteria as a gold standard in our comparison of the diagnostic speeds of the three criteria sets in the present study. We then compared the diagnostic speeds based on MOF establishment and outcomes among the three sets of criteria, similar to the method used in our previous study (2).

The ISTH has defined non-overt DIC criteria to improve the clinical outcomes for conditions associated with DIC. Non-overt DIC is characterized by a stressed but compensated hemostatic system, clearly distinguishable from a stressed but decompensated hemostatic system (overt DIC) (1). The ISTH subcommittee has proposed a framework for a non-overt DIC scoring system. However, the ISTH has not yet proposed detailed methods for applying the non-overt DIC criteria in a clinical setting. In the present study, we used our own values and diagnostic cutoff points for application of the non-overt DIC criteria without using the specific criteria.

We previously carried out a prospective comparison between the old Japanese criteria and the ISTH criteria (2). That study showed that the non-overt DIC criteria were highly sensitive for diagnosis (FIG. 2) and predicted outcomes

more accurately than the overt DIC criteria did (2). However, the non-overt DIC criteria had two weak points: 1) the criteria could not diagnose DIC early despite the high sensitivity (2); and 2) molecular markers used in the specific criteria were not always available everywhere. Actually, we were not able to use the specific criteria in our previous and present studies (2). Several reports indicated the importance of early recognition of DIC and prompt treatment (8-11). In that light, we suggested the importance of strictly defining the specific criteria, including molecular markers that are appropriate and always available.

Our earlier results indicated the need for DIC diagnostic criteria that are sensitive and effective early enough to identify DIC at the bedside, while minimally sacrificing specificity (2). Furthermore, the diagnosis of DIC should be simultaneous with its treatment. The new Japanese criteria were established based on these two fundamentals. The characteristics of the new Japanese criteria include the incorporation of SIRS criteria as well as the platelet count reduction rate. Esmon CT (3) found that the cross talk between inflammation and coagulation progresses to microvascular injury and organ dysfunction, creating a vicious cycle. To prevent or stop this vicious cycle, we should monitor the degree of changes in inflammation and coagulation. Rangel-Frausto MS et al. (4) demonstrated the first evidence that SIRS to septic shock is a hierarchical continuum of infection. They have also pointed out that there are stepwise increases in DIC and other organ dysfunctions in this hierarchy. Based on these studies (3,4), we propose here a concept of SIRS-associated coagulopathy and include SIRS scores in the new Japanese criteria. This new criteria set includes both the absolute value of platelet counts and the platelet count reduction rate;

the latter is an important sign of DIC. Clinically, a sudden reduction in platelet count frequently precedes the consumption of coagulation factors and the elevation of fibrin-related markers. We believe that the inclusion of SIRS criteria as well as of the platelet count reduction rate in the new Japanese criteria explains the results of the present study.

In the present study, we found that patients diagnosed with DIC by the new Japanese criteria mostly overlapped with those diagnosed by the non-overt DIC. The patients diagnosed by the old Japanese criteria were also diagnosed by the new Japanese criteria and by the non-overt criteria (FIG. 3). Although the new Japanese criteria had almost the same diagnostic sensitivity as the non-overt DIC criteria, the new Japanese criteria diagnosed DIC earlier than the other two criteria sets did (TABLE 4). Treatment of DIC should not be directed at the amelioration of DIC itself, but at the improvement of organ dysfunction or mortality. The prediction of organ dysfunction is important in improving the prognosis of critically ill patients. The new Japanese criteria could allow for the diagnosis of more DIC patients before MOF establishment than the other two criteria sets do (TABLE 7). A great difference in mortality rates between patients with and those without DIC was detected on the basis of the new Japanese criteria (FIG. 1). These results suggest that the new Japanese criteria enable earlier and more accurate diagnosis of DIC compared to the other two criteria sets.

In conclusion, the diagnostic sensitivity of the new Japanese criteria was as high as that of the non-overt DIC criteria. Furthermore, the new Japanese criteria allowed for the earliest diagnosis and the most accurate outcome

prediction of DIC diagnosis among the three diagnostic criteria sets compared.

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FIGURE LEGENDS

FIG. 1. **Mortality rates by the 28th day for patients with and those without disseminated intravascular coagulation (DIC). Shaded columns show DIC patients; open columns show non-DIC patients.**

FIG. 2. **Correlations of disseminated intravascular coagulation (DIC) diagnoses among the overt DIC, the non-overt DIC, and the old Japanese DIC criteria sets (2).**

FIG. 3. **Correlations of disseminated intravascular coagulation (DIC) diagnoses among the non-overt DIC and the old and new Japanese DIC criteria sets. Two peculiar patients (Cases 1 and 2 in the Results section) are excluded in this figure.**

TABLE 1. Disseminated intravascular coagulation (DIC) diagnosis standards by the Japanese Ministry of Health and Welfare

	Score
Etiology of DIC	
Yes	1
No	0
Clinical symptoms	
Bleeding symptom	
Yes	1
No	0
Organ dysfunction	
Yes	1
No	0
Laboratory tests	
Fibrin/fibrinogen degradation products (mg/L)	
≥40	3
≥20, <40	2
≥10, <20	1
<10	0
Platelet count (10^9/L)	
≤50	3
≤80, >50	2
≤120, >80	1
>120	0
Fibrinogen level (g/L)	
≤1	2
≤1.5, >1	1
>1.5	0
Prothrombin time (value of patient / normal value)	
≥1.67	2
≥1.25, <1.67	1
<1.25	0
Diagnosis	
≥7	DIC

TABLE 2. The new Japanese DIC criteria for critically ill patients

	Score
SIRS score	
≥3	1
≤2	0
Platelet count (10^9/L)	
<80 or 50% decrease within 24 hours	3
<120, ≥80, or 30% decrease within 24 hours	1
≥120	0
Prothrombin time (value of patient / normal value)	
≥1.2	1
<1.2	0
Fibrinogen level (g/L)	
<3.5	1
≥3.5	0
Fibrin/fibrinogen degradation products (mg/L)	
≥25	3
≥10, <25	1
<10	0
Diagnosis	
≥5 or 4-point positives	DIC

SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular coagulation.

TABLE 3. Clinical and laboratory criteria and a scoring system for overt DIC by the International Society on Thrombosis and Haemostasis

	Score
Platelet count (10^9/L)	
<50	2
<100, >50	1
>100	0
Elevated fibrin-related marker	
Strong increase	3
Moderate increase	2
No increase	0
Prolonged prothrombin time (sec)	
>6	2
<6, >3	1
<3	0
Fibrinogen level (g/L)	
<1	1
>1	0
Diagnosis	
$\geq$5	Overt DIC

DIC, disseminated intravascular coagulation.

TABLE 4. Clinical and laboratory criteria and a scoring system for non-overt DIC by the International Society on Thrombosis and Haemostasis

Etiology of DIC						
Yes	2					
No	0					
Major criteria						
Platelet count (10^9/L)			Rising	Stable	Falling	
<100	1	+	-1	0	1	
>100	0					
Prolonged prothrombin time			Falling	Stable	Rising	
>3 sec	1	+	-1	0	1	
<3 sec	0					
Soluble fibrin or FDP			Falling	Stable	Rising	
Raised	1	+	-1	0	1	
Normal	0					
Specific criteria						
Antithrombin						
Low	1					
Normal	-1					
Protein C						
Low	1					
Normal	-1					
TAT complexes						
High	1					
Normal	-1					
…..						
Abnormal	1					
Normal	-1					
Calculate score						

DIC, disseminated intravascular coagulation; FDP, fibrin/fibrinogen degradation products; TAT, thrombin-antithrombin.

TABLE 5. Clinical backgrounds of the patients

Etiology	n
Sepsis / severe infection	
Infection focus	
1) Lung	10
2) Intraperitoneum	7
3) Blood / catheter related	5
4) Urinary tract	4
5) Soft tissue	2
6) Bowel	2
Multiple trauma	
Main injury	
1) Head	4
2) Chest	2
3) Abdomen	8
4) Pelvis / extremity	3
Surgery	
1) Heart	2
2) Great vessel	7
Burn	2
Severe hepatic failure	6
Severe pancreatitis	3
Others	7
Total	74

TABLE 6. The first days when DIC was diagnosed on the basis of each criteria set

		Overt DIC					No DIC	Total
		Day 0	Day 1	Day 2	Day 3	Day 4		
Non-overt DIC	Day 0	10	2	0	0	1	3	16
	Day 1	3	3	4	0	1	4	15
	Day 2	3	0	1	0	0	9	13
	Day 3	0	2	0	0	0	2	4
	Day 4	0	0	0	0	0	7	7
No DIC		2[a]	0	0	0	0	17	19
Old Japanese DIC	Day 0	17	3	1	0	1	5	27
	Day 1	0	4	1	0	0	2	7
	Day 2	0	0	3	0	0	2	5
	Day 3	0	0	0	0	1	0	1
	Day 4	0	0	0	0	0	0	0
No DIC		1*	0	0	0	0	33	34
New Japanese DIC	Day 0	18	5	3	0	1	21	48
	Day 1	0	2	2	0	1	1	6
	Day 2	0	0	0	0	0	1	1
	Day 3	0	0	0	0	0	3	3
	Day 4	0	0	0	0	0	0	0
No DIC		0	0	0	0	0	16	16
Total		18	7	5	0	2	42	74

Shadowed areas indicate patients who were diagnosed with DIC earlier by each criteria set than by the overt DIC criteria ($p = 0.0005$).

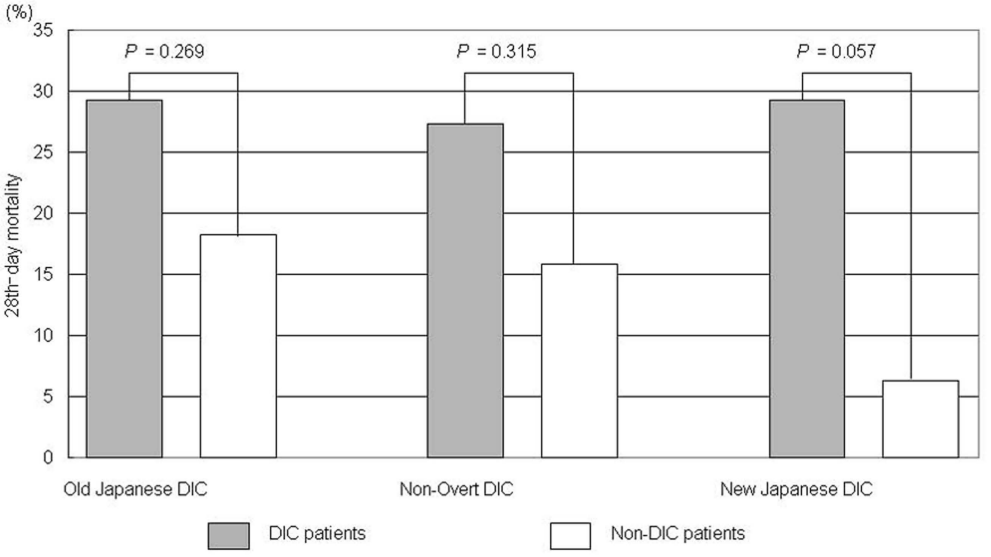
*Details of these cases are presented in the Results section.

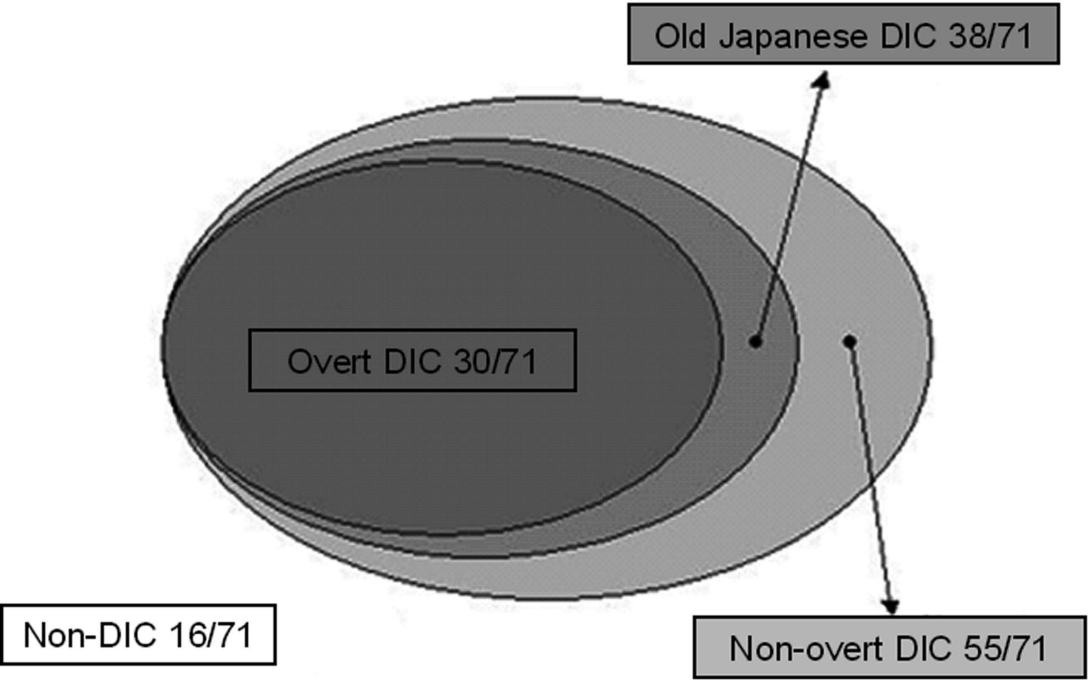
DIC, disseminated intravascular coagulation.

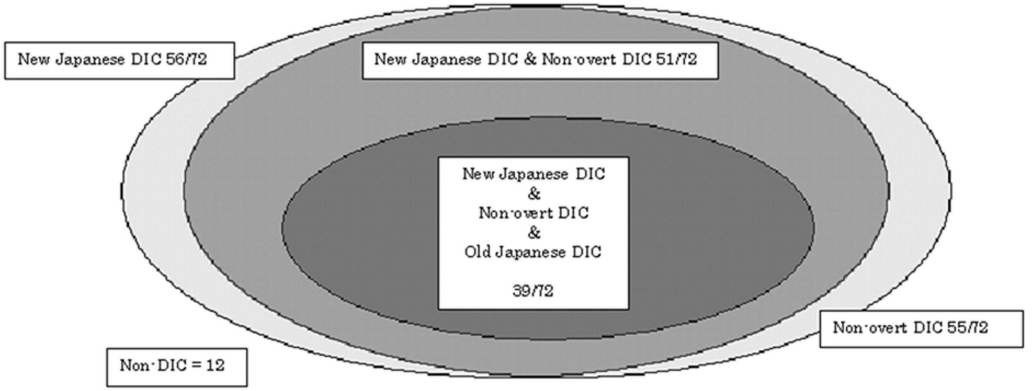
TABLE 7. The first days when MOF was established and DIC was diagnosed on the basis of each criteria set

		MOF					No MOF	Total
		Day 0	Day 1	Day 2	Day 3	Day 4		
Non-overt DIC	Day 0	8	2	0	1	1	4	16
	Day 1	4	2	2	0	1	6	15
	Day 2	5	2	0	1	1	4	13
	Day 3	1	0	0	0	0	3	4
	Day 4	3	0	0	0	0	4	7
	No DIC	8	0	0	0	0	11	19
Old Japanese DIC	Day 0	14	1	0	2	1	9	27
	Day 1	3	1	0	0	0	3	7
	Day 2	2	1	2	0	0	0	5
	Day 3	0	0	0	0	1	0	1
	Day 4	0	0	0	0	0	0	0
	No DIC	10	3	0	0	1	20	34
New Japanese DIC	Day 0	19	4	2	2	2	19	48
	Day 1	2	1	0	0	1	2	6
	Day 2	0	1	0	0	0	0	1
	Day 3	2	0	0	0	0	1	3
	Day 4	0	0	0	0	0	0	0
	No DIC	6	0	0	0	0	10	16
Total		29	6	2	2	3	32	74

Shadowed areas indicate patients diagnosed with DIC by each criteria set before MOF establishment (P = 0.0232).
MOF, multiple organ failure; DIC, disseminated intravascular coagulation.


(%)
35
30
25
20
15
10
5
0
28th-day mortality
P = 0.269
P = 0.315
P = 0.057
Old Japanese DIC
Non-Overt DIC
New Japanese DIC
DIC patients
Non-DIC patients


Old Japanese DIC 38/71
Overt DIC 30/71
Non-DIC 16/71
Non-overt DIC 55/71
Total patients = 71


New Japanese DIC 56/72
New Japanese DIC & Non-overt DIC 51/72
New Japanese DIC
&
Non-overt DIC
&
Old Japanese DIC
39/72
Non-overt DIC 55/72
Non-DIC = 12
Total patients = 72