Title
A Prospective Comparative Study of Three Sets of Criteria for Disseminated Intravascular Coagulation. ISTH Criteria vs. Japanese Criteria

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Shortened title
ISTH DIC vs. Japanese DIC

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**Summary:** Clinical and laboratory criteria and a scoring system for disseminated intravascular coagulation (DIC) were recently published by the International Society on Thrombosis and Haemostasis (ISTH). In Japan, the DIC Diagnostic Standards published in 1988 have been widely used for more than 10 years. In a general intensive care unit, we prospectively compared the diagnostic properties of the overt DIC, non-overt DIC, and Japanese DIC criteria sets, and investigated the influences of each set on patient morbidity and mortality. Seventy-four patients with platelet counts below 150 x 10^9/L were included in this study. Blood samples were collected daily from day 0 to day 4 after inclusion in the study. The Japanese DIC included the overt DIC and both of these were included in the non-overt DIC. The Japanese DIC criteria diagnosed DIC earlier than the non-overt DIC criteria did ($p = 0.020$). The DIC patients diagnosed by the Japanese criteria and those diagnosed by the overt DIC criteria showed a higher incidence of multiple organ failure than those without DIC ($p = 0.013$ and $p = 0.022$, respectively). The Japanese and the non-overt DIC criteria tended to predict patient prognoses effectively. In conclusion, the Japanese and the non-overt DIC criteria are of value in predicting outcome. However, the non-overt DIC criteria take more time to diagnose DIC than the Japanese criteria do. A more precise clinical study is needed to determined appropriate specific criteria and cut-off points in the non-overt DIC criteria set.

**Key words:** Disseminated intravascular coagulation, Diagnostic criteria, Hemostatic disorders, International Society on Thrombosis and Haemostasis, Japan
Systemic inflammatory response syndrome (SIRS) was defined the responses noted to be in common with sepsis, trauma, and other severe clinical insults (1). Recently, increasing numbers of patients with SIRS have been reported in intensive care units and emergency departments. Rangel-Frausto MS et al (2) have demonstrated the first evidence of a clinical hierarchical progression from SIRS to sepsis to severe sepsis and septic shock. They have also pointed out stepwise increases in disseminated intravascular coagulation (DIC) and other organ dysfunctions in this hierarchy in critically ill patients (2). Disseminated intravascular coagulation compromises the blood supply to organs and, in conjunction with hemodynamic and metabolic derangements, contributes to the failure of multiple organs (3). Recently, the effectiveness of several anticoagulants, such as activated protein C (4,5), antithrombin (6), and thrombomodulin (4) for sepsis or DIC patients has been reported. The early recognition and prompt treatment of DIC are certainly important (7).

Although DIC was first observed in the 19th century (3), only recently have an international diagnostic standard and a useful scoring system become available. The disseminated Intravascular Coagulation Diagnostic Standards were published in 1988 by the Japanese Ministry of Health and Welfare (8). These criteria have been widely used for more than 10 years in Japan. However, a good definition and scoring system for global use have remained unavailable. In 2001, clinical and laboratory criteria and a scoring system for DIC were published by the International Society on Thrombosis and Haemostasis (ISTH) (9). The ISTH established two sets of criteria: one set to diagnose a stressed but compensated hemostatic system (non-overt DIC), and another set to diagnose a stressed but decompensated hemostatic system (overt DIC) (9). To establish the
availability and predictive value of these ISTH criteria sets in patients with DIC, prospective validation of the scoring system is now under way.

In the present study, we prospectively compared the three sets of DIC diagnostic criteria (the Japanese set and the two ISTH sets) to investigate each set’s influences on patient morbidity and mortality.

MATERIALS AND METHODS

Patients

With the approval of our Institutional Review Board and with the informed consent of the patients or next of kin, we studied 74 consecutive patients who were admitted to our general intensive care unit (ICU) between January 2002 and December 2002, who met the inclusion criteria of this study, and about whom sequential data could be collected. Patients whose platelet counts were below $150 \times 10^9/L$ 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 who had received liver transplantation within the past four weeks. Organ dysfunction and failure were evaluated according to sequential organ failure assessment (SOFA) scores (10, 11).

Definitions

The Japanese criteria consist of clinical symptoms and global coagulation tests (TABLE 1.). Organ dysfunction in the Japanese criteria was
defined as a SOFA score $\geq 2$. A total DIC score $\geq 7$ establishes a diagnosis of Japanese DIC. The overt DIC criteria, meanwhile, are composed of global coagulation tests (TABLE 2.). We used fibrin/fibrinogen degradation products (FDP) to evaluate the elevated fibrin-related marker. 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 3.). In the non-overt DIC criteria, “rising” and “falling” of platelet counts were defined as an increase and a decrease, respectively, of more than $10 \times 10^9$/L. The “rising” and “falling” of prothrombin time 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. 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 has not defined a cutoff value for the diagnosis of non-overt DIC, we defined that value as $\geq 5$ in this study, in accordance with the presentation of the Scientific Subcommittee on DIC by Toh CH at the ISTH Consensus Meeting in Birmingham, UK, in July 2003. Organ failure was defined as a SOFA score of $\geq 3$. Multiple organ failure (MOF) was defined as the failure of two or more organs. In SOFA score calculations, coagulation scores were always excluded.

**Measurement and Protocol**

A blood samples 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 on days 1 through 4. Immediately after each sample was taken, platelet count, fibrinogen, prothrombin time, and FDP were measured for the diagnosis of DIC. Platelets were counted by a Coulter® Gen-S™ Hematology Analyzer (Beckman Coulter, Inc., Fullerton, CA, USA). Fibrinogen was measured by thrombin time 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 a latex agglutination method using LPIA-FDP (Dia-latron, Tokyo, Japan). Simultaneously, we evaluated the patients for symptoms of bleeding and organ dysfunction. In the non-overt DIC diagnosis, the laboratory data at day 0 could not be compared with those obtained the day before day 0.

Statistical Analysis

The StatView 5.0 statistical software package (SAS Institute Inc., Cary, NC, USA) was used for all statistical calculation analyses. Comparisons between the groups were made using the Chi-square test, the Mann-Whitney test, or the Kruskal-Wallis test. A $p$ value of $< 0.05$ was considered statistically significant. All data were expressed as means $\pm$ SEM.

RESULTS

During the study period, a total of 1205 patients were transferred to our tertiary emergency center, and 768 of them were admitted to the tertiary emergency center. Of those 768 patients, 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 these patients was 61 ± 16 years. The mean Acute Physiology and Chronic Health Evaluation II score was 22.4 ± 9.3. The clinical backgrounds of the enrolled patients are shown in TABLE 4. During the study period, DIC was diagnosed in 55.4% (41/74) of the patients based on the Japanese criteria, in 74.3% (55/74) based on the non-overt DIC criteria, and in 43.2% (32/74) based on the overt DIC criteria.

Comparison Between the Japanese and Overt DIC Criteria

Forty-one patients (41/74, 55.4%) were diagnosed with DIC during the study period based on either the Japanese or the overt DIC criteria set. Diagnostic agreement between those two criteria sets was obtained for 86.5% (64/74) of the patients. One patient (Case 1) was diagnosed with overt DIC but did not meet the Japanese criteria. He was a trauma patient and his overt DIC was diagnosed only on the day of admission (day 0) by virtue of elevated FDP and prolonged PT in the acute phase of trauma. The results are presented in TABLE 5.

Comparison Between the Japanese and Non-overt DIC Criteria

Based on either the 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. The results are presented in TABLE 6. Two patients (Cases 2 and 3) were diagnosed by the Japanese criteria but not by the non-overt DIC criteria. Case 2 died on admission day (day 0). We diagnosed Case 3 with DIC by the Japanese criteria on days 0 and 1. The condition of this patient improved daily. Seventeen cases were diagnosed by the non-overt DIC criteria but not by the Japanese criteria. Among those 17 cases, 13 were diagnose with DIC on only one day of five observation days and
improved the next day, 3 case were intermittently diagnosed with DIC on two of the five days; and the remaining case was diagnosed with DIC on consecutive days.

Comparison Between the Overt and Non-overt DIC Criteria

Fifty-seven patients (57/74, 77.0%) were diagnosed with DIC based on either the overt or the non-overt DIC criteria. Diagnostic agreement between these sets was obtained for 63.5% (47/74) of the patients. Two patients were diagnosed with overt DIC without meeting the non-overt DIC criteria. These patients were Cases 1 and 2 mentioned above. The results are presented in TABLE 7.

We compared the speed with which the Japanese and the non-overt criteria sets led to DIC diagnoses based on the overt DIC criteria (TABLE 8.). In 97.6% (40/41) of the patients, the Japanese criteria diagnosed DIC earlier than the overt DIC criteria did; in 2.4% (1/41), the Japanese criteria took longer. Compared to the overt DIC criteria, the non-overt criteria diagnosed DIC earlier in 82.5% (47/57) of the patients and later in 17.5% (10/57). The speed difference was statistically significant between the Japanese and the non-overt DIC criteria ($p = 0.020$).

Forty-five patients were complicated by MOF during the study period. The incidence of MOF was calculated between patients with and those without DIC, based on each criteria set. The DIC patients diagnosed by the Japanese and overt DIC criteria sets showed higher incidences of MOF than those without DIC ($p = 0.013$ and $p = 0.022$, respectively). However, we found no difference in the MOF complication rate between patients with non-overt DIC and those without. The results are presented in FIG. 1.
FIG. 2. shows the mortality rates of patients with and those without DIC on the 28th day based on each criteria set. The Japanese and the non-overt DIC criteria tended to predict prognoses more effectively than the overt DIC criteria did.

**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 (9). This suggests that DIC strongly influences critically ill patients’ morbidity and mortality through two serious complications: hemorrhage and organ failure. Wada et al. (7) investigated the outcomes of DIC patients in relation to their Japanese DIC scores obtained at the beginning of treatment (7). They found that patients with higher DIC scores had poorer outcomes, and they emphasized the importance of the early diagnosis and treatment of DIC (7).

The early diagnosis of DIC requires sensitive diagnostic criteria. Three sets of criteria are now available: the Japanese criteria set and the two ISTH criteria sets (overt and non-overt). The main differences between the Japanese and the ISTH criteria lie in their handling of clinical symptoms such as bleeding and organ dysfunction. The ISTH scoring system does not include the clinical assessment of bleeding or of organ dysfunction, since the DIC score itself constitutes a part of the score for organ dysfunction (9). Moreover, the non-overt DIC criteria include molecular markers such as antithrombin and protein C. The
ISTH subcommittee emphasized that molecular markers are important for diagnosing non-overt DIC because of the great value of looking at both endothelial injury and hemostatic activation (9). Although the non-overt DIC criteria include molecular markers as specific criteria, the ISTH subcommittee has not strictly decided what kinds of molecular markers should be used (9). Consequently, our study did not use specific criteria in the non-overt DIC criteria.

The diagnostic criteria for DIC should have highly sensitive, minimally sacrificing specificity for early diagnosis, as this would allow clinically useful decision making for treatment. However, clinically applicable DIC diagnostic criteria are somewhat arbitrary, because no gold standard for diagnostic criteria has emerged. The absence of such a standard makes it hard to determine the diagnostic test quality of the DIC diagnostic criteria. To overcome this, in the present study we regarded the overt DIC criteria as the standard by which to compare the diagnostic speeds of the Japanese and the non-overt DIC criteria sets. We then compared the speed of DIC diagnosis, the predictive value of MOF, and outcome among the three sets.

We found that Japanese DIC includes overt DIC and is included in non-overt DIC (FIG. 3). This result was almost the same as that reported by Wada et al. (12) and Gando et al (13). When the speed of DIC diagnosis was compared among the sets, the Japanese criteria diagnosed DIC significantly earlier than the non-overt DIC criteria did, based on the overt DIC criteria. Although non-overt DIC included both Japanese and overt DIC, the non-overt DIC criteria were unable to diagnose DIC earlier than the Japanese criteria. Although ISTH proposed a hierarchical progression from non-overt DIC to overt DIC (9), non-overt DIC was not always diagnosed before overt DIC (TABLE 8).
In the present study, we were unable to elucidate the exact mechanisms underlying these discrepancies. However, the discrepancies may have been influenced by the inclusion of clinical symptoms in the Japanese criteria, our exclusion of specific criteria, and our application of our own values and cutoff points to the non-overt DIC criteria. These problems should be solved after a firm framework for the non-overt DIC criteria is established.

Treatment of DIC should not be directed at the amelioration of DIC itself but rather at the improvement of organ dysfunction or mortality. The accurate prediction of organ dysfunction is important in order to improve the prognoses of critically ill patients. In the present study, we demonstrated that patients with Japanese and overt DIC were complicated by MOF at a higher rate than patients without Japanese and overt DIC. However, we found no such difference in patients when we applied the non-overt DIC criteria. The results are not be surprising: the Japanese criteria use clinical symptoms of organ dysfunction defined by SOFA scores, and the overt DIC criteria diagnose decompensated DIC. The results further suggest that these two criteria sets have higher DIC diagnostic specificity for MOF establishment than does the non-overt DIC criteria set. Unlike the almost identical mortality rates obtained using the overt DIC criteria, the DIC patients diagnosed by the Japanese and the non-overt DIC criteria tended to have higher mortality rates than those without DIC. These results suggest that the overt DIC criteria may miss patients who should be diagnosed with DIC. Gando et al. (13) reported that the mortality of patients with overt DIC was higher than that of patients without overt DIC in their retrospective study. In the present study, we examined mortality rates on the 28th day, while Gando et al. (13) did not state at what point mortality rates were recorded in their
study. The time at which mortality rates were recorded thus may differ between the two studies, and may have contributed to the discrepancy between the results of Gando’s study (13) and those of our own. The results of the present study reconfirm the moderate sensitivity and specificity of the Japanese criteria not only for diagnosing DIC but also for predicting morbidity and mortality in DIC patients.

In conclusion, the efficacy of the overt DIC criteria for diagnosing a stressed but decompensated hemostatic system was reconfirmed. The non-overt DIC criteria and Japanese criteria accurately predicted the outcome. On the other hand, we found the non-overt DIC criteria were unable to diagnose DIC earlier than the Japanese criteria. The non-overt DIC criteria are not sufficient for the early diagnosis and treatment of DIC. To overcome these weak points, a more precise clinical study is necessary to decide appropriate specific criteria and cutoff points in the non-overt DIC criteria.
REFERENCES


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Fig. 1 Incidence of multiple organ failure (MOF) in patients with and those without disseminated intravascular coagulation (DIC). Shaded columns show DIC patients; open columns show non-DIC patients.

Fig. 2 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. 3 Correlations of disseminated intravascular coagulation (DIC) diagnoses among the three sets of criteria. Japanese DIC includes overt DIC and is included in non-overt DIC. Three peculiar patients (Cases 1, 2, and 3) are excluded in this figure. The peculiarities of each case are described in the Results section.
The diagram illustrates the 28-day mortality percentages for different categories of DIC: Japanese DIC, Overt DIC, and Non-overt DIC. The p-values for the comparisons are as follows:

- Japanese DIC vs. Overt DIC: p = 0.22
- Overt DIC vs. Non-overt DIC: p = 0.99
- Japanese DIC vs. Non-overt DIC: p = 0.31
Japanese DIC 38/71

Overt DIC 30/71

Non-DIC 16/71

Non-overt DIC 55/71

Total patients = 71