Laboratory investigation in normal and pathologic coagulation

Bakhtiari, K.

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Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation

Kamran Bakhtiari, BSc; Joost C.M. Meijers, PhD; Evert de Jonge, MD; Marcel Levi, MD

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Abstract

Objectives: A diagnosis of disseminated intravascular coagulation (DIC) is hampered by the lack of an accurate diagnostic test. Based on the retrospective analysis of studies in patients with DIC, a scoring system (0–8 points) using simple and readily available routine laboratory tests has been proposed. The aim of this study was to prospectively validate this scoring system and assess its feasibility, sensitivity, and specificity in a consecutive series of intensive care patients.

Design: Prospective cohort of intensive care patients.

Setting: Adult intensive care unit in a tertiary academic center.

Patients: Consecutive patients with a clinical suspicion of disseminated intravascular coagulation.

Interventions: Patients were followed during their admission to the intensive care unit, and the DIC score was calculated every 48 hrs and compared with a “gold standard” based on expert opinion. In addition, an activated partial thromboplastin time (aPTT) waveform analysis, which has been reported to be a good predictor for the absence or presence of DIC, was performed.

Measurements and Main Results: We analyzed 660 samples from 217 consecutive patients. The prevalence of DIC was 34%. There was a strong correlation between an increasing DIC score and 28-day mortality (for each 1 point increment in the DIC score, the odds ratio for mortality was 1.25). The sensitivity of the DIC score was 91% and the specificity 97%. An abnormal aPTT waveform was seen in 32% of patients and correlated well with the presence of DIC (sensitivity 88%, specificity 97%). In 19% of patients, the aPTT waveform-based diagnosis of DIC preceded the diagnosis based on the scoring system.

Conclusions: A diagnosis of DIC based on a simple scoring system, using widely available routine coagulation tests, is sufficiently accurate to make or reject a diagnosis of DIC in intensive care patients with a clinical suspicion of this condition. An aPTT waveform analysis is an interesting and promising tool to assist in the diagnostic management of DIC.

Keywords: disseminated intravascular coagulation; scoring system; diagnostic test
INTRODUCTION

Disseminated intravascular coagulation (DIC) is a frequently occurring complication of severe sepsis, polytrauma, and several other conditions (1). DIC may contribute to the pathogenesis of multiple organ dysfunction and is an independent predictor of mortality (2). New therapeutic strategies aimed at modifying the coagulation and inflammation that occur in DIC, such as administration of recombinant activated protein C, have proven to be successful in clinical trials (3). Interestingly, the greatest benefit of this treatment in reducing mortality was seen in the subgroup of patients who had full-blown DIC. Hence, a diagnosis of DIC may have important clinical consequences. However, a proper diagnosis of DIC has been hampered by the lack of a specific diagnostic test. No single clinical sign or laboratory test has been found to possess sufficient diagnostic accuracy for confirming or rejecting the diagnosis of DIC (4).

A combination of clinical and laboratory findings, including tests for molecular markers of thrombin generation and fibrin turnover, may in most cases allow for an adequate diagnosis of DIC (5, 6), but this is only helpful in a highly specialized and/or research setting since most of these complicated tests are not routinely available. For some years now, a Japanese scoring system for DIC has been developed but has not been widely adopted, potentially due to some practical limitations (7).

To facilitate the diagnosis of DIC in the clinical situation, the subcommittee on DIC of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis (ISTH) has proposed a scoring system, based on the outcome of a combination of several laboratory tests (8). One of the advantages of this scoring system is that it uses simple, widely available routine coagulation assays (Table 1). Based on retrospective studies, a cutoff point of 5 was chosen; that is, a score of ≥5 is compatible with the diagnosis of overt DIC. Obviously, prospective validation of this scoring system is required.

In this article, we report on the feasibility and the sensitivity and specificity of the ISTH DIC score for the diagnosis of DIC in a consecutive series of intensive care patients with a clinical suspicion of DIC. In addition, since the presence of an abnormal biphasic waveform during activated partial thromboplastin time (aPTT) measurement
on an automated coagulation machine has been proposed as an accurate test for the presence of DIC (9), we also evaluate this test in our prospective series of patients.

**METHODS**

**Patients.**
The study was approved by the Institutional Review Board of the Academic Medical Center in Amsterdam, the Netherlands. Consecutive patients who were admitted to the intensive care unit (ICU) in our hospital with a clinical and laboratory suspicion of DIC were eligible for the study. A suspicion of DIC was defined as a prolongation of the prothrombin time or aPTT, the occurrence of thrombocytopenia ($<150 \times 10^9$/L), or

<table>
<thead>
<tr>
<th><strong>Table 1:</strong> International Society of Thrombosis and Haemostasis disseminated intravascular coagulation (DIC) scoring system</th>
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</table>
| 7. Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?  
If yes, proceed; if no, do not use this algorithm. |
| 8. Order global coagulation tests (platelet count, prothrombin time, fibrinogen, soluble fibrin monomers, or fibrin degradation products). |
| 9. Score global coagulation test results.  
- platelet count ($>100$, 0; $<100$, 1; $<50$, 2)  
- Elevated fibrin-related marker (e.g. soluble fibrin monomers/fibrin degradation products)  
  (no increase, 0; moderate increase, 2; strong increase, 3)  
- Prolonged prothrombin time  
  ($<3$ secs, 0; $>3$ secs but $<6$ secs, 1; $>6$ secs, 2)  
- Fibrinogen level  
  ($>1.0$ g/L, 0; $<1.0$ g/L, 1) |
| 10. Calculate score |
| 11. If $\geq 5$, compatible with overt DIC; repeat scoring daily. |
| 12. If $<5$, suggestive (not affirmative) for nonovert DIC; repeat next 1-2 days. |
Prospective validation of ISTH scoring system

a decrease in platelet count of \( >50 \times 10^9/L \) per 24 hrs in a patient with an underlying disorder known to be associated with DIC, according to the list of the ISTH (8). Global clotting times and platelet count were measured at least once per 24 hrs in every intensive care patient. Exclusion criteria were the use of anticoagulant agents, such as heparin at a therapeutic dose or vitamin K antagonists, the presence of a known congenital or acquired coagulation disorder or hematologic disease, and the inability to obtain informed consent from the patient or his or her relatives. None of the patients were receiving antithrombin or (activated) protein C concentrate. Fresh frozen plasma and platelet transfusion were given only in case of bleeding, according to the ICU protocol.

**DIC Score.**
The DIC score was calculated every 48 hrs during the ICU stay, from the beginning of the clinical suspicion of DIC until discharge. Platelets were measured by flow cytometry in a standard automated cell counter. Global clotting times for prothrombin time and aPTT were assayed according to standard onestage clotting assays on an automated clotting analyzer (STA-R, Roche Diagnostics, The Netherlands). Plasma levels of fibrinogen were assayed using STA Fibrinogen reagent (Diagnostica Stago, France) according to the method of Clauss (10). Fibrin-related marker D-dimer levels were assayed with a quantitative rapid enzyme linked immunosorbent D-dimer assay (Vidas DD; bioMérieux, Paris, France). A level of \(<0.4 \mu g/mL\) (the upper limit of normal of this D-dimer assay) was considered as normal, a level between 0.4 and 4.0 \(\mu g/mL\) was considered as moderately increased, and a level of \(^{>4.0} \mu g/mL\) (ten times the upper limit of normal) was considered as strongly increased. These cutoff values were used in a previous clinical study in patients with sepsis (11).

**“Gold Standard” for DIC by Expert Opinion.**
To compare the diagnostic accuracy of the DIC score for the presence or absence of DIC, the outcome of the score needs to be compared with a gold standard for DIC. In the absence of such a gold standard, we decided to use expert opinion and to perform in each sample an extensive series of coagulation tests, including highly
sensitive and specific assays for thrombin generation (prothrombin fragment F1+ 2 and thrombin-antithrombin [TAT] complexes) (12) as well as assays for soluble fibrin, plasma levels of coagulation factors VII and V (to assess the potential presence of vitamin K deficiency), and plasma levels of antithrombin and protein C. The results of these assays, in combination with clinical data on organ failure and the occurrence of bleeding, were presented to a panel consisting of two experts in haemostasis and intensive care medicine. Each of the two panel members reached a decision on the presence or absence of DIC independently, and subsequently the results were compared. If no consensus was reached, a third (decisive) opinion was asked from a third expert. The experts were not involved in the clinical care of the patients in the study and were not aware of the DIC score of the patient.

Measurement of F1+2 and TAT complexes was done by enzyme linked immunosorbent assays (Behringwerke AG, Marburg, Germany), according to the instructions of the manufacturers. Soluble fibrin was measured by spectrophotometric assay (Berichrom FM; Dade Behring, Leusden, Netherlands). Plasma levels of coagulation factors were determined by a one-stage clotting assay on an automated clotting analyzer (STA-R). Antithrombin and protein C activity levels were measured by chromogenic assay (Chromogenix, Stockholm, Sweden). Organ failure was assessed with the Sequential Organ Failure Assessment (SOFA) score as previously published (13).

**Waveform Analysis.**

The aPTT waveform analysis was done on an MDA 180 (BioMerieux, Durham, NC) analyzer using Platelin LS. The methodology has been described in detail elsewhere (9). In brief, the MDA 180 uses a variable wavelength photo-optical detection system that can quantify changes in light transmission when the plasma clots after activation and recalcification. A biphasic profile occurs when light transmission decreases before clot formation in the first part of the curve. On the MDA system, this abnormality is quantified by the slope-1 parameter, which is derived from the light transmission between time 0 (100%) and the value recorded at clot time. To define an abnormal slope-1, we analyzed 150 healthy volunteers and set a threshold limit for abnormal
slope-1 as the 99th percentile of normal. The presence of a biphasic waveform was defined by a slope-1 of < -8 (NTU/sec).

**Statistical Analysis.**
To compare the distribution of baseline characteristics between patient groups with or without DIC, chi-square and Wilcoxon rank-sum tests were performed. To evaluate whether the presence of DIC was a predictor of 28-day mortality, a logistic regression model was fit to 28-day all-cause mortality using age, gender, SOFA score, and ISTH DIC score as continuous predictors. The continuous relation between the number of ISTH points and mortality was analyzed by analysis of variance.

**RESULTS**

**Patients.**
Between January and December 2001, 263 consecutive ICU patients had a clinical suspicion for DIC. Of these, 46 patients were excluded from the study because of the use of anticoagulants (ten patients), presence of a hematologic disorder (six patients), or inability to obtain informed consent (30 patients). From the included patients, 660 paired measurements of the DIC score and the gold standard were available for analysis. The kappa between the expert reviewers for the diagnosis of DIC was 0.81. Patient characteristics at study entry are given in Table 2. The majority of the patients were surgical patients, and the most frequent diagnoses were severe sepsis, trauma, major general surgery, and pneumonia with respiratory insufficiency.

**Prevalence of DIC and Prognosis.**
DIC was diagnosed according to the expert opinion using sensitive laboratory tests and clinical information in 74 patients (34%) during their clinical course on the ICU. DIC was more frequently seen in medical patients (incidence in medical patients 44% vs. 29% in surgical patients, p = .02). Patients with severe sepsis, urosepsis, and abdominal sepsis and a suspicion of DIC were more likely to have a diagnosis of DIC confirmed, whereas cardiac surgery patients with a clinical suspicion of DIC were less likely to have a diagnosis of DIC (Table 2). Organ failure, as reflected by a higher
Chapter 2

cardiovascular and renal SOFA score, was significantly higher in patients with DIC. Also, Acute Physiology and Chronic Health Evaluation II scores were significantly higher in patients with DIC. A DIC score ≥5 according to the ISTH scoring system was present in 70 patients (32%) during their ICU admission (Fig. 1). The DIC score remained ≥5 for 2.8 (_2.2) days after the diagnosis of DIC.

Table 2. Characteristics of all patients in the study and patients with or without DIC

<table>
<thead>
<tr>
<th></th>
<th>AllPatients</th>
<th>DIC</th>
<th>NoDIC</th>
<th>DICVs. NoDICGroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 217</td>
<td>N= 74</td>
<td>N= 143</td>
<td></td>
</tr>
<tr>
<td>Meanage, yrs, mean (sd)</td>
<td>59.2(5.2)</td>
<td>61.7(6.5)</td>
<td>57.9(4.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender, n(%)</td>
<td>137(63)</td>
<td>45(61)</td>
<td>92(64)</td>
<td>NS</td>
</tr>
<tr>
<td>Medical patients, n(%)</td>
<td>70(32)</td>
<td>31(42)</td>
<td>39(27)</td>
<td>.01</td>
</tr>
<tr>
<td>Surgical patients, n(%)</td>
<td>147(68)</td>
<td>43(58)</td>
<td>104(73)</td>
<td>.02</td>
</tr>
<tr>
<td>Diagnosis, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe sepsis (source unclear)</td>
<td>42(19)</td>
<td>21(28)</td>
<td>21(15)</td>
<td>.02</td>
</tr>
<tr>
<td>Pneumonia + respiratory insufficiency</td>
<td>31(14)</td>
<td>11(15)</td>
<td>20(14)</td>
<td>NS</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>14(6)</td>
<td>8(11)</td>
<td>6(4)</td>
<td>.05</td>
</tr>
<tr>
<td>Abdominal sepsis</td>
<td>25(12)</td>
<td>17(23)</td>
<td>8(6)</td>
<td>.01</td>
</tr>
<tr>
<td>Major general surgery</td>
<td>49(23)</td>
<td>5(7)</td>
<td>44(31)</td>
<td>.01</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>14(6)</td>
<td>1(1)</td>
<td>13(9)</td>
<td>NS</td>
</tr>
<tr>
<td>Trauma</td>
<td>35(16)</td>
<td>10(14)</td>
<td>25(17)</td>
<td>NS</td>
</tr>
<tr>
<td>Other diagnosis</td>
<td>7(3)</td>
<td>1(1)</td>
<td>6(4)</td>
<td>NS</td>
</tr>
<tr>
<td>SOFA scores, mean (sd)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2.5(1.2)</td>
<td>3.0(1.3)</td>
<td>2.3(1.1)</td>
<td>.01</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2.4(1.0)</td>
<td>2.5(1.4)</td>
<td>2.4(1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Renal</td>
<td>1.3(0.9)</td>
<td>1.7(1.2)</td>
<td>1.1(0.8)</td>
<td>.04</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1.1(0.5)</td>
<td>0.8(0.3)</td>
<td>1.2(0.5)</td>
<td>NS</td>
</tr>
<tr>
<td>APACHE II score, mean (sd)</td>
<td>21.3(4.3)</td>
<td>24.1(1.9)</td>
<td>18.2(2.4)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

In patients who were diagnosed with DIC (according to the expert opinion) 28-day mortality was 45%, whereas 28-day mortality in patients without DIC was 25%. DIC was an independent predictor of mortality (odds ratio adjusted for age, SOFA, and Acute Physiology and Chronic Health Evaluation score, 2.39; 95% confidence interval, 1.32–4.33). Mortality in comparison with the ISTH DIC score (at admission in the study) is shown in Figure 2. There was a strong correlation between an increased DIC score at inclusion and increased 28-day mortality (for each 1-point increment in DIC score, the odds ratio for mortality was 1.25).
Diagnostic Accuracy of the ISTH Scoring System.

When comparing the confirmation or rejection of a diagnosis of DIC by means of the ISTH DIC score (based on the cutoff point of 5) with the expert opinion in each of the 660 samples, the sensitivity of the ISTH DIC score was 91% and the specificity 97%. When the analysis was done on a per patient basis, the sensitivity was 93% and the specificity 98%. This means that in our consecutive series of ICU patients, the positive predictive value of an ISTH DIC score of ≥5 for the diagnosis of DIC is 96% and the negative predictive value of a score <5 for the absence of DIC is 97%.

Most of the points in the DIC score were contributed by the platelet count, the prolongation of the prothrombin time, and increased levels of plasma D-dimer. A decreased plasma fibrinogen level (<1.0 g/L) was seen in only four patients with DIC (5.4%), and in only one patient this resulted in a positive ISTH DIC score where it otherwise would have been negative.
Consequently, we hypothesized that exclusion of all fibrinogen levels from the calculation of the ISTH DIC score would hardly affect the accuracy of the scoring system. Indeed, when the sensitivity and specificity of the ISTH DIC score were recalculated without fibrinogen in each patient, the sensitivity was 92% and the specificity remained 98%.

There was an interesting correlation between increased ISTH DIC scores and decreased plasma levels of antithrombin or protein C (Fig. 3). However, no clear cutoff value for antithrombin or protein C could be identified that was helpful in discriminating between the presence and absence of DIC in individual patients. The mean results of the assays for antithrombin activity, protein C activity, TAT complexes, and soluble fibrin are given in Table 3. There are significant differences for each of these assays between patients with and without DIC; however, none of these markers itself has sufficient diagnostic accuracy to confirm or reject a diagnosis of DIC.

**Table 3.** Laboratory values of coagulation inhibitors and sensitive markers for coagulation activation of all patients in the study and patients with or without disseminated intravascular coagulation (DIC).

<table>
<thead>
<tr>
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<th>AllPatients</th>
<th>DIC</th>
<th>NoDIC</th>
<th>DICVs. NoDIC</th>
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<td></td>
<td>N= 217</td>
<td>N= 74</td>
<td>N= 143</td>
<td></td>
</tr>
<tr>
<td>Antithrombin activity, %</td>
<td>68± 4</td>
<td>52± 7</td>
<td>74± 12</td>
<td>.01</td>
</tr>
<tr>
<td>Protein C activity, %</td>
<td>51± 3</td>
<td>43± 8</td>
<td>59± 5</td>
<td>.03</td>
</tr>
<tr>
<td>Thrombin-antithrombin complexes, µg/L</td>
<td>9.8± 2.4</td>
<td>17.4± 8.2</td>
<td>6.3± 3.0</td>
<td>.01</td>
</tr>
<tr>
<td>Soluble fibrin, µg/L</td>
<td>149± 27</td>
<td>251± 29</td>
<td>111± 43</td>
<td>.02</td>
</tr>
</tbody>
</table>

Values are mean ± sd.
Biphasic Waveform Analysis.

An abnormal biphasic aPTT waveform was seen in 65 of 74 patients with DIC (sensitivity 88%). In five of 143 patients without a diagnosis of DIC, a biphasic waveform was observed (specificity 97%). The absence or presence of a biphasic aPTT against the ISTH DIC score is shown in Figure 4. In 14 patients with DIC (19%), an abnormal waveform was seen 48 hrs before the DIC score became abnormal, whereas in two patients (3%) the DIC score was ≥5 in the sample taken 48 hrs before the waveform became abnormal. In the majority of patients, the DIC score and the waveform analysis were abnormal at the same time point. If compared with test result of TAT complexes alone or soluble fibrin alone (with the normal values of these assays as cutoff points), the biphasic waveform had a somewhat lower sensitivity (93% for the TAT assay and 95% for the soluble fibrin assay), but its specificity of 97% compared favorably with the specificity of each of these two assays (79% for TAT assay and 70% for soluble fibrin assay). Patients with a biphasic aPTT waveform had a higher mortality in comparison to patients with a normal aPTT waveform (45% vs. 32%, \( p = .02 \)).

DISCUSSION

In virtually all critically ill patients, some degree of activation of coagulation is detectable (5, 14). Coagulation activation spans a spectrum from minimal activity that can only be detected by highly sensitive tests for molecular markers of coagulation activation to stronger activation, which is reflected in consumption of platelets and coagulation factors. The activation of coagulation is insufficiently counterbalanced by an impaired function of physiologic anticoagulant systems, such as antithrombin or
Our prospective study confirms the utility of the International Society of Thrombosis and Haemostasis disseminated intravascular coagulation scoring system by demonstrating an acceptable accuracy for the diagnosis of disseminated intravascular coagulation in critically ill patients with a clinical suspicion of this syndrome.

protein C (1, 2). This is due to impaired synthesis of these proteins, leakage in the extravascular space, and degradation by elastase from activated neutrophils. The protein C pathway is further harmed by a downregulation of protein C activation, due to a down-regulation of endothelial thrombomodulin. Antithrombin activity may be particularly low due to consumption, since this protease inhibitor forms 1:1 complexes with thrombin. In its most fulminant form, systemic and widespread activation of coagulation occurs with consequent deposition of fibrin in small and midsize vessels and thereby contributes to organ dysfunction, which has been termed disseminated intravascular coagulation. The relevance of the presence of DIC has been shown in clinical and experimental studies (15, 16). However, the clinical management of full blown DIC has for a long time been hampered by lack of consensus criteria for its diagnosis, which makes clinical studies more difficult. In 2001, the Subcommittee on DIC of the ISTH proposed a simple scoring system based on routinely available laboratory tests. Based on retrospective observations, a cutoff value of 5 was chosen to discriminate between the presence and absence of DIC. In this study, we present our prospective validation of the DIC score in a sample of consecutive ICU patients with a clinical suspicion of DIC. The feasibility of the scoring system was demonstrated as we were able to obtain a score in all patients included in the study. Comparing the DIC score with the expert diagnosis based on an extensive panel of simple and sophisticated coagulation assays and clinical information on the patient, we determined the diagnostic accuracy of the DIC score in a blinded fashion. The sensitivity of the DIC score was 93% and the specificity 98%. Although this is not perfect, we believe that with this simple scoring system, clinicians in virtually all clinical
settings would be able to confirm or reject a diagnosis of DIC with sufficient confidence. Importantly, this scoring system also allows for a more standardized patient stratification in clinical trials of critically ill patients who are treated with interventions that are aimed at the coagulation system. Interestingly, a recent post hoc analysis of the pivotal phase III clinical trial of recombinant human activated protein C in patients with severe sepsis (3) revealed that the presence of DIC, as calculated with the ISTH DIC score, identified a subgroup of patients who had numerically much larger benefit of activated protein C (11). The relative risk reduction in mortality of patients with sepsis and a DIC score of ≥5 who received activated protein C was 38%, compared with a relative risk reduction of 18% in patients with sepsis who had a DIC score of <5. At present, it is not clear whether subgroups of patients with DIC in the recent two trials of antithrombin or recombinant TFPI in patients with severe sepsis (17, 18), which turned out to be negative for the whole group of patients included, would show a benefit of these interventions. Clearly, such a benefit demonstrated by post hoc analysis would subsequently need confirmation in a prospective trial.

Good diagnostic accuracy of a DIC scoring system would also be important to test new diagnostic modalities that can further improve or facilitate the diagnosis of DIC. In our study, we have evaluated the presence of a biphasic waveform pattern during aPTT measurement on an MDA coagulation analyzer. Previous studies had indicated that there is a correlation between this abnormal waveform and the presence of DIC (9, 19, 20). In our prospective series, sensitivity and specificity of an abnormal waveform for a diagnosis of DIC were 88% and 97%, respectively, which are in line with previous studies. Therefore, detection of an abnormal biphasic waveform in patients with a clinical suspicion of DIC may be a helpful test. However, this test can only be done on the MDA coagulation analyzer, which is available in a limited number of laboratories. It may be that detection of a similar abnormal clotting pattern on other equipment can be a helpful tool for the diagnosis of DIC in the future.

Our studies have focused on the validation of the scoring system for overt DIC, as defined by the ISTH subcommittee on DIC. Currently, a scoring system for nonovert DIC is under construction (8). This system is likely to use additional coagulation assays, such as assays for antithrombin or protein C. Our results show that there is a fair
correlation with increasing DIC scores and decreasing concentrations of these anticoagulant proteins, which indeed seem to play an essential role in the pathogenesis of DIC (21). Also, the nonovert scoring system may be more appropriate to assess the coagulation disturbances over time, which can be less well studied with the algorithm for overt DIC.

A limitation of our study may be that a 100% accurate gold standard for the diagnosis of DIC is not available. We think, however, that with our studies we have tried to approach the most accurate replacement that is practically feasible. The fact that the presence or absence of DIC by this method correlates well with 28-day mortality adds to the suggestion that this diagnosis of DIC is a relevant clinical observation.

CONCLUSIONS
Our prospective study confirms the utility of the ISTH DIC scoring system by demonstrating an acceptable accuracy for the diagnosis of DIC in critically ill patients with a clinical suspicion of this syndrome. The scoring system appears to correlate well with clinical outcome and may be useful in clinical practice or in clinical studies to better define or stratify subgroups of patients. New diagnostic tests (such as detection of the aPTT biphasic waveform) may further facilitate the diagnosis of DIC in the future and can be calibrated against the ISTH DIC score.

REFERENCES
Prospective validation of ISTH scoring system


9. Toh CH, Samis J, Downey C, et al: Biphasic transmittance waveform in the APTT coagulation assay is due to the formation of a Ca(__)-dependent complex of C-reactive protein with very-low-density lipoprotein and is a novel marker of impending disseminated intravascular coagulation. Blood 2002; 100:2522–2529


