

Analytic Validation and Clinical Evaluation of the STA LIATEST Immunoturbidimetric D-Dimer Assay for the Diagnosis of Disseminated Intravascular Coagulation

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Abstract

To evaluate the diagnostic performance of a quantitative, immunoturbidimetric D-dimer assay and compare it with other components of the proposed International Society on Thrombosis and Haemostasis disseminated intravascular coagulation (DIC) diagnostic algorithm, we retrospectively analyzed the D-dimer, platelet count, prothrombin time, and fibrinogen results for all eligible hospitalized patients ($n = 241$) who had a D-dimer assay ordered during a 12-month period. A receiver operating characteristic (ROC) curve constructed from the maximum D-dimer measurement for all patients was significant ($P < .001$) with an area under the curve (AUC) of 0.94. The ROC curves of the other tests were each significant ($P < .001$), but the AUCs of the prothrombin time (0.74), fibrinogen level (0.70), and platelet count (0.67) did not approach that of the D-dimer. A D-dimer cutoff of 8.2 $\mu\text{g/mL}$ (8,200 $\mu\text{g/L}$) optimized sensitivity and negative predictive value for the total population and patients with a predisposing condition. Validation against 286 additional patients in a separate analysis verified the diagnostic performance of the aforementioned cutoff. A sensitive, immunoturbidimetric D-dimer assay, by itself, provides excellent sensitivity and negative predictive value for the diagnosis of DIC.

Disseminated intravascular coagulation (DIC) remains a clinical diagnosis supported by laboratory data but with no universally accepted diagnostic algorithm. The Japanese Ministry of Health and Welfare (JMHW) proposed criteria for the diagnosis of DIC 2 decades ago.¹ The JMHW criteria include semiquantitation of fibrin degradation products as 1 component of the scoring system. The complexity of the algorithm and the current use of D-dimer assays limits the applicability of this scoring system. The International Society on Thrombosis and Haemostasis (ISTH) recently proposed a DIC scoring system based on 4 laboratory parameters and the presence of a predisposing condition.² Elevation of a fibrin-related marker, such as D-dimer, represents a key element of the ISTH algorithm, which also scores elevations in the prothrombin time (PT) and decreases in the platelet count and fibrinogen concentration.

Quantitative, rapid D-dimer assays with clinical performance characteristics comparable to conventional enzyme-linked immunosorbent assays have become widely available during the last several years.^{3,4} The immunoturbidimetric D-dimer assays represent a relatively new class of automated D-dimer tests that are based on photo-optical detection of microlatex particle agglutination.^{5,6}

Little is known about the performance of these sensitive D-dimer assays in the context of patient evaluation for suspected DIC. Therefore, we evaluated the analytic and clinical performance of the STA LIATEST (Diagnostica Stago, Parsippany, NJ) immunoturbidimetric D-dimer assay in healthy people, in hospitalized patients not suspected of having DIC, and in patients who have had D-dimer assays ordered for suspected DIC. Because the measurement of D-dimer has not been harmonized among

marketed assays, cutoff values for scoring D-dimer elevations in the ISTH algorithm need to be assay-specific.⁷ By using receiver operating characteristic (ROC) curve analysis, we identified a prospective cutoff that maximizes sensitivity and specificity of the immunoturbidimetric D-dimer assay. By using this cutoff, we compared the diagnostic performance of the immunoturbidimetric D-dimer assay with the ISTH scoring system.

Materials and Methods

Participants and Specimen Collection

The University of Utah (Salt Lake City) Institutional Review Board approved the study as a waived study for people 19 years or older. Specimens analyzed for PT, partial thromboplastin time (PTT), fibrinogen level, and D-dimer were obtained by peripheral phlebotomy or “line-draw” into evacuated tubes containing 3.2% sodium citrate. Specimens analyzed for platelet count were obtained by peripheral phlebotomy or line-draw into evacuated tubes containing potassium EDTA. All specimens were analyzed routinely within 4 hours of collection.

Samples from 26 men and 18 women ranging in age from 21 to 53 years were obtained for the reference range validation study. Reference range candidates were screened to exclude acute illness, treatment for chronic illness, history of hematologic or hemostatic disorders, use of prescription medications (including contraceptive medications), and pregnancy.

We selected 63 specimens from the daily clinical laboratory workload during a 2-month period for comparison of the manual latex and immunoturbidimetric D-dimer assays. To evaluate the clinical specificity of the immunoturbidimetric D-dimer assay, D-dimer levels were measured in specimens obtained from 59 hospitalized patients from medical and surgical services for whom coagulation testing was ordered as part of their care and who had normal PT and PTT values, did not have diagnoses of venous thromboembolism or cancer, and were not suspected of having DIC.

To establish the range of values expected in a population of patients suspected of having clinical DIC, we retrospectively analyzed all D-dimer results of institutional review board-eligible, hospitalized patients for whom a D-dimer assay was ordered during a 12-month period (cohort 1). The population consisted of 134 women and 107 men ranging in age from 19 to 91 years. We reviewed the medical record of each of the 241 patients and determined whether the patient had clinical manifestations consistent with a diagnosis of DIC.⁸ Criteria consistent with a diagnosis of DIC included the presence of an underlying disorder known to be associated with the development of DIC,² clinical manifestations

consistent with DIC (eg, hemorrhage and/or thrombosis, organ failure, fever, hypotension, acidosis, hypoxia), and the presence of laboratory evidence of thrombin generation in the form of a D-dimer or fibrin(ogen) degradation products (FDPs) level higher than the normal range. Laboratory findings considered supportive but not diagnostic of DIC included thrombocytopenia, hypofibrinogenemia, and an elevated PT in the absence of liver disease.

D-dimer diagnostic cutoff values derived from the analysis of cohort 1 were validated against a second cohort (cohort 2) of 286 eligible, consecutive, hospitalized patients for whom D-dimer levels were ordered during the 9 months immediately after the 12-month study interval of cohort 1.

Assays

PT, PTT, and fibrinogen levels were measured on the STA-Compact (Diagnostica Stago) analyzer. The international sensitivity index of the NEOPLASTINE CI Plus PT reagent (Diagnostica Stago) was 1.3. Platelet counts were measured on the ADVIA 120 hematology analyzer (Bayer, Tarrytown, NY). D-dimer was measured by the Fibrinosticon manual latex agglutination method (bioMérieux, Marcy-l’Etoile, France) and by the automated STA LIATEST immunoturbidimetric D-dimer assay performed on the STA-Compact analyzer. Precision of the STA LIATEST was verified by using lyophilized control material produced by the manufacturer for the D-dimer assay. Control samples were prepared according to the manufacturer’s directions and analyzed in duplicate once a day for a total of 11 days on each of 2 instruments. Estimates of precision are given as coefficients of variation. The detection limit of the STA LIATEST D-dimer assay was calculated by analyzing 12 replicates of the zero diluent for D-dimer on each instrument. The detection limit was defined as the value obtained at 2 SD above the mean for a sample free of D-dimer. The reportable range was validated by using a sample-dilution linearity study. The observed values were plotted against the expected values, and a linear regression analysis was performed.

The accuracy of the STA LIATEST D-dimer assay was evaluated by comparison of results with those of the Fibrinosticon manual latex agglutination assay. A total of 63 samples from the daily workload during a 2-month period were analyzed by both methods. All other patient D-dimer measurements were performed using only the STA LIATEST.

Statistics

ROC curve analysis, linear regression, Mann-Whitney *U* tests, and distributional analyses were performed using SPSS 11.5 (SPSS, Chicago, IL). Cutoffs maximizing the sensitivity and specificity of the D-dimer ROC curves were

generated by Cbstat 4.3 (American Association for Clinical Chemistry, Washington, DC).

Results

Performance Characteristics of the Immunoturbidimetric D-Dimer Assay

The mean detection limit of the assay was determined to be 0.23 µg/mL (230 µg/L), consistent with the manufacturer’s claim of 0.20 µg/mL (200 µg/L). The within-run precision estimates (coefficient of variation) at mean levels of 0.17 µg/mL (170 µg/L) and 2.40 µg/mL (2,400 µg/L) were 19.2% and 2.9%, respectively. The total imprecision estimates at the same levels were 26.5% and 4.4%, respectively. The linear range was determined to be 0.2 to 4.0 µg/mL (200-4,000 µg/L). Plasma D-dimer values in 44 healthy men and women ranging in age from 21 to 53 years were all less than or equal to 0.5 µg/mL (500 µg/L), validating the manufacturer’s recommended reference interval of less than 0.5 µg/mL (<500 µg/L). Accuracy was determined by comparison of results with those of a manual latex method. A linear relationship between the assays was evident, with the immunoturbidimetric assay producing D-dimer values roughly 3 times those of the manual assay (Figure 1). Transformation of the x and y values to equalize variance across the range of measured values produced a linear relationship with the equation: $1.67(x^{0.5}) = y^{0.5}$; $r = 0.97$.

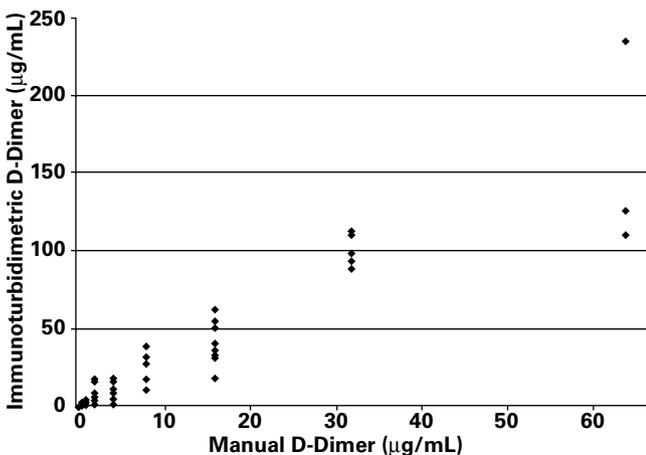


Figure 1 Comparison of D-dimer quantitation by the automated immunoturbidimetric assay vs semiquantitation by the manual latex agglutination assay. Each point represents measurements made by the 2 assays on a unique patient specimen.

Clinical Usefulness of the Immunoturbidimetric D-Dimer Assay

Serial D-dimer measurements in a patient with DIC demonstrates the improved usefulness of the immunoturbidimetric assay for patient monitoring (Figure 2). The results of the immunoturbidimetric assay peaked on the second measurement, followed by a relatively smooth decline in D-dimer values. The manual method, with an expected precision of ± 1 dilution, failed to clearly demonstrate the peak or the ensuing steady decline in D-dimer levels.

To evaluate the clinical specificity of the more analytically sensitive immunoturbidimetric assay, D-dimer levels were measured in specimens obtained from 59 hospitalized patients from medical and surgical services who had normal PT and PTT values, did not have diagnoses of venous thromboembolism or cancer, and were not suspected of having DIC. The median D-dimer value in this population was 1.2 µg/mL (1,200 µg/L), with 95th and 99th percentile values of 2.6 and 3.9 µg/mL (2,600 and 3,900 µg/L), respectively. Approximately 70% of the values exceeded the reference interval of 0.5 µg/mL (500 µg/L). By comparison, 27 patients with cancer with normal PT and PTT values and without clinically evident deep venous thrombosis or DIC had a median D-dimer level of 2.0 µg/mL (2,000 µg/L), with 95th and 99th percentile values of 27.9 µg/mL (27,900 µg/L) and 30.4 µg/mL (30,400 µg/L), respectively. Approximately 90% of the values in this population exceeded the reference interval.

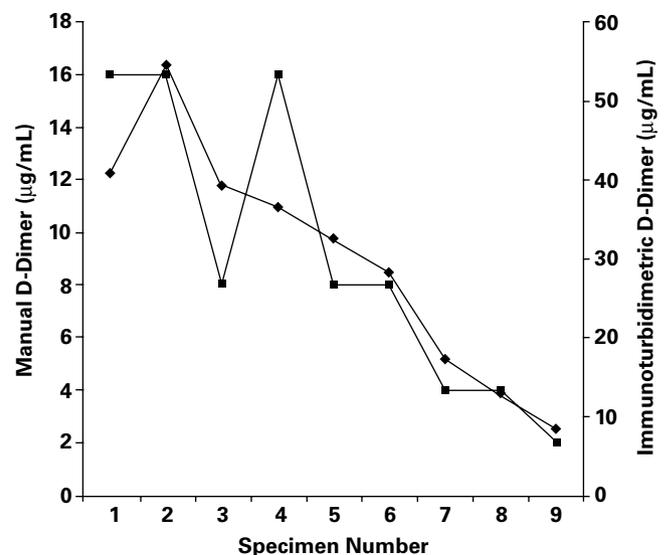


Figure 2 Serial D-dimer measurements made by the automated immunoturbidimetric (diamonds) assay and the manual latex agglutination assay (squares) on specimens from 1 patient.

Immunoturbidimetric D-Dimer Values in DIC

To establish the range of values expected in a population of patients suspected of having clinical DIC, we retrospectively analyzed all D-dimer results of patients in cohort 1. Of the 241 patients, 95 (39.4%) did not have a clear predisposing condition for the development of DIC.² One quarter of these were obstetric patients. The prevalence of DIC among the total population was 22.4% (54/241). Three of 54 patients diagnosed with DIC did not have a recognizable predisposing condition. The majority of patients with DIC had sepsis or cancer (Figure 3). Of the patients for whom at least 1 D-dimer assay was ordered, 19 (29%) of 65 with cancer and 21 (42%) of 50 with sepsis had clinical DIC based on our evaluation.

The distribution of the patients' maximum D-dimer values for the total population had a median value of 3.7 $\mu\text{g/mL}$ (3,700 $\mu\text{g/L}$) with a range of 161.2 $\mu\text{g/mL}$ (161,200 $\mu\text{g/L}$). Of the patients, 94.2% had a D-dimer maximum value greater than 0.5 $\mu\text{g/mL}$ (500 $\mu\text{g/L}$). Patients with clinical DIC had a median and range of D-dimer values of 21.7 $\mu\text{g/mL}$ (21,700 $\mu\text{g/L}$) and 160.7 $\mu\text{g/mL}$ (160,700 $\mu\text{g/L}$), respectively, whereas the D-dimer median and range for

patients whose condition was not consistent with DIC were 2.7 $\mu\text{g/mL}$ (2,700 $\mu\text{g/L}$) and 38.5 $\mu\text{g/mL}$ (38,500 $\mu\text{g/L}$), respectively. These 2 distributions were significantly different ($P < .001$; Mann-Whitney U test).

An ROC curve constructed from D-dimer maximum measurements in the total population was highly significant ($P < .001$) with an area under the curve (AUC) of 0.94 (Figure 4). A test with no discriminatory value would have an AUC of 0.50, while a perfect test would have an AUC of 1.00. The AUCs for the PT, fibrinogen level, and platelet count, the other laboratory tests included in the ISTH scoring system, also were highly significantly different from 0.50 but did not approach the value of the D-dimer (Table 1). Adjusting the platelet and PT values for the effects of platelet concentrate or fresh frozen plasma transfusions immediately before measurement did not increase the AUCs for those tests (Table 2). When testing was limited to patients with a condition known to predispose to DIC, the AUCs decreased, but all tests used in the ISTH algorithm remained significant except the platelet count (Table 1).

A D-dimer maximum cutoff of 8.2 $\mu\text{g/mL}$ (8,200 $\mu\text{g/L}$) optimized the sum of sensitivity and specificity for the total population and the predisposed population. For the total population ($n = 241$), the cutoff value had a sensitivity of 0.98, a specificity of 0.86, a positive predictive value of 0.66, and a negative predictive value of 0.99, given a prevalence of 0.22. For the predisposed population ($n = 146$), the cutoff

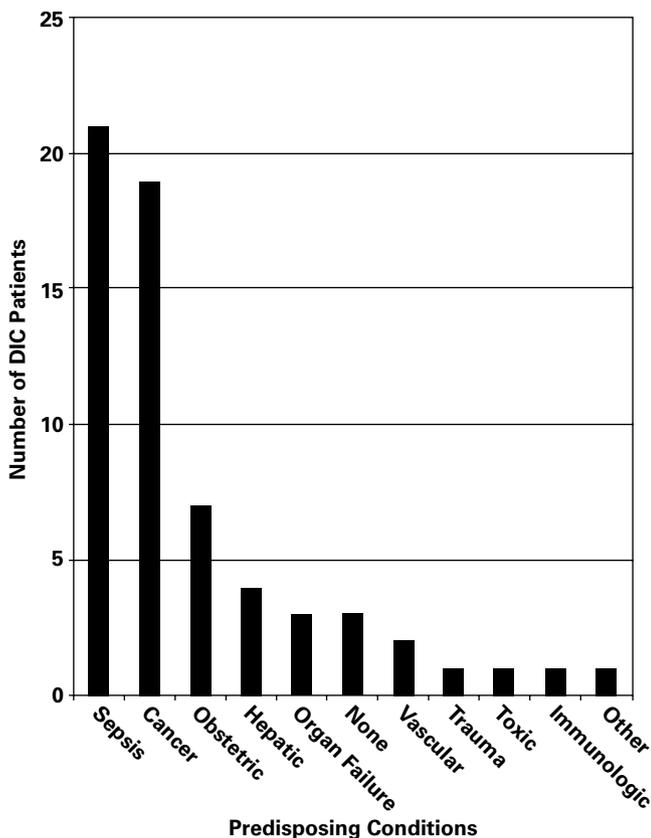


Figure 3 Distribution of predisposing conditions in patients with disseminated intravascular coagulation (DIC). Patients with more than one predisposing condition were counted more than once.

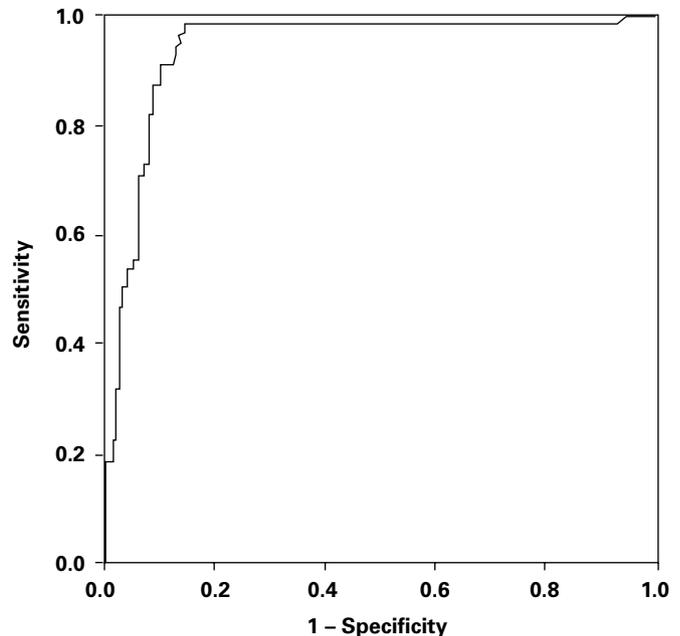


Figure 4 Immunoturbidimetric D-dimer assay receiver operating characteristic curve for all patients undergoing D-dimer testing. A test with no discriminatory value would plot on the diagonal $y = x$.

Table 1
ROC Curve Parameters for Patients Evaluated for DIC*

Laboratory Assay	AUC (95% CI) for All Patients	<i>P</i>	AUC (95% CI) for Patients With Predisposing Condition	<i>P</i>
Immunoturbidimetric D-dimer	0.94 (0.90-0.98)	<.001	0.93 (0.88-0.98)	<.001
Prothrombin time	0.74 (0.67-0.81)	<.001	0.69 (0.60-0.78)	<.001
Fibrinogen level	0.70 (0.60-0.79)	<.001	0.70 (0.60-0.79)	<.001
Platelet count	0.67 (0.59-0.75)	<.001	0.56 (0.47-0.70)	.210

AUC, area under the curve; CI, confidence interval; DIC, disseminated intravascular coagulation; ROC, receiver operating characteristic.

* The ROC curve evaluates the diagnostic accuracy of a clinical laboratory test. An AUC of 1.00 indicates a perfect test; an AUC of 0.50 indicates a test with no discriminatory value.

value had a sensitivity of 0.98, a specificity of 0.81, a positive predictive value of 0.74, and a negative predictive value of 0.99, given a prevalence of 0.35.

To validate the D-dimer maximum cutoff value, we applied the 8.2 µg/mL (8,200 µg/L) cutoff to cohort 2 tested during a subsequent 9-month period. In cohort 2, a D-dimer maximum cutoff of 8.2 µg/mL (8,200 µg/L) produced a sensitivity of 0.96, a specificity of 0.92, a positive predictive value of 0.72, and a negative predictive value of 0.99, given a prevalence of 0.18 in the total cohort 2 population (n = 286). In the predisposed population (n = 171), the 8.2 µg/mL (8,200 µg/L) cutoff value had a sensitivity of 0.96, a specificity of 0.88, a positive predictive value of 0.75, and a negative predictive value of 0.98, given a prevalence of 0.28. When the results from the 2 cohorts were combined, the D-dimer maximum cutoff of 8.2 µg/mL (8,200 µg/L) produced a sensitivity of 0.97, a specificity of 0.89, a positive predictive value of 0.69, and a negative predictive value of 0.99, given a prevalence of 0.20 in the total population (n = 527). In the predisposed population (n = 317), the 8.2 µg/mL (8,200 µg/L) cutoff produced a sensitivity of 0.97, a specificity of 0.85, a positive predictive value of 0.74, and a negative predictive value of 0.98, given a prevalence of 0.31.

Because serial D-dimer values might be necessary to make the diagnosis of DIC, we assessed the diagnostic performance of the first D-dimer assay obtained for each patient in cohort 1. D-dimer levels obtained more than 7 days before all subsequent levels were not included in the analysis.⁹ An ROC curve analysis of the first D-dimer measurement in the total patient population demonstrated a decrease in the AUC from 0.94 (D-dimer maximum) to 0.87 (first D-dimer) (*P* < .05). A cutoff of 6.3 µg/mL (6,300 µg/L) maximized the sensitivity (0.85) and specificity (0.82) of the first D-dimer measurement. In the population with a predisposing condition, the AUC decreased from 0.93 (D-dimer maximum) to 0.86 (first D-dimer) (*P* < .05). Again, a cutoff of 6.3 µg/mL (6,300 µg/L) maximized the sensitivity (0.86) and specificity (0.79) of the first D-dimer measurement in the predisposed population.

Table 2
ROC Curve Parameters for Patients Evaluated for DIC

Laboratory Assay	Pretransfusion AUC (95% CI)	Posttransfusion AUC (95% CI)
Prothrombin time	0.74 (0.67-0.81)	0.74 (0.67-0.81)
Platelet count	0.67 (0.60-0.75)	0.67 (0.59-0.75)

AUC, area under the curve; CI, confidence interval; DIC, disseminated intravascular coagulation; ROC, receiver operating characteristic.

To assess the value of the D-dimer alone and in combination with other testing, we assigned a score of 3 to a D-dimer value greater than 8.2 µg/mL (8,200 µg/L) in cohort 1 and applied the ISTH scoring system² to the population with a predisposing condition. The ISTH score produced a sensitivity of 0.69, a specificity of 0.94, a positive predictive value of 0.85, and a negative predictive value of 0.85.

Discussion

Evidence for activation of the fibrinolytic system is considered a critical laboratory finding supporting a diagnosis of DIC.¹⁰ Consequently, existing and proposed diagnostic algorithms assign greater weight to indirect measures of fibrinolysis.^{1,2} The D-dimer assay has replaced measurement of FDPs as the preferred assay owing to the greater specificity of D-dimer assays for detecting fibrinolysis vs fibrinogenolysis. In addition, the detection of circulating D-dimer has greater sensitivity for the diagnosis of DIC.¹⁰ Historically, semiquantitative assays of low precision were all that were available for measuring D-dimer levels. However, sensitive, quantitative D-dimer assays have become available on automated coagulation analyzers, creating the opportunity to more precisely define laboratory-specific cutoffs.

Our evaluation of the STA LIATEST immunoturbidimetric D-dimer assay performed on the STA-Compact analyzer validated the analytic performance claims of the manufacturer for limit of detection, linearity, precision, and

reference range. As demonstrated in Figure 1, the excellent precision of this assay in the range of values observed in hospitalized patients should improve the clinician's ability to assess the effect of therapy on the status of a patient's DIC. An analysis of D-dimer values found in hospitalized patients without overt DIC revealed that 70% to 90% had levels greater than the upper limit of the reference interval. Therefore, diagnostic algorithms that define positive D-dimer levels as values exceeding the reference interval will have poor specificity and positive predictive value.¹¹

The ISTH recently proposed a scoring system for the diagnosis of DIC based on 4 laboratory parameters and the presence of a predisposing condition.² Elevation of a fibrin-related marker, such as D-dimer, represents a key element of the scoring system. Because the measurement of D-dimer levels has not been harmonized across marketed assays,⁷ it is left to the individual laboratory to define D-dimer cutoff values for use in the ISTH scoring system.

We used ROC curve analysis to define potential cutoffs for inclusion in the ISTH algorithm. Our analysis demonstrates that for the STA LIATEST immunoturbidimetric D-dimer assay, a D-dimer maximum cutoff of 8.2 µg/mL (8,200 µg/L) optimized the sum of sensitivity and specificity for the total population tested and the predisposed population. Our data also confirmed that a sensitive D-dimer assay, by itself, can provide excellent sensitivity and negative predictive value for the diagnosis of DIC.¹⁰ Because hospitalized patients without overt DIC frequently have sensitive D-dimer levels exceeding the upper limit of the reference interval,¹²⁻¹⁴ the ability to rule out DIC with high negative predictive value is particularly helpful for directing the workup of a patient with a newly discovered coagulopathy or a low platelet count. In cohort 1, for example, 39.4% of the patients had an isolated, abnormal PT or platelet count, and approximately half of those patients had evidence of bleeding or thrombosis. This suggests that the test is being ordered not only to confirm DIC but also to evaluate coagulopathies and thrombocytopenia in general. However, the immunoturbidimetric D-dimer assay, by itself, has insufficient positive predictive value to "rule in" a diagnosis of DIC. Using a cutoff of 8.2 µg/mL (8,200 µg/L) in the ISTH algorithm produced a diagnostic sensitivity and negative predictive value less than the D-dimer result by itself but demonstrated superior specificity (0.94 vs 0.81) and positive predictive value (0.85 vs 0.74).

Wada et al,¹⁵ assaying for FDPs rather than D-dimer, also demonstrated reduced sensitivity of the ISTH algorithm, in this case relative to the JMHW scoring system, and those authors recommended modification of the cutoff points for the global coagulation tests used in the algorithm to improve sensitivity. Modifications to the ISTH algorithm should be directed at improving the capacity of the ISTH algorithm to rule in DIC.

The ISTH algorithm excludes patients without a recognized, predisposing condition at the time of evaluation. Our analysis of 527 adults undergoing D-dimer testing at our tertiary care hospital led us to believe that modifying the scoring system to permit evaluation of all patients, as in the JMHW algorithm, might avoid missed diagnoses owing to disagreements over the definition of a predisposing condition. The ISTH also has recommended serial D-dimer testing for diagnosis and monitoring of treatment effect. Our data demonstrated the improved diagnostic performance of the maximum D-dimer result over the initial D-dimer result and, therefore, support the ISTH recommendation.

There are potential shortcomings to our retrospective analysis. The total number of patients with DIC (n = 106) might be insufficient to adequately define the characteristics of such a heterogeneous population. For example, few of the patients were trauma patients, potentially limiting the relevance of the ROC curve and cutoff calculations for those patients. In addition, because the diagnosis of DIC relies on evidence of fibrinolytic activation and no other marker of thrombin formation (eg, FDP) was measured consistently in our patient population, the diagnostic value of the D-dimer might have been overestimated because it was not possible to blind the authors to the D-dimer values. However, our estimates of the sensitivity and specificity of the ISTH scoring system are consistent with the estimates of Wada et al,¹⁵ suggesting that our diagnostic classification scheme was comparable to the classification produced by the modified JMHW criteria. Therefore, our analysis provides sufficient information about diagnostic outcomes using the STA LIATEST immunoturbidimetric D-dimer assay to rationally select and evaluate cutoff values for validation of the ISTH DIC diagnostic algorithm using this D-dimer assay.

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