D-Dimer Testing for the Exclusion of Pulmonary Embolism Among Hospitalized Patients With COVID-19

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Introduction

For more than 2 decades, the plasma D-dimer assay has been used in conjunction with clinical prediction scores to rule out pulmonary embolism (PE) among patients with a low pretest probability of having this condition without the need for more costly and invasive methods.\(^1\)\(^2\) The increased thrombotic risk among patients hospitalized with COVID-19 (ie, those with high pretest probability of PE) and increased D-dimer levels in the absence of thrombosis diverge considerably from the study population used to originally validate this assay.\(^3\) However, the availability of D-dimer samples routinely collected from patients hospitalized with COVID-19 and the heterogeneity of early, smaller studies generated uncertainty regarding the clinical utility of the assay in this setting.\(^4\) Therefore, we conducted a diagnostic accuracy study to characterize the performance of D-dimer using various threshold values to exclude PE among patients hospitalized with COVID-19.

Methods

This diagnostic study was approved by the University of South Florida institutional review board, which granted a waiver of informed consent because this study analyzed deidentified medical records. This study used the Standards for Reporting of Diagnostic Accuracy (STARD) reporting guideline for diagnostic studies.

A retrospective, cross-sectional sample of 1541 patients consecutively hospitalized with COVID-19 at a single hospital from January 1, 2020, to February 5, 2021, was collected. Plasma D-dimer concentrations from an automated, standardized assay (expressed as fibrinogen equivalent units) were compared with the criterion standard of computed tomographic pulmonary angiography (CTPA) among 287 patients with suspected PE. D-dimer distributions among patients with and without PE were compared using descriptive statistics and linear regression (after log-normal transformation at \(\alpha = .05\)). The ability of plasma D-dimer concentrations collected the day of CTPA to correctly classify patients with PE was evaluated with a static threshold of 0.5 \(\mu\)g/mL or more (to convert to nanomoles per liter, multiply by 5.476) and an age-adjusted threshold (ie, D-dimer value, \(0.01 \times [\text{age} - 50 \text{ years}]\)) for individuals aged older than 50 years.\(^5\) Receiver operator characteristic curves (ROCs) were evaluated for thresholds and an expanded set of D-dimer values ranging from 0.5 \(\mu\)g/mL to 20 \(\mu\)g/mL. Data were analyzed using Stata statistical software version 13 (StataCorp) from May through August 2021.

Results

Among 287 patients with COVID-19 and suspected PE (177 [51.4%] men; mean [SD] age, 58.2 [16.1] years), 118 patients required intensive care unit levels of care (41.1%) and 27 patients died during hospitalization (9.4%). Of 287 patients with CTPA, 37 patients had radiographic evidence of PE (12.9%) and 250 patients did not (87.1%); 265 patients had plasma D-dimer levels of 0.05 \(\mu\)g/mL or more (92.3%), including all patients with PE and 225 of 250 patients without PE (91.2%). The median...
D-dimer values were 1.0 (0.6-1.8) μg/mL for 250 patients without PE and 6.1 (2.0-19.4) μg/mL for 37 patients with PE. D-dimer values ranged from 0.2 μg/mL to 128 μg/mL among patients without PE and from 0.5 μg/mL to more than 10,000 μg/mL among patients with PE, and patients without PE had statistically significantly decreased mean (SD) D-dimer values (8.7 [11.6] μg/mL vs 1.2 [2.8] μg/mL; \( P < .001 \)).

A D-dimer concentration of 0.05 μg/mL was associated with a sensitivity of 100%, specificity of 8.8%, negative predictive value (NPV) of 100%, positive predictive value (PPV) of 13.9%, and negative likelihood ratio (NLR) of less than 0.1. The age-adjusted threshold was associated with a sensitivity of 94.6%, specificity of 22.8%, NPV of 96.6%, PPV of 13.9%, and NLR of 0.24. The ROC analyses (Figure) yielded areas under the curve that were not statistically significantly different using the 0.5 μg/mL threshold compared with the age-specific threshold (0.81 vs 0.80; \( P = .67 \)).

Performance measures for thresholds 0.5 μg/mL (sensitivity, 100%; specificity, 9.3%; accuracy, 21.0%; positive likelihood ratio [PLR], 110; NLR, 0) to 20 μg/mL (sensitivity, 20.0%; specificity, 96.6%; accuracy, 86.7%; PLR, 5.90; NLR, 0.57) are presented in the Table.

![Figure](https://jamanetwork.com/)

**Figure.** Receiver Operator Characteristic Curve for Plasma D-Dimer Concentrations in μg/mL

The receiver operator characteristic curve of plasma D-dimer concentration to classify pulmonary embolism diagnosed by computed tomographic pulmonary angiography at all values of plasma D-dimer in micrograms per milliliter is presented. The performance characteristics at all observed D-dimer concentrations (blue dots), a smoothed, parametric estimation function (solid line), and an uninformative hypothetical test (dashed line) are presented. AUC indicates area under the curve.

**Table.** Performance Measures of Plasma D-Dimer Over Range of Cutoff Points

<table>
<thead>
<tr>
<th>D-dimer cutoff point, μg/mL</th>
<th>Performance, %</th>
<th>PLR</th>
<th>NLR</th>
</tr>
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<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Accuracy</td>
</tr>
<tr>
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<td>100</td>
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<tr>
<td>0.6</td>
<td>97.1</td>
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<tr>
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<td>97.1</td>
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<tr>
<td>0.8</td>
<td>94.3</td>
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<td>20.0</td>
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<td>86.7</td>
</tr>
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</table>

Abbreviations: NLR, negative likelihood ratio; PLR, positive likelihood ratio.

SI conversion factors: To convert micrograms to millimeters per liter, multiply by 5.476.

* The performance measures of a plasma D-dimer assay to classify pulmonary embolism diagnosed by computed tomographic pulmonary angiography with classification cutoff points from 0.5 μg/mL to 20 μg/mL are presented.
Discussion

This diagnostic study found that all hospitalized patients with COVID-19 and radiographic evidence of PE had plasma D-dimer levels of 0.05 μg/mL or greater. If using D-dimer to exclude patients with PE, the increased values we found among 92.3% of patients suggest that this assay would be less useful than in the populations in which it was originally validated, among which a minority of patients had increased D-dimer values. Setting higher D-dimer thresholds was associated with improved specificity at the cost of an increased false-negative rate that could be associated with an unacceptable patient safety risk. The inclusion of patients with D-dimer and CTPA results was necessary to estimate diagnostic performance; however, this may have introduced selection bias by excluding patients unable to undergo CTPA. Nonetheless, given the high pretest probability of PE and low specificity observed in this and other studies, these results suggest that the use of D-dimer levels to exclude PE among patients hospitalized with COVID-19 may be inappropriate and have limited clinical utility.

ARTICLE INFORMATION

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REFERENCES


