

# Improving risk prediction for pulmonary embolism in COVID-19 patients using echocardiography

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## Abstract

SARS-CoV-2 infection is associated with increased risk for pulmonary embolism (PE), a fatal complication that can cause right ventricular (RV) dysfunction. Serum D-dimer levels are a sensitive test to suggest PE, however lacks specificity in COVID-19 patients. The goal of this study was to identify a model that better predicts PE diagnosis in hospitalized COVID-19 patients using clinical, laboratory, and echocardiographic imaging predictors. We performed a cross-sectional study of 302 adult patients admitted to the Johns Hopkins Hospital (March 2020–February 2021) for COVID-19 infection who underwent transthoracic echocardiography and D-dimer testing; 204 patients had CT angiography. Clinical, laboratory and imaging predictors including, but not limited to, D-dimer and RV dysfunction were used to build prediction models for PE using logistic regression. Model discrimination was assessed using area under the receiver operator curve (AUC) and calibration using Hosmer-Lemeshow  $\chi^2$  statistic. Internal validation was performed. The prevalence of PE was 7.6%. The model with positive D-dimer above 5 mg/L, RV dysfunction on echocardiography, and troponin had an AUC of 0.77, and cross-validated AUC of 0.74. D-dimer (>5 mg/L) had a positive association with PE (adj odds ratio = 4.40; 95% confidence interval: [1.80, 10.78]). We identified a model including clinical, imaging and laboratory variables that predicted PE in hospitalized COVID-19 patients. Positive D-dimer >5, RV dysfunction on echocardiography, and troponin were important predictors for calculating likelihood of PE diagnosis. This approach may be useful to aid

**Abbreviations:** AIC, akaike information criterion; ASE, American Society of Echocardiography; AUC, area under receiver operating curve; BMI, body mass index; BNP, b-type natriuretic peptide; CI, confidence interval; COVID-19, Coronavirus Disease 2019; CT, computed tomography; cvAUC, cross validated area under receiver operating curve; ICU, intensive care unit; LV, left ventricular; NPV, negative predictive value; OR, odds ratio; PE, pulmonary embolism; PPV, positive predictive value; RV, right ventricular; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiogram (echocardiography).

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in clinical decision-making related to diagnostic imaging and treatment. Prospective studies are needed to evaluate impact on patient outcomes.

**KEYWORDS**

cardiac biomarkers, D-dimer, prediction modeling, right ventricular dysfunction

## INTRODUCTION

Infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2), the virus causing coronavirus disease 19 (COVID-19), is associated with a high risk of thromboembolism, a significant cause of morbidity and mortality in hospitalized patients.<sup>1–4</sup> In particular, COVID-19 patients are at increased risk for pulmonary embolism (PE), a potentially fatal complication that can cause right ventricular (RV) dysfunction commonly detected on noninvasive imaging with transthoracic echocardiography (TTE). The initial approach to diagnose PE is often with serum D-dimer levels, the breakdown product of fibrin from blood clots. D-dimer is considered a first line test that is used as a screening tool with high sensitivity, with the additional value in ruling out PE with a negative test in low risk patients.<sup>5,6</sup> However, D-dimer testing lacks specificity for the diagnosis of PE in COVID-19 patients, reported in the range of 10%–15% according to prior studies.<sup>7,8</sup> Further, patients with suspected PE have significant overlap in terms of symptoms of COVID-19, making the diagnosis challenging.<sup>9</sup> This may prevent an underlying PE from being detected and appropriately treated. There is a need for better predictors for the diagnosis of PE to improve the low specificity of D-dimer testing to facilitate appropriate patient triage and further testing.

Prior echocardiographic studies performed on hospitalized COVID-19 patients have revealed a relatively high prevalence of RV dysfunction (up to 39%), RV dilation, and left ventricular (LV) dysfunction.<sup>10–15</sup> Multiple potential contributing factors may lead to RV dysfunction in the setting of COVID-19, which include sepsis, Acute Respiratory Distress Syndrome, pulmonary microthrombi and PE.<sup>12,16,17</sup> When RV dysfunction occurs in the setting of PE, this confers a worse prognosis, as PE can have significant hemodynamic effects on the RV.<sup>18</sup> The right heart is a low-pressure system designed to accommodate a low-resistance afterload in the pulmonary arterial system. However, in the setting of a PE, the resulting increase in afterload can compromise the RV leading to RV dilation and dysfunction.<sup>19</sup> Therefore, the detection of RV dysfunction on TTE may aid in the specificity of a PE diagnosis in COVID-19 patients who have a positive D-dimer level ( $>0.5$  mg/L).<sup>6</sup>

Additionally, other clinical and lab parameters such as body mass index (BMI), and cardiac markers like B-type natriuretic peptide (BNP) and troponin may also be important in predicting a PE diagnosis in COVID-19 patients. Both obesity and troponin have been shown to be associated with poor disease prognosis and outcomes in COVID-19 patients.<sup>20,21</sup>

The primary objective of this study was to conduct predictive modeling and analysis to investigate the role of RV dysfunction on TTE, and other clinical and lab parameters as potential predictors for a PE diagnosis with D-dimer among hospitalized COVID-19 patients. We hypothesized that the presence of RV dysfunction, along with a positive D-dimer would be a significant predictor of PE in COVID-19 patients, with or without the presence of other important risk factors and cardiac biomarkers known to be associated with poor outcomes in COVID-19.<sup>20,22</sup> We further hypothesized that higher cutoffs of D-dimer values would improve risk prediction in our models due to the low specificity of standard D-dimer values for PE in hospitalized COVID-19 patients.

## MATERIALS AND METHODS

### Design and sample

We performed a cross-sectional study of 302 consecutive adult patients ( $>18$  years of age) with confirmed COVID-19 by reverse transcriptase polymerase chain reaction test, who were admitted to Johns Hopkins Hospital and died, or were discharged between March 1, 2020 and February 1, 2021, and who underwent clinically indicated TTE according to American Society of Echocardiography (ASE) guidelines<sup>23</sup> within 5 days of hospital admission, and had D-dimer testing. Additionally, the RV had to be adequately visualized on TTE for patients to be included in the study. A total of 2662 patients were admitted for COVID-19 during the time period of study, and the study cohort was a subset of the patients ( $N = 302$ ). Clinical indications for TTE included dyspnea and/or hypoxia to evaluate for cardiac function ( $n = 249$ ), suspected PE to evaluate for right heart function ( $n = 20$ ), hypotension to evaluate for cardiac function ( $n = 19$ ) with the remaining having other indications ( $n = 14$ ). Among the 302 patients, chest computed

tomography (CT) angiogram was performed in 204 patients for clinically suspected PE.

## Data collection and measures

Data were obtained from the Johns Hopkins Health System COVID-19 Precision Medicine Analytic Platform Registry (JH-CROWN) on a racially and ethnically diverse patient population.<sup>24</sup> This registry extrapolates data from the health system using electronic medical records.

Comorbidities and clinical events including PE were obtained using international classification of diseases (ICD)–10 codes or key words. PE events that were identified were then adjudicated by physicians who reviewed the medical records. A diagnosis of PE required confirmation by chest CT angiography. Sex, race, and ethnicity were self-identified. All laboratory data were obtained for at least one of the following timepoints: the first recorded value during hospitalization (admission), within 24 h of the TTE if available, and a peak value during hospital stay. Values at the time of TTE were used if available. If they were not available, then values at admission, followed by peak values were used.

Bedside TTE examinations were performed for clinical indications by experienced sonographers using Vivid E9 ultrasound system (General Electric Vingmed Ultrasound). Standard 2D, Doppler echocardiography and speckle tracking TTE images were acquired. Measurements including LV and RV parameters and diastology were performed by an experienced sonographer based on the ASE guidelines and were over-read by a cardiologist, board certified in echocardiography.<sup>23</sup> The presence of RV dysfunction was ascertained by two echocardiography readers blinded to clinical information, and determination was made according to ASE guidelines, based on visual assessment and quantitative variables such as tricuspid annular plane systolic excursion (TAPSE) when available.<sup>25</sup> To limit exposure to patients and staff, standard TTE measures were performed offline, removed from the patient's room, and limited studies were performed according to COVID-19 specific imaging guidelines.<sup>23</sup> TTE measures were entered into RedCap by a research staff member.

A deidentified data set was created using the data from the sources described above (see Supporting Information 1 for variables collected and included in the analysis). The study was approved by the Johns Hopkins University Institutional Review Board and an exemption was granted. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

## Primary data analysis

The deidentified data were analyzed using STATA version 16. Initially, analyses were performed in patients stratified based on PE status (yes/no). Baseline patient characteristics were compared between the two PE status groups. These baseline characteristics included demographics, comorbidities, lab parameters, and RV TTE parameters. A  $\chi^2$  test was used for binary variables and counts (percentages) were reported. Normality of distributions for continuous variables was conducted using Shapiro–Wilk test. A *t* test was used and means (SDs) were reported for continuous variables with normal distribution. A median test was used and medians (interquartile ranges [IQRs]) were reported for continuous variables that did not have a normal distribution. Age, BMI and troponin level were continuous variables. Sex and race were coded as binary variables with race coded as Black and Non-Black patients. Black patients who were Hispanic or non-Hispanic were included in the Black patient category. Nonblack patients who were Hispanic or non-Hispanic were included in the non-Black patient category. The primary variable RV dysfunction on TTE was analyzed as a binary variable (present/absent). D-dimer levels were dichotomized at various thresholds including 0.5, 2, 5, and 9 mg/L. Although 0.5 mg/L is the standard D-dimer cutoff, studies have shown that many COVID-19 patients have elevated baseline D-dimer levels above 2 mg/L.<sup>6,26,27</sup>

Thus, thresholds of 2, 5, and 9 mg/L were studied in addition to 0.5 mg/L.

The primary outcome was PE diagnosed on chest CT angiography, as per the physician adjudication. Sensitivities and specificities of the various D-dimer thresholds and presence of RV dysfunction in predicting PE were assessed. Additionally, various prediction models were built using patient demographics, D-dimer levels collected at the time of TTE, RV dysfunction, BMI, and cardiac laboratory parameters, specifically troponin. BNP was not included in the models, as only variables with at least 90% of the data available were included. Logistic regression models were used to build the models since the prevalence of PE was less than 10%.

The bivariate (crude) model only included the D-dimer status (for each D-dimer threshold) as a predictor of PE. Next the multivariable (adjusted) models were built by adding the following predictors: age, sex, race, BMI, RV dysfunction on TTE, and troponin levels, which were selected based on clinical knowledge and prior literature.<sup>13,16–18,21,28</sup> Finally, based on the statistical results of incremental value of individual variables, a final model was created.

Since the goal of this analysis was prediction of PE, model discrimination and calibration were assessed. Discrimination was assessed using the area under the receiver operating curve (AUC). Calibration was assessed using the Hosmer–Lemeshow  $\chi^2$  statistic for goodness-of-fit. Additionally, odds ratios (ORs), 95% confidence intervals (CI), and two-sided  $p$  values for each of the model variables were obtained to assess the association between the predictor and outcome. Internal cross validation was performed by the  $k$ -fold method, using fivefolds. Predictive discrimination of the model was assessed by using the cross-validated AUC. Predictive discrimination assesses the ability for the model to discriminate risk of PE diagnosis in future COVID-19 patients. Akaike Information Criterion (AIC) values were obtained for each of the models to identify the model with the best overall predictive accuracy, taking into account the differences in the number of covariates between the models.

## RESULTS

In our study cohort of 302 hospitalized COVID-19 patients who underwent echocardiography and D-dimer testing, the overall prevalence of PE was 7.6%. The mean and median D-dimer levels were 4.20 and 1.50 mg/L, respectively, suggesting a positive skew. Out of the 302 patients in our study, 234 (77%) required supplemental oxygen (within 48 h of admission). A total of 222 (74%) patients out of the 302 were either in the intensive care unit (ICU) or a step down unit (intermediate care); 141 (47%) were in traditional ICU and 81 (27%) were in a step down unit. Additionally, 138 (46%) patients out of the 302 were on mechanical ventilation. Table 1 compares baseline patient characteristics including demographics, comorbidities, and lab parameters acquired at the time of TTE, between groups stratified by PE status. There were no significant differences in sex, race, age, or BMI between those with PE and without PE (Table 1). In addition, there were no significant differences in BNP, troponin, or D-dimer levels between those with PE and those without PE.

D-dimer levels were dichotomized at various thresholds (0.5 mg/L, 2 mg/L, 5 mg/L, and 9 mg/L). There were no significant differences in the proportion of patients with a positive D-dimer, using a threshold of  $\geq 0.5$  mg/L, in the PE compared to the no PE group. However, there was a significantly higher proportion of patients with a positive D-dimer for thresholds of 2, 5, and 9 mg/L in the PE group as compared to the no PE group ( $p = 0.02, 0.001, 0.002$ ). There was also no significant difference in the proportion of patients with RV dysfunction between the PE and no PE group of patients.

The sensitivity and specificity for a PE diagnosis in COVID-19 patients were calculated using a D-dimer test at various thresholds, as shown in Table 2. The specificity of D-dimer for PE in COVID-19 patients improved with using higher cut-points. Additionally, the sensitivity and specificity were calculated for RV dysfunction on TTE to diagnose PE (Table 2). The presence of RV dysfunction had high specificity (0.85).

Prediction models for a PE in COVID-19 patients were built using patient demographics, D-dimer status, RV dysfunction, BMI, and cardiac lab parameters. Since a D-dimer threshold of 0.5 mg/L had low specificity (0.13), and a D-dimer threshold of 9 mg/L had low sensitivity (0.35), prediction models were built using D-dimer thresholds of 2 and 5 mg/L.

Table 3 compares the various prediction models built using positive D-dimer ( $>2$  mg/L), age, sex, race, BMI, RV dysfunction, and troponin levels. The cross-validated area under the receiver operating curve (cvAUC) represents the predictive discrimination, or the ability for the model to discriminate risk of PE diagnosis in future COVID-19 patients. The crude model with D-dimer  $>2$  mg/L had a cvAUC of 0.60. Adding age, sex, race, and BMI decreased the cvAUC (Model 2) to 0.52. However, adding RV dysfunction and troponin improved the AUC and predictive discrimination (Table 3). Both models containing RV dysfunction and troponin levels (Models 3 and 4) had good model calibration as they had  $p$  values greater than 0.05 for the Hosmer–Lemeshow  $\chi^2$  statistic assessing goodness-of-fit (HL- $p = 0.94, 0.45$ ). Furthermore, in both models, D-dimer  $>2$  mg/L had a statistically significant positive association with PE (adj OR = 2.81 [95% CI: 1.14, 6.92] and 3.03 [95% CI: 1.21, 7.59]), respectively.

Table 4 compares the various prediction models built using positive D-dimer ( $>5$  mg/L), age, sex, race, BMI, RV dysfunction, and troponin. The crude model with D-dimer  $>5$  mg/L had a cvAUC of 0.63. Adding age, sex, race, BMI and RV dysfunction did not improve the cvAUC. However, adding troponin to this multivariate model did improve the cvAUC to 0.69 (Model 8). This suggests that adding troponin to a model adjusted for age, sex, race, and BMI improves predictive discrimination. Additionally, Model 8 had good model calibration, and D-dimer  $>5$  mg/L had a statistically significant positive association with PE (adj OR = 4.96; 95% CI: [1.99, 12.38]).

Based on the results of the models from Tables 3 and 4 and literature showing an association between RV dysfunction and PE in the general population,<sup>29,30</sup> a final model was created. Since there were only 23 PE events, the final model was limited to 3 predictors to reduce the risk of overfitting the data. Models with D-dimer  $>5$  mg/L had higher cvAUC values and lower AIC values

**TABLE 1** Baseline patient characteristics by pulmonary embolism status

Baseline patient characteristic	Pulmonary embolism (N = 23)	No pulmonary embolism (N = 279)	P value
Female, No. (%)	9 (39)	141 (51)	0.29
Race, No. (%)			0.88
Black	11 (48)	129 (46)	
Non-Black	12 (52)	150 (54)	
Hispanic, No. (%)	5 (22)	51 (18)	0.68
Age, median (IQR), years	60 (50–71)	64 (52–73)	0.66
Body mass index, median (IQR), kg/m <sup>2</sup>	27.7 (26.0–34.7)	30.0 (25.7–35.6)	0.39
History of hypertension, No. (%)	13 (57)	209 (75)	0.05
Diabetes mellitus, No. (%)	6 (26)	125 (45)	0.08
Coronary artery disease, No. (%)	3 (13)	49 (18)	0.57
Stroke, No. (%)	1 (4)	26 (9)	0.42
Autoimmune disease, No. (%)	3 (13)	18 (7)	0.24
Systolic blood pressure on admission, mean (SD), mmHg	126 (28)	127 (27)	0.87
Diastolic blood pressure on admission, median (IQR), mmHg	71 (60–80)	69 (59–80)	0.93
Oxygen saturation on admission, median (IQR)(%)	96 (92–97)	94 (90–97)	0.12
Heart rate on admission, mean (SD), beats per minute	92 (19)	97 (20)	0.24
Troponin, <sup>a</sup> median (IQR), ng/mL	0.03 (0.03–0.04)	0.04 (0.03–0.11)	0.12
B-type natriuretic peptide at time of TTE, median (IQR), pg/mL	314 (132–966)	572 (176–3008)	0.25
D-dimer at time of TTE			
D-dimer levels, median (IQR), mg/L	4.28 (0.82–15.07)	1.44 (0.78–3.86)	0.18
Positive D-dimer (≥0.5 mg/L), No. (%)	22 (96)	244 (87)	0.24
Positive D-dimer (>2 mg/L), No. (%)	15 (65)	114 (41)	0.02*
Positive D-dimer (>5 mg/L), No. (%)	11 (48)	50 (18)	0.001**
Positive D-dimer (>9 mg/L), No. (%)	8 (35)	32 (11)	0.002**
Right ventricular dysfunction on TTE, No. (%)	5 (22)	41 (15)	0.37

Abbreviation: TTE, transthoracic echocardiogram.

<sup>a</sup>Troponin levels either on admission, at time of TTE, or peak during hospital stay.

\* $p < 0.05$ ; \*\* $p < 0.01$ .

compared to their respective models with D-dimer > 2 mg/L. This indicates that models with D-dimer > 5 mg/L had higher predictive accuracy, and thus this threshold was selected for the final model.

Table 5 summarizes the ORs and prediction statistics for the final model (Model 9), which includes D-dimer > 5 mg/L, troponin levels, and RV dysfunction. There was a statistically significant positive association between D-dimer > 5 mg/L and PE (adj OR = 4.40; 95% CI: [1.80, 10.78]). Model 9 had the highest model discrimination and predictive (cross-validated) discrimination (AUC = 0.77, cvAUC = 0.74), and was identified as being statistically the best for predicting a future PE diagnosis as it had the lowest

AIC (AIC = 154). Figure 1 shows the receiver operating curve for Model 9. Additionally, the positive predictive value (PPV) and negative predictive value (NPV) were calculated for the model. The predicted probabilities for PE from our model ranged from 0% to 33% for a given patient's parameters (of D-dimer, RV dysfunction, and troponin). Therefore, a cutoff of 16% was used to classify a positive test. For a given patient's parameters, a predictive probability for PE of 16% or greater indicated a "positive" test. A probability of less than 16% indicated a "negative" test. Using this cutoff, the PPV was 18% and the NPV was 94% (Table 5). A NPV of 94% suggests that our model may be used to exclude a PE diagnosis with a negative test.

**TABLE 2** Sensitivity and specificity of D-dimer and right ventricular dysfunction for pulmonary embolism

Diagnostic parameter	Sensitivity	Specificity
Positive D-dimer ( $\geq 0.5$ mg/L)	0.96	0.13
Positive D-dimer ( $> 2$ mg/L)	0.65	0.59
Positive D-dimer ( $> 5$ mg/L)	0.48	0.82
Positive D-dimer ( $> 9$ mg/L)	0.35	0.89
RV dysfunction on TTE	0.22	0.85

Abbreviations: RV, right ventricular; TTE, transthoracic echocardiogram.

These study results suggest that D-dimer  $> 5$  mg/L is a statistically significant predictor of PE diagnosis in COVID-19 patients. While RV dysfunction and troponin may alone not be statistically significant predictors of PE, they are important variables combined with D-dimer  $> 5$  mg/L for calculating risk of PE diagnosis using the model, as including them yielded the highest predictive accuracy (Figure 2).

## DISCUSSION

In conclusion, our study demonstrated that a model incorporating a combination of clinical, lab and imaging variables performed well for PE prediction in hospitalized COVID-19 patients. The model that had the highest predictive (Model 9, cross-validated) discrimination with an AUC of 0.77 for PE diagnosis included the combination of D-dimer (threshold of  $> 5$  mg/L), troponin, and RV dysfunction on TTE. First, our study confirmed prior reports that D-dimer has poor specificity for PE in COVID-19 patients at a standard threshold ( $\geq 0.5$  mg/L) which improved with a higher threshold ( $> 5$  mg/L), however with reduced sensitivity. Second, the addition of RV dysfunction along with other clinical and lab parameters such as troponin levels improved the predictive ability of D-dimer. Third, our model also showed value in excluding a PE diagnosis with a negative test result as indicated by a NPV of 94%. This suggests a potentially additive value of RV imaging and assessment of cardiac biomarkers when determining the need for further diagnostic workup for PE.

The clinical evaluation for PE may be challenging because symptoms of PE overlap with other COVID-19 related respiratory symptoms, and imaging studies may not

be feasible in all patients. This accessible, bedside testing approach (with echocardiography) may help in the triage of patients, aid in resource allocation for diagnostic imaging studies such as CT, and limit unnecessary exposure and the need for patient transportation to a CT scanner during acute infection. Further studies are needed to prospectively evaluate the ability of the model to predict PE including after hospital discharge. The overall PE prevalence in the cohort was 7.6%, which is intermediate in value compared to prior studies with PE prevalence ranging from 0.7% to 16% among hospitalized COVID-19 patients.<sup>8</sup> Differences compared to prior studies may be due to hospital specific anticoagulation guidelines and differences in patient populations.

D-dimer tests are commonly used diagnostic tools for PE, with high clinical value in ruling out PE with a negative test. In COVID-19 patients, a D-dimer test has been shown to have high sensitivity (96%) but very low specificity (10%) for predicting a PE.<sup>8</sup> Our study supports these findings showing a sensitivity and specificity of a positive D-dimer test in predicting a PE diagnosis to be 96% and 13%, respectively. This indicates that while many COVID-19 patients may have positive D-dimer levels ( $\geq 0.5$  mg/L), only a fraction will actually have a PE. Therefore, a D-dimer test may be used as a screening tool for PE in COVID-19 patients due to its high sensitivity with most utility as a “rule out” when values are negative; however, it is not adequate for predicting a PE diagnosis at a 0.5 mg/L threshold. Prior studies followed serial D-dimer measures for venous thromboembolism events including PE, and reported a baseline D-dimer level of 2.2 mg/L, and a peak D-dimer level above 9 mg/L among COVID-19 patients who had a PE.<sup>26,27</sup> Additionally, other studies in hospitalized COVID-19 patients reported intermediate value D-dimer levels in the same range for a diagnosis of venous thromboembolism.<sup>26,27</sup> Given the results of our study and prior observations, the prediction models were created using intermediate D-dimer thresholds of 2 and 5 mg/L. In all of the models, D-dimer had a strong and statistically significant association with PE.

Our study explores the additive value and role of RV dysfunction on TTE as a potential predictor of a PE diagnosis among COVID-19 patients. Many hospitalized COVID-19 patients receive bedside TTE which has value in the rapid triage of patients and can aid in resource allocation when used appropriately.<sup>23</sup> Our study suggests that the presence of RV dysfunction in combination with a higher D-dimer threshold and other easily attainable clinical variables (serum troponin levels) may help in directing patients for further testing for PE diagnosis, which confers high morbidity and mortality in COVID-19.<sup>2,4</sup> One study in hospitalized COVID-19

**TABLE 3** Logistic regression analyses: predictive modeling for pulmonary embolism, using D-dimer threshold of 2 mg/L

Predictor	Model 1		Model 2		Model 3		Model 4	
	Crude OR [95% CI]	P value	Adj OR <sup>a</sup> [95% CI]	P value	Adj OR <sup>a</sup> [95% CI]	P value	Adj OR <sup>a</sup> [95% CI]	P value
Positive D-dimer (>2 mg/L)	2.71 [1.11, 6.61]	0.028*	2.85 [1.16, 7.01]	0.023*	2.81 [1.14, 6.92]	0.025*	3.03 [1.21, 7.59]	0.018*
Age (years)	-	-	0.99 [0.97, 1.02]	0.72	0.99 [0.97, 1.02]	0.68	1.00 [0.97, 1.03]	0.87
Female	-	-	0.58 [0.24, 1.42]	0.23	0.55 [0.23, 1.37]	0.20	0.56 [0.23, 1.40]	0.22
Black	-	-	1.09 [0.46, 2.60]	0.85	1.07 [0.45, 2.57]	0.88	1.03 [0.43, 2.49]	0.94
BMI (kg/m <sup>2</sup> )	-	-	1.00 [0.94, 1.05]	0.89	0.99 [0.94, 1.05]	0.84	1.00 [0.94, 1.06]	0.96
RV Dysfunction on TTE	-	-	-	-	1.72 [0.59, 5.05]	0.33	-	-
Troponin (ng/mL)	-	-	-	-	-	-	0.0042 [10 <sup>-6</sup> , 10.35]	0.17
AUC	0.62		0.66		0.68		0.71	
Hosmer-Lemeshow GOF P value	n/a <sup>b</sup>		0.98		0.94		0.45	
Cross validated AUC	0.60		0.52		0.56		0.59	
AIC	162		168		169		164	

Abbreviations: Adj, adjusted; AIC, akaike information criterion; AUC, area under receiver operating curve; BMI, body mass index; CI, confidence interval; GOF, goodness-of-fit; OR, odds ratio; RV, right ventricular; TTE, transthoracic echocardiogram.

<sup>a</sup>Adjusted for variables in the respective models.

<sup>b</sup>Could not calculate due to limited outcome variability.

\*p < 0.05.

**TABLE 4** Logistic regression analyses: predictive modeling for pulmonary embolism, using D-dimer threshold of 5 mg/L

Predictor	Model 5		Model 6		Model 7		Model 8	
	Crude OR [95% CI]	P value	Adj OR <sup>a</sup> [95% CI]	P value	Adj OR <sup>a</sup> [95% CI]	P value	Adj OR <sup>b</sup> [95% CI]	P value
Positive D-dimer (>5 mg/L)	4.19 [1.75, 10.06]	0.001*	4.40 [1.81, 10.69]	0.001*	4.23 [1.73, 10.34]	0.002*	4.96 [1.99, 12.38]	0.001*
Age (years)	-	-	1.00 [0.97, 1.03]	0.93	1.00 [0.97, 1.03]	0.87	1.00 [0.97, 1.03]	0.85
Female	-	-	0.56 [0.23, 1.38]	0.21	0.55 [0.22, 1.36]	0.19	0.54 [0.21, 1.37]	0.19
Black	-	-	1.08 [0.45, 2.62]	0.86	1.06 [0.44, 2.58]	0.89	1.00 [0.41, 2.45]	0.99
BMI (kg/m <sup>2</sup> )	-	-	1.00 [0.94, 1.05]	0.89	0.99 [0.94, 1.05]	0.85	1.00 [0.94, 1.06]	0.98
RV dysfunction on on TTE	-	-	-	-	1.45 [0.48, 4.39]	0.51	-	-
Troponin (ng/mL)	-	-	-	-	-	-	0.0040 [10 <sup>-6</sup> , 7.49]	0.15
AUC	0.65		0.68		0.70		0.77	
Hosmer-Lemeshow GOF P value	n/a <sup>b</sup>		0.63		0.90		0.85	
Cross validated AUC	0.63		0.62		0.62		0.69	
AIC	157		163		165		158	

Abbreviations: Adj, adjusted; AIC, akaike information criterion; AUC, area under receiver operating curve; BMI, body mass index; CI, confidence interval; GOF, goodness-of-fit; OR, odds ratio; RV, right ventricular; TTE, transthoracic echocardiogram.

<sup>a</sup>Adjusted for variables in the respective models.

<sup>b</sup>Could not calculate due to limited outcome variability.

\* $p < 0.01$ .



**TABLE 5** Logistic regression analyses: final prediction model for pulmonary embolism

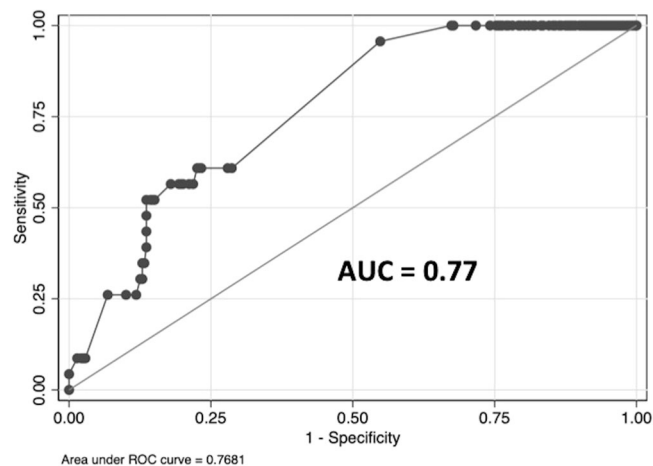
Predictor	Model 9	
	Adj OR <sup>a</sup> [95% CI]	P value
Positive D-dimer (>5 mg/L)	4.40 [1.80, 10.78]	0.001*
Troponin (ng/mL)	0.0035 [10 <sup>-6</sup> , 7.26]	0.15
RV Dysfunction on TTE	1.51 [0.50, 4.56]	0.46
AUC	0.77	
Hosmer-Lemeshow GOF P value	0.48	
Cross validated AUC	0.74	
AIC	154	
PPV <sup>b</sup> (%)	18	
NPV <sup>b</sup> (%)	94	

Abbreviations: Adj, adjusted; AIC, akaike information criterion; AUC, area under receiver operating curve; CI, confidence interval; GOF, goodness-of-fit; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RV, right ventricular; TTE, transthoracic echocardiogram.

<sup>a</sup>Adjusted for variables in the respective models.

<sup>b</sup>A predicted probability cutoff of 16% was used to classify a positive vs. negative test result.

\* $p < 0.01$ .

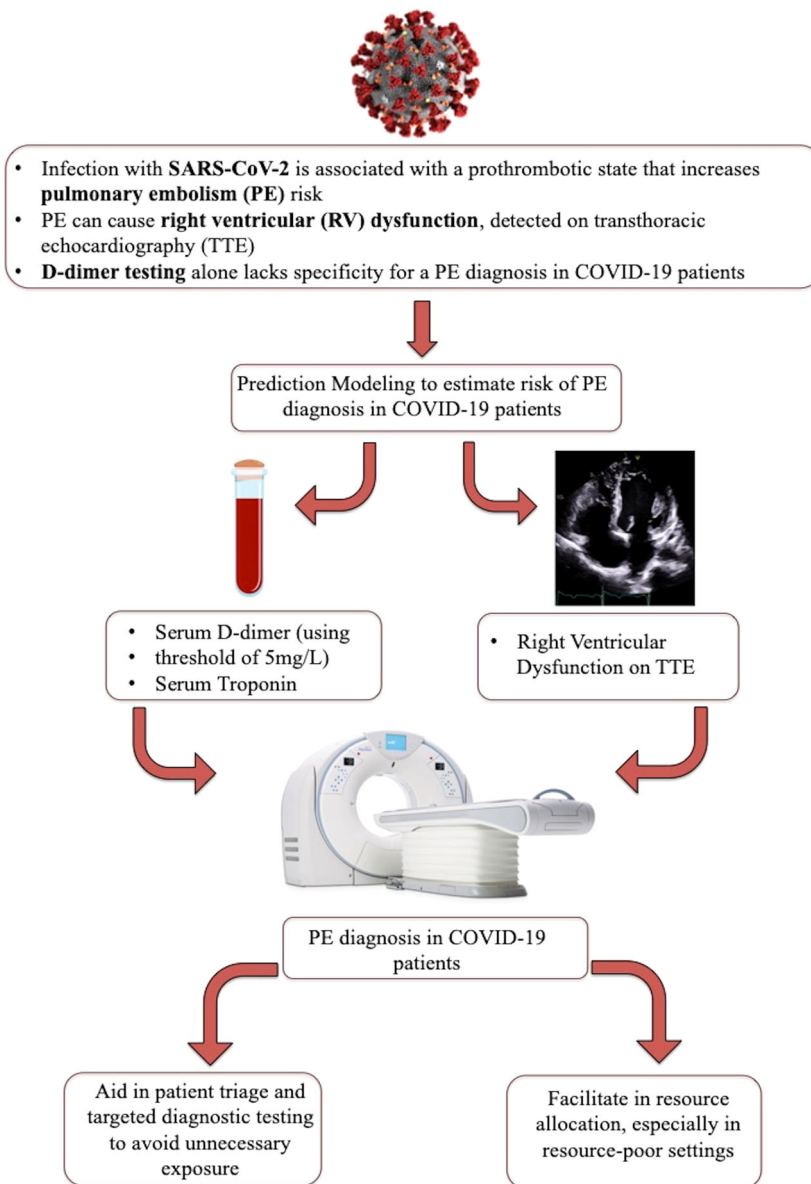
**FIGURE 1** Area under the receiver operating curve (AUC) for final Model 9 indicating model discrimination for predicting pulmonary embolism diagnosis in COVID-19 patients

patients showed an association between abnormal TAPSE (a parameter of RV dysfunction) and PE.<sup>31</sup> However, based on our study findings, it appears that while RV dysfunction alone may not have a statistically significant association with PE, together with troponin it improves the predictive value of D-dimer for PE significantly. A model with D-dimer >5 mg/L, RV dysfunction, and troponin levels gave the highest predictive

discrimination for predicting PE. Although several studies in non-COVID patients have shown an association between RV dysfunction and PE,<sup>29,30</sup> in patients with COVID-19 it appears that the association is not as straightforward and other variables including troponin levels improve the predictive value of D-dimer and RV dysfunction for PE significantly. Furthermore, an advantage of this approach is that it may help in better resource allocation for chest CT angiography and limit unnecessary exposure to radiation and contrast use, especially in countries with limited resources.<sup>32</sup>

Given the potential role of systemic inflammation and cardiac injury in COVID-19 morbidity,<sup>28,33</sup> we explored the role of cardiac markers as potential predictors of PE in COVID-19 patients. The addition of troponin levels to models significantly improved risk prediction as seen by the cross validated AUC. Troponin levels, however, had an inverse association with PE in all of the models, although not statistically significant. A potential reason for this could be the time troponin was measured relative to the PE event, and that troponin is more specific for myocardial injury and infarction. Some PE patients may have a negative troponin test result initially, but may have elevated troponin levels 6–12 h after the PE event<sup>34</sup> which may be due to a sudden increase in RV wall tension leading to myocardial injury. In our study, troponin was measured at admission, at the time of TTE, and a peak value during the hospital stay. However, measuring troponin 6–12 h after a PE event may affect the association with PE risk. This model not only performed well for predicting a PE diagnosis in COVID-19 patients, but also appeared to have utility in ruling out PE with a negative test (as seen by the high NPV). Therefore, obtaining cardiac biomarkers such as troponin and assessing the RV with echocardiography may be important for PE work up and patient triage.

Although this model performed well for PE prediction in COVID-19 patients, there are several limitations to the model. First, a larger sample size may be needed. Although our cohort had over 300 patients with data for the predictors, there were only 23 PE events. We chose to focus our study on COVID-19 inpatients as they are at high risk for thromboembolic complications and regarded to be in a hypercoagulable state.<sup>2,3</sup> Although it would be ideal to also study a control group without COVID-19, we did not as there was incomplete data in most of these patients with few echocardiograms or biomarkers of inflammation available. However, studying our model in datasets without COVID-19 will be an important next step. Another limitation is that only COVID-19 patients who underwent a clinically indicated TTE and D-dimer testing were included, which may introduce bias with regard to the cohort's clinical



**FIGURE 2** Diagram of final testing algorithm for predicting pulmonary embolism in hospitalized COVID-19 patients

Illustration made by Monika A. Satoskar

**Image Sources:**

TTE image taken by Allison G. Hays

Disease caused by the novel coronavirus officially has a name: Covid-19. *Stat*, <https://www.statnews.com/2020/02/11/disease-caused-by-the-novel-coronavirus-has-name-covid-19/> (2020, accessed 20 July 2021).

Freepik, [https://www.freepik.com/premium-vector/illustration-glass-tube-blood-blood-test-cartoon-style-test-tubes-with-blood-isolated-object-medical-research\\_4980009.htm](https://www.freepik.com/premium-vector/illustration-glass-tube-blood-blood-test-cartoon-style-test-tubes-with-blood-isolated-object-medical-research_4980009.htm)

(2021, accessed 20 July 2021).

New state-of-the-art Toshiba CT scanner for the Holly Private Hospital. *The Holly Private Hospital*, <https://www.theholly.com/new-state-of-the-art-toshiba-ct-scanner-for-the-holly-private-hospital/> (2017, accessed 20 July 2021).

parameters. In addition, 98 patients out of the 302 did not undergo CT angiography due to low clinical suspicion or due to contraindications. Therefore, it is possible that the true prevalence of PE in our cohort may be higher. One study showed that COVID-19 patients admitted to the ICU who underwent CT screening for PE, 47% of the patients had pulmonary arterial complications, of which only 7% were clinically suspected.<sup>35</sup> Furthermore, because this was a cross-sectional study, the chest CT angiogram for PE ascertainment was assumed to have

occurred at the same time as when the TTE and laboratory parameters were obtained. However, the CT was performed several days after the TTE, and this could possibly affect the association. Additional parameters such as BNP, C reactive protein, interleukin-6, ferritin may be needed for more accurate prediction; however, these biomarkers were not available in the majority of patients, and we would risk over-fitting the data by introducing more than three predictors into the model for the given sample size and number of events.

Furthermore, blood oxygen saturation was not included in the models as oxygen requirements often changed throughout the course of the hospitalization, as well as the method of delivery, and the nuanced variation of oxygen delivery was not consistently captured across participants in our registry.

In conclusion, our study showed that D-dimer status (using D-dimer threshold of 5 mg/L), RV dysfunction on TTE, and troponin levels together may be important for estimating likelihood of a PE diagnosis in hospitalized COVID-19 patients. A positive D-dimer ( $\geq 0.5$  mg/L) may be used as a screening tool for PE in COVID-19 patients as seen by its high sensitivity, however, its low specificity makes D-dimer at this threshold a poor predictor of PE in COVID-19 patients. We identified a model with a combination of D-dimer status (using a higher threshold than the standard lab cutoff), presence of RV dysfunction and troponin levels to have the highest cross validated area under the receiver operating curve and best predictive ability for PE. This indicates that in COVID-19 patients who have a positive D-dimer, it may be clinically useful to obtain cardiac biomarkers such as troponin, and echocardiographic imaging for RV assessment when working up a possible diagnosis of PE. Future studies should investigate the role of more quantitative RV parameters on TTE such as degree of RV dilation and function; however, attaining these measures are challenging, as visualization of the RV is often limited. In addition, exploring the role of other inflammatory markers such as C reactive protein and interleukin-6 as potential predictors of PE in COVID-19 patients may be warranted. Having a better understanding of the predictors for a PE event in COVID-19 patients may allow clinicians to make more informed decisions related to patient management and targeted diagnostic testing.

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### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

### ETHICS STATEMENT

Johns Hopkins School of Medicine Institutional Review Board (IRB00249051).

### AUTHOR CONTRIBUTIONS

Monika A. Satoskar, Allison G. Hays, and Wendy S. Post contributed to the conception of this study. Allison G. Hays, Madeline Schiminger, Alborz Soleimanifard, and Julie K. Shade contributed to data acquisition and extraction. Monika A. Satoskar contributed to the analysis of the data. Monika A. Satoskar, Allison G. Hays, and Wendy S. Post contributed to the interpretation of the data. Monika A. Satoskar contributed to drafting the article. Allison G. Hays, Wendy S. Post, Erin D. Michos, Monica Mukherjee, Alborz Soleimanifard, Madeline Schiminger, Natalia A. Trayanova, Julie K. Shade and Thomas Metkus contributed to reviewing the article and providing approval of the version to be published.

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