Radiology

# Pulmonary Embolism in Hospitalized Patients with COVID-19: A Multicenter Study

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**Background:** Pulmonary embolism (PE) commonly complicates SARS-CoV-2 infection, but incidence and mortality reported in single-center studies, along with risk factors, vary.

**Purpose:** To determine the incidence of PE in patients with COVID-19 and its associations with clinical and laboratory parameters.

**Materials and Methods:** In this HIPAA-compliant study, electronic medical records were searched retrospectively for demographic, clinical, and laboratory data and outcomes among patients with COVID-19 admitted at four hospitals from March through June 2020. PE found at CT pulmonary angiography and perfusion scintigraphy was correlated with clinical and laboratory parameters. The D-dimer level was used to predict PE, and the obtained threshold was externally validated among 85 hospitalized patients with COVID-19 at a fifth hospital. The association between right-sided heart strain and embolic burden was evaluated in patients with PE undergoing echocardiography.

**Results:** A total of 413 patients with COVID-19 (mean age, 60 years ± 16 [standard deviation]; age range, 20–98 years; 230 men) were evaluated. PE was diagnosed in 102 (25%; 95% CI: 21, 29) of 413 hospitalized patients with COVID-19 who underwent CT pulmonary angiography or perfusion scintigraphy. PE was observed in 21 (29%; 95% CI: 19, 41) of 73 patients in the intensive care unit (ICU) versus 81 (24%; 95% CI: 20, 29) of 340 patients who were not in the ICU ($P$ = .37). PE was associated with male sex (odds ratio [OR], 1.74; 95% CI: 1.1, 2.8; $P$ = .02); smoking (OR, 1.86; 95% CI: 1.0, 3.4; $P$ = .04); and increased D-dimer ($P$ < .001), lactate dehydrogenase ($P$ < .001), ferritin ($P$ = .001), and interleukin-6 ($P$ = .02) levels. Mortality in hospitalized patients was similar between patients with PE and those without PE (14% [13 of 102]; 95% CI: 8, 22] vs 13% [40 of 311]; 95% CI: 9, 17; $P$ = .98), suggesting that diagnosis and treatment of PE were not associated with excess mortality. The D-dimer levels greater than 1600 ng/mL [8.761 nmol/L] helped predict PE with 100% sensitivity and 62% specificity in an external validation cohort. Embolic burden was higher in patients with right-sided heart strain among the patients with PE undergoing echocardiography ($P$ = .03).

**Conclusion:** Pulmonary embolism (PE) incidence was 25% in patients hospitalized with COVID-19 suspected of having PE. A D-dimer level greater than 1600 ng/mL [8.761 nmol/L] was sensitive for identification of patients who needed CT pulmonary angiography.

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*Online supplemental material is available for this article.*

SARS-CoV-2 binds the angiotensin-converting enzyme-2 receptors on endothelial cells, especially within the kidneys, heart, lungs, and liver (1). Endothelial cell damage leads to thrombosis, which can be a defense mechanism that compartmentalizes infection and prevents further dissemination (2). However, with COVID-19, widespread thrombosis has been reported to cause numerous thrombotic complications, including deep vein thrombosis, pulmonary embolism (PE), myocardial infarction, stroke, and disseminated intravascular coagulation (3,4).

Grillet et al (5) reported a 23% positive rate for CT pulmonary angiography studies. In New York, Kaminetzky et al (6) reported that when CT pulmonary angiography was performed, it was positive for PE in 37% of patients

with COVID-19 compared with 14.5% of patients before the pandemic. A meta-analysis of 4382 patients hospitalized with COVID-19 showed a 17.6% incidence of PE, with a substantially higher rate among patients with severe (ie, admitted to the intensive care unit [ICU]) versus general (ie, not admitted to the ICU) disease (21.7% vs 12.5%) (7). Thus, the incidence of PE varies widely in the literature, and uncertainty remains about who should be imaged. A high prevalence of right-sided heart strain has also been noted (8), suggesting that PE may be more fatal in patients with COVID-19; however, the risk factors for PE in COVID-19 are not well established.

The purpose of this study was to determine the multicenter incidence of PE in COVID-19 and its associations

## Abbreviations

ICU = intensive care unit, IQR = interquartile range, PE = pulmonary embolism, PT = prothrombin time, RT-PCR = reverse transcription polymerase chain reaction, VTE = venous thromboembolism

## Summary

Pulmonary embolism was found in 25% of hospitalized patients with COVID-19 who underwent chest CT or perfusion scintigraphy and was predicted with 100% sensitivity with a D-dimer level greater than 1600 ng/mL [8.761 nmol/L].

## Key Results

- Pulmonary embolism (PE) was diagnosed in 102 of 413 (25%) hospitalized patients with COVID-19 suspected of having PE who underwent CT (*n* = 408) or perfusion scintigraphy (*n* = 5).
- The rate of PE was greater in men (odds ratio [OR], 1.7; *P* = .02) and smokers (OR, 1.8; *P* = .04) but did not significantly differ between patients in the intensive care unit (ICU) (21 of 73 [29%]) and those not in the ICU (81 of 340 [24%]; *P* = .37).
- In an external validation cohort of 85 patients with COVID-19, PE was predicted with 100% sensitivity and 62% specificity with a D-dimer level greater than 1600 ng/mL [8.761 nmol/L].

with clinical and laboratory parameters. Secondary objectives were to assess the predictive value of D-dimer level and the relationship between right-sided heart strain and clot burden. We evaluated patients with COVID-19 admitted to four hospitals and developed a predictive model to identify patients with CO-VID-19 at high risk for PE. The model was validated with data from another institution.

## Materials and Methods

### Patients

The institutional review boards of Weill Cornell Medicine and Bridgeport Hospital approved this retrospective, Health Insurance Portability and Accountability Act–compliant review of existing medical records and waived the requirement for informed consent. This project used data extracted from the electronic medical records of four large New York-Presbyterian hospitals for all admitted patients who met the following inclusion criteria: age of at least 18 years, COVID-19 diagnosis confirmed with a positive result on a SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) assay (obtained via nasopharyngeal swab), and chest CT pulmonary angiography or perfusion scintigraphy performed after admission for COVID-19. Patients with PE before the first RT-PCR test were excluded. Data were extracted primarily by 4th-year medical students and confirmed by research fellows for COVID-19 admissions from March 3 to June 5, 2020. For external validation, data were extracted manually according to the same criteria for an additional cohort of patients with COVID-19 hospitalized and undergoing CT pulmonary angiography for suspected PE at Bridgeport Hospital in Connecticut (hereafter called the external validation cohort).

This patient population overlaps somewhat with a patient population described in a published letter: In that report, 41 patients with PE from the same COVID-19 database were evaluated for risk and D-dimer cutoff of venous thromboembolism (VTE) (9).

### Data Extraction

Data extracted included RT-PCR diagnosis date, as well as demographic, clinical, and laboratory data, collected within 72 hours of imaging. These included age; sex; race or ethnicity; body mass index; smoking status; D-dimer, fibrinogen, ferritin, C-reactive protein, and creatine kinase levels; platelet counts; prothrombin time (PT) and activated partial thromboplastin time; heart rate; systolic and diastolic blood pressure; percentage of arterial oxygen saturation; duration and route of supplemental oxygen administration; history of chronic lung disease, cardiovascular disease, chronic kidney disease, hypercoagulability, deep vein thrombosis, diabetes mellitus, or HIV infection; and anticoagulant use at least 48 hours before imaging. For hypercoagulability, diagnosis was further confirmed by checking the International Classification of Diseases, 10th Revision, codes, including D68 and I82 and their derivatives for thrombophilia and chronic thromboembolism, in the electronic medical record.

We also extracted intubation date, number of days on a ventilator, discharge status, and death. Prospectively generated chest CT reports were reviewed to extract the following imaging features: PE, presence and location of ground-glass opacities, crazy paving pattern, septal thickening without mention of crazy paving, consolidation, air bronchograms, pleural effusion, right-sided heart strain, and any artifacts. Right-sided heart strain was defined according to echocardiographic findings obtained within 1 day after CT or perfusion scintigraphy for patients in whom such findings were available. The prospectively reported location of a PE was used to determine a score of embolic burden by using the Qanadli method (10); images were reviewed as necessary to resolve any ambiguities about reporting of emboli location.

### Imaging Protocol

CT pulmonary angiography was performed on 64- or 256-section scanners (Optima, Discovery, or Revolution; GE Healthcare) during breath holding, with injection of 70–100 mL of iohexol (Omnipaque 300; GE Healthcare) or ioversol (Optiray 350; Mallinckrodt). Bolus timing to peak contrast enhancement of the pulmonary artery was performed by using SmartPrep (GE Healthcare) sampling on the mid superior vena cava and right pulmonary artery. Images were reconstructed in the axial plane with 1.25- and 2.5-mm section thicknesses, as well as 8-mm maximum intensity projections and in coronal and sagittal planes at 2-mm section thickness and with 5-mm maximum intensity projections. Examination findings were reported primarily by fellowship-trained chest radiologists working with residents at two of the hospitals and by general radiologists at the other hospitals. All nuclear medicine images were interpreted by fellowship-trained nuclear medicine radiologists.

Perfusion scintigraphy was performed by using 4-mCi technetium-99m macroaggregated albumin. Imaging was performed with SPECT, and multiple planar images were obtained.

### Statistical Analysis

Continuous variables were tested for normality and are reported as mean ± standard deviation or median and interquartile range
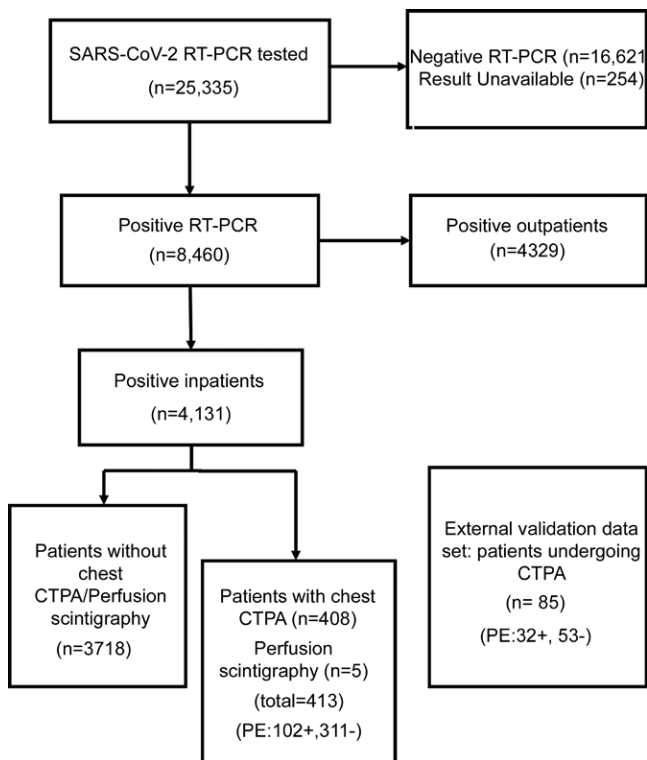
**Figure 1:** Patient flowchart. CTPA = CT pulmonary angiography, PE = pulmonary embolism, RT-PCR = reverse transcription polymerase chain reaction.

**Table 1: Demographic and Clinical Data from 413 Patients with COVID-19 Evaluated for Pulmonary Embolism with Chest CT (n = 408) and Perfusion Scintigraphy (n = 5)**

| Variable | PE Present (n = 102) | PE Absent (n = 311) | P Value |
|---|---|---|---|
| Age (range) (y)* | 61 ± 16 (22–90) | 59 ± 16 (20–94) | .49 |
| Men/women† | 67/35 (1.9) | 163/148 (1.1) | .02 |
| Body mass index* | 28.1 ± 7.2 | 28.5 ± 7 | .65 |
| Smoking (any history) | 19 (19) | 34 (11) | .04 |
| Medical history | | | |
|   Hypercoagulability/ venous thromboembolism | 18 (18) | 42 (14) | .31 |
|   Coronary artery disease | 12 (12) | 48 (15) | .36 |
|   Hypertension | 46 (45) | 152 (49) | .51 |
|   Diabetes mellitus | 30 (29) | 98 (32) | .69 |
|   HIV infection | 2 (2) | 10 (3) | .51 |
| Vital signs | | | |
|   Heart rate (beats/min)* | 101 ± 20 | 96 ± 21 | .03 |
|   Respiratory rate (breaths/min)* | 23 ± 7 | 21 ± 5 | .01 |
|   Blood pressure (mm Hg)* | | | |
|     Systolic* | 129 ± 20 | 126 ± 22 | .19 |
|     Diastolic* | 79 ± 12 | 75 ± 13 | .01 |
|   Oxygen saturation (%)‡ | 95 (93–98) | 96 (94–99) | .008 |

Note.—Unless otherwise noted, data are number of patients, with the percentage in parentheses. PE = pulmonary embolism.
* Data are mean ± standard deviation, and data in parentheses are the range.
† Data in parentheses are the ratio.
‡ Data are the median, with the interquartile range in parentheses.

(IQR). The Student $t$ test or Mann-Whitney $U$ test was used to compare differences between groups for these variables. Categorical variables are reported as frequency and percentage, and the significance of between-group comparisons was assessed by using the $\chi^2$ test.

We used a subsample of 408 patients who underwent chest CT pulmonary angiography to build a random forest model for predicting acute PE. We did not include the five patients with perfusion scintigraphy in this analysis to maintain consistency in the method of outcome detection. Missing values were imputed in variables with less than 10% missing data points by using the missForest (11) method of imputation. The total study sample was randomly divided into a training set that maintained the outcome proportion, including two-thirds of the patients, and a test set (ie, the remaining one-third) for model building and internal validation, respectively. Because acute PE was a rare event, the synthetic minority oversampling technique, or SMOTE, was applied in the training set to balance the data by upsampling the minority group (12). A random forest model was fitted on the balanced training set to predict acute PE. The independent variables were age; sex; body mass index; smoking history; history of chronic lung disease, cardiovascular disease, and VTE or hypercoagulability; interval from COVID-19 symptoms to CT pulmonary angiography (in days); duration of hospital stay (in days); thromboprophylaxis at least 48 hours before CT pulmonary angiography; number of days on a ventilator; intubation; need for supplemental oxygen at arrival; noninvasive ventilation; heart rate; systolic blood pressure; percentage of oxygen saturation; D-dimer, C-reactive protein, fibrinogen, and ferritin levels;

platelet count; and PT and activated partial thromboplastin time. Variable importance was determined by using permutation importance (ie, mean decrease in accuracy). A 10 × 10 cross-validation technique was used to train the model on the training set. Predictions were then made by using the random forest model on the test set. The area under the receiver operating characteristic curve was calculated to assess the model performance on the validation set. The Youden index was then used to establish a threshold for the predictions for diagnosis of acute PE.

Univariate logistic regression was used to assess the predictive performance of D-dimer level as a continuous variable. Subsequently, sensitivity analysis was performed by using the Youden J index to determine the optimal cutoff point in D-dimer levels for PE prediction by using D-dimer level alone. This cutoff was then externally validated by using the external validation cohort described earlier.

The significance level was set to .05, and statistical analysis was performed with R software, version 4.0.2 (R Core Team).

## Results

From March 3 to June 5, 2020, 25 335 SARS-CoV-2 RT-PCR tests at four hospitals served to identify 8460 patients with

**Table 2: Laboratory Data from 413 Patients with COVID-19 Evaluated for Pulmonary Embolism with Chest CT (*n* = 408) and Perfusion Scintigraphy (*n* = 5)**

| Variable | PE Present (*n* = 102) | PE Absent (*n* = 311) | *P* Value |
|---|---|---|---|
| Platelet count (cells/µL) | 308 ± 163 | 305 ± 1744 | .86 |
| Partial thromboplastin time (sec)* | 32.4 (29.5–36.7) | 32.5 (29.5–36.4) | .86† |
| Prothrombin time (sec)* | 14.6 (13.3–15.9) | 14 (13–15.3) | .07† |
| Fibrinogen level (mg/dL) | 607.9 ± 273 | 569 ± 218 | .26 |
| Alanine aminotransferase level (U/L)* | 45 (22–65) | 31 (17–60.5) | .06† |
| Albumin level (g/dL)* | 3.1 (2.3–3.6) | 3 (2.4–3.6) | .68† |
| Aspartate aminotransferase level (U/L)* | 37 (24–58) | 33 (22–55) | .23† |
| Lactate dehydrogenase level (U/L) | 552 ± 475 | 410 ± 249 | <.001 |
| Creatinine level (mg/dL) | 1.06 ± 0.8 | 1.02 ± 1.21 | .78 |
| Lymphocytes (absolute) (×10³/µL)* | 1.09 (0.7–1.64) | 1.1 (0.64–1.55) | .70† |
| Creatine kinase level (U/L)* | 93 (53–191) | 73 (39–181) | .06† |
| Ferritin level (ng/mL)* | 809 (490–1434) | 595 (300–1167) | .001† |
| B-type natriuretic protein level (pg/mL)* | 62 (14–395) | 60 (20–196) | .76† |
| Troponin I level (ng/mL)* | 0.04 (0.03–0.25) | 0.03 (0.03–0.07) | .71 |
| Erythrocyte sedimentation rate (mm/h) | 78.5 ± 37.9 | 75.9 ± 37 | .54 |
| C-reactive protein level (mg/dL)* | 22.4 (8.2–131.8) | 16.1 (4.4–92) | .17 |
| D-dimer level (ng/mL)* | 4262 (1839–13246) | 1200 (496–3410) | <.001† |
| Interleukin-6 level (pg/mL)* | 42 (13.3–93.5) | 13 (5.5–40.5) | .02 |

Note.—Unless otherwise noted, data are mean ± standard deviation. To convert alanine aminotransferase level to SI units (µkat/L), multiply by 0.0167. To convert aspartate aminotransferase level to SI units (µkat/L), multiply by 0.0167. To convert lactate dehydrogenase level to SI units (µkat/L), multiply by 0.0167. To convert creatinine level to SI units (µmol/L), multiply by 88.4. To convert D-dimer level to SI units (nmol/L), multiply by 5.476. PE = pulmonary embolism.

* Data are the median, with the interquartile range in parentheses.

† Mann-Whitney *U* test was used because of nonnormal distribution.

positive results; of these patients, 4131 were admitted (Fig 1). The research data repository had detailed information, including laboratory data and vital signs of all patients with positive RT-PCR test results. For a subset of 413 patients who underwent CT pulmonary angiography (*n* = 408) or perfusion scintigraphy (*n* = 5), laboratory data and vital signs data within 72 hours of the ordering of imaging were collected. CT reports described reduced diagnostic confidence in 40 studies due to motion artifact (*n* = 30), suboptimal bolus timing (*n* = 11), parenchymal disease (*n* = 6), and streak artifact (*n* = 5) (some patients had more than one issue). In these scans, diagnostic confidence was reduced primarily for segmental and subsegmental arteries. Nuclear medicine perfusion scintigraphy was used to evaluate for PE in five patients hospitalized with COVID-19 infection. Ventilation scanning was not performed because of COVID-19 contamination risk, so the assessment for matched defects had to be based on comparison with chest radiographic findings and any other images available.

## Pulmonary Embolism

The incidence of PE diagnosis was 25% (102 of 413; 95% CI: 21, 29) in patients who underwent CT pulmonary angiography or perfusion scintigraphy. The incidence was 29% (95% CI: 19, 40; 21 of 73 patients) for patients in the ICU at the time of imaging and 24% (95% CI: 20, 29; 81 of 340 patients) for patients not in the ICU. This difference was not significant (*P* = .37). The

demographic, laboratory, vital signs, pre-existing conditions, and outcome data for 102 patients with PE and for 311 patients with negative results at CT pulmonary angiography or perfusion scintigraphy are shown in Tables 1–3.

## Bivariate Analysis in Patients Undergoing CT Pulmonary Angiography

Comparison of patients with PE-positive (*n* = 102) and PE-negative (*n* = 311) findings showed that men and smokers had 74% (odds ratio, 1.74; 95% CI: 1.1, 2.8; *P* = .02) and 86% (odds ratio, 1.86; 95% CI: 1.01, 3.4; *P* = .04) (Table 1) greater odds of having acute PE. Levels of alanine aminotransferase, lactate dehydrogenase, ferritin, D-dimer, and interleukin-6; heart rate; respiratory rate; and diastolic blood pressure were significantly higher in the PE group, whereas percentage of oxygen saturation was significantly lower (*P* < .05) (Tables 1, 2). Patients with PE-positive findings had a shorter interval between their first RT-PCR assay and imaging compared with patients with findings negative for PE (median, 1 day [IQR, 0–10 days] vs 3 days [IQR, 0–16 days]; *P* = .01). Incidence of acute deep vein thrombosis was higher in with patients with PE-positive findings than in those with PE-negative findings (22 of 102 [22%] vs 22 of 311 [7%]; *P* < .001) (Table 3). There was a trend toward significantly higher PT and creatine kinase levels among those with PE. CT pulmonary angiographic findings are summarized in Table E1 (online).

### Right-sided Heart Strain and Embolic Burden

Of 102 patients with findings positive for PE, 30% (n = 31) underwent echocardiography within 24 hours after PE diagnosis. Right-sided heart strain was present in eight of the 31 (26%). Mann-Whitney U test showed higher embolic burden for patients with right-sided heart strain (median Qanadli score, 11

[IQR, 8.3–13.3] vs 6 [IQR, 2–7.5]; P = .03) among patients with findings positive for PE (Figs 2, 3).

### D-Dimer Level

Figure 4 shows the relative importance of the predictor variables calculated by mean decrease in accuracy in the final random forest model, trained on the training set. In general, the greater the mean decrease in accuracy when the variable was omitted from the model, the more important the variable. The D-dimer level was the dominant predictor in this model. The results of the sensitivity analysis of the final random forest model on the test set are presented in Table E2 (online).

Subsequently, we analyzed the utility of D-dimer level alone in the prediction of PE in 383 patients without missing D-dimer measurement (PE-positive, 98 patients; PE-negative, 285 patients; D-dimer measurement was missing in 30 patients [7%]). The univariable logistic regression model showed an area under the receiver operating characteristic curve of 0.75 (95% CI: 0.69, 0.80), a sensitivity of 83% (95% CI: 73, 89 [true-positive rate, 80 of 98]), a specificity of 56% (95% CI: 51, 62 [true-negative rate, 161 of 285]), and accuracy of 63% (95% CI: 58, 68), with D-dimer level used as a continuous variable. The optimal cutoff point for D-dimer was 1600 ng/mL (8.761 nmol/L), with the Youden index used in the entire internal sample.

Application of the D-dimer cutoff to the external validation cohort showed a sensitivity of 100% (95% CI: 89, 100 [true-positive rate, 32 of 32]), a specificity of 62% (95% CI: 48, 73 [true-negative rate, 20 of 53]), and an accuracy of 76% (95% CI: 66, 85) for diagnosis of PE.

**Table 3: Clinical Outcomes for 413 Hospitalized Patients with COVID-19 Evaluated for Pulmonary Embolism with Chest CT (n = 408) or Perfusion Scintigraphy (n = 5)**

| Variable | PE Present (n = 102) | PE Absent (n = 311) | P Value |
|---|---|---|---|
| Duration of hospital stay (d)* | 11 (5–25) | 12 (4–35) | .72 |
| Interval from RT-PCR assay to imaging (d)*† | 1 (0–10) | 3 (0–16) | .01 |
| Intensive care unit | 21 (21) | 52 (17) | .37 |
| Intubation | 25 (25) | 71 (23) | .73 |
| Death | 13 (14) | 40 (13) | .98 |
| Acute renal failure | 24 (24) | 59 (19) | .26 |
| Acute respiratory distress syndrome | 26 (25) | 78 (25) | .93 |
| Deep vein thrombosis | 22 (22) | 22 (7) | <.001 |
| Anticoagulation | 36 (35) | 107 (34) | .87 |

Note.—Unless otherwise indicated, data are number of patients, with the percentage in parentheses. PE = pulmonary embolism, RT-PCR = reverse transcription polymerase chain reaction.

* Data in parentheses are the range.

† Period between the first SARS-CoV-2 RT-PCR assay to contrast material–enhanced CT or perfusion scintigraphy.
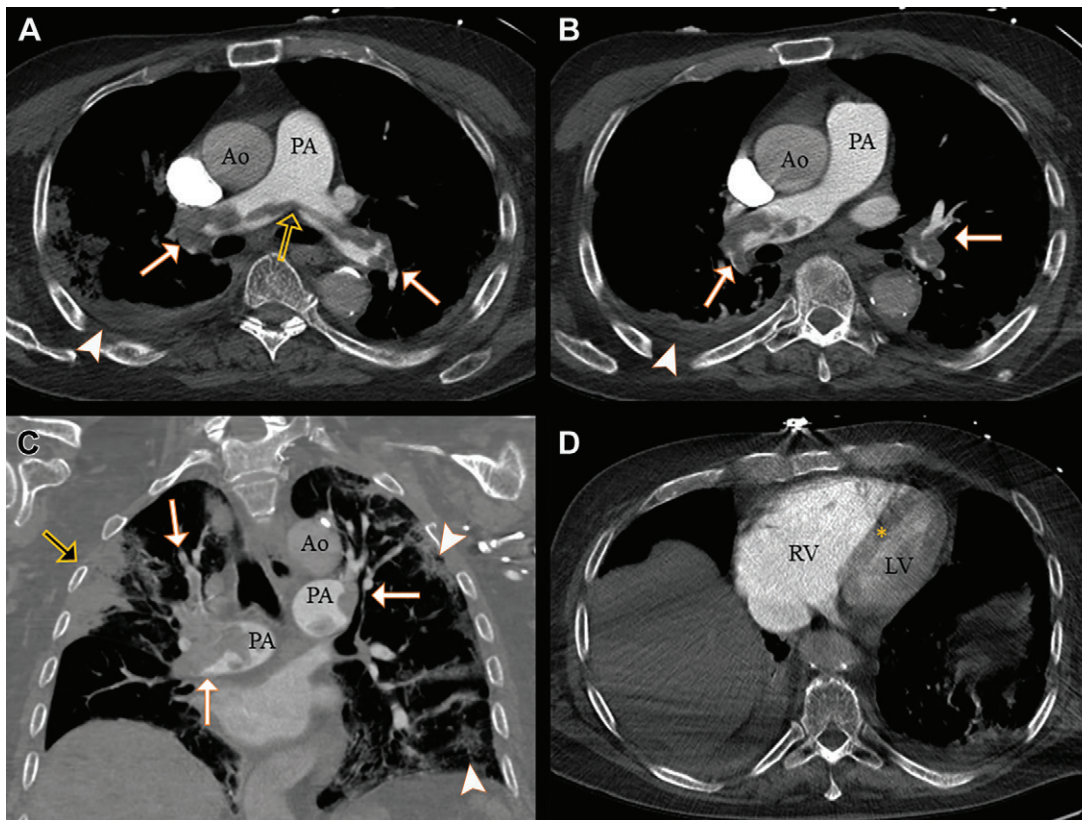


**Figure 2:** CT pulmonary angiograms in a 77-year-old man with COVID-19 and a saddle embolus to pulmonary arteries (black arrow in **A**) extending into right and left pulmonary arteries (white arrows) in **(A, B)** axial and **(C)** coronal planes. Arrowheads show pulmonary changes associated with COVID-19 and possible lung infarction (black arrow in **C**). **(D)** Axial image at the level of the ventricles shows right-sided heart strain with interventricular septal flattening (∗). Ao = aorta, LV = left ventricle, PA = pulmonary artery, RV = right ventricle.
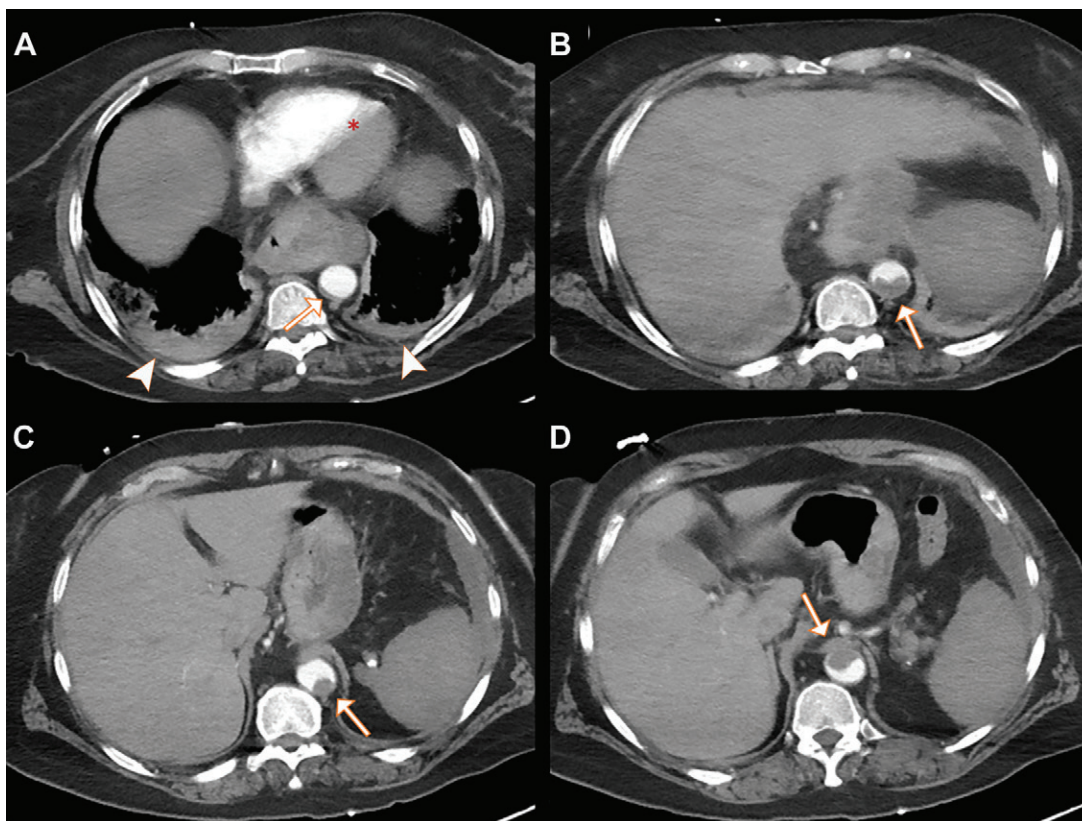
**Figure 3:** Contrast-enhanced CT scans in a 63-year-old woman with COVID-19 and a history of antiphospholipid syndrome. **(A)** Axial image shows paucity of vessels at lung bases with flattening of the interventricular septum (∗). **(B–D)** Axial images show aortic mural clot (arrows).

## Discussion

In this multicenter study of 413 patients hospitalized with CO-VID-19 and suspected of having a pulmonary embolism (PE), PE was found in 25% of patients (95% CI: 21, 29). Although use of CT pulmonary angiography and perfusion scintigraphy in patients with COVID-19 can be cumbersome because of the complex logistics of transporting sick patients infected with COVID-19 to the radiology department, there may be a benefit because we observed no excess mortality when PE was diagnosed and treated. Our random forest model demonstrated D-dimer level was the dominant predictor; a D-dimer level greater than 1600 ng/mL (8.761 nmol/L) had 100% sensitivity and 62% specificity for diagnosis of PE on external validation when used alone. Patients with PE-positive findings and right-sided heart strain confirmed with echocardiography had higher embolic burden than those without right-sided heart strain.

The 25% incidence of PE in all hospitalized patients with COVID-19 is higher than the 17.6% (95% CI: 12.3, 23.5) overall PE incidence and is closer to the 21.7% (95% CI:14.8, 29.3) incidence in the severe group reported by Liu et al in a systematic review and meta-analysis (7). We also did not find significantly higher PE incidence in patients in the ICU. This might reflect that hospitalized patients in our multicentric cohort had severe illness. The large range in PE incidence reported by Liu et al reflects the heterogeneity and small sample size of the studies included, with most studies having fewer than 100 patients from single institutions.

We found that male sex was significantly associated with PE, in line with previous reports (7,13,14). A similar sex bias regarding COVID-19 and other infectious diseases was previously reported. In a meta-analysis including more than 3 million reported global COVID-19 cases, men were almost three times more likely to require admittance to an intensive treatment unit and had 40% higher odds of death than women (15). This female advantage in COVID-19 may be explained by the sex differences in the immune system (15). The effects of androgen on endothelial function have also been suspected to be a contributing factor, making male sex a potential risk factor for VTE, more so in the context of COVID-19 (7).

The D-dimer level was higher in patients with COVID-19 with PE than in those without PE (16), and this has been confirmed in nearly every publication on this topic (9,17). The D-dimer measures fibrin breakdown products and has been used for prediction and prognosis of VTE among patients with COVID-19 (7,9,17–21). One study showed that D-dimer level peaks as the measurements approached the day of US examination for deep vein thrombosis, following an inverse U shape (19). It is thought that the sensitivity of D-dimer measurement for diagnosis of VTE diminishes with time (17,22). The 1600-ng/mL (8.761 nmol/L) D-dimer threshold we found is lower than most thresholds previously reported for PE or VTE prediction, ranging from 2600 to 7500 ng/mL (14.2–41.0 nmol/L) (9,16,23) and is closer to the 1500-ng/mL (8.21-nmol/L) cutoff proposed by Cui et al (24) in 81 patients
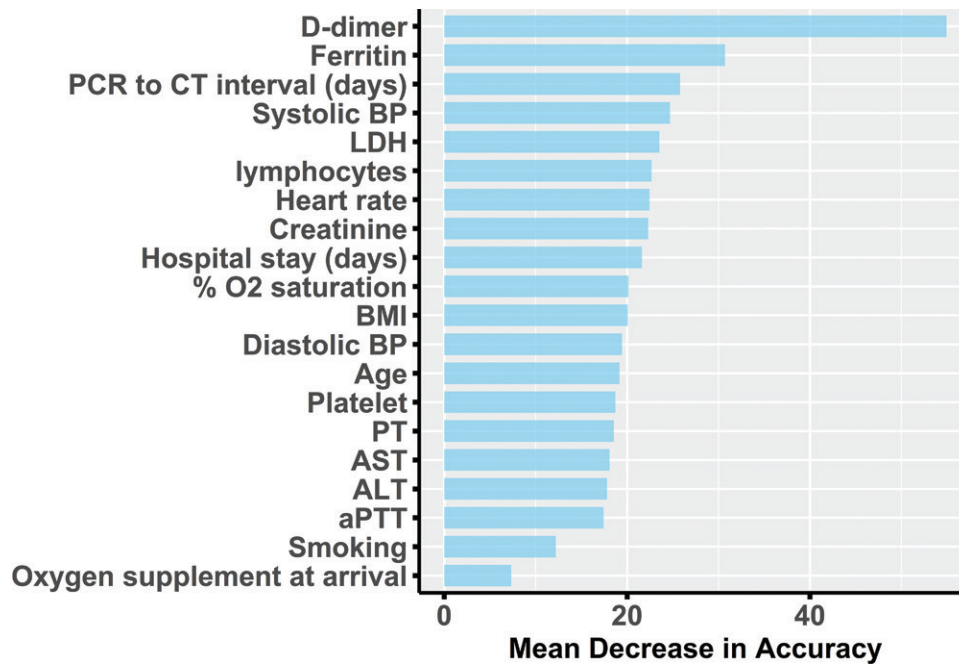
**Figure 4:** Relative variable importance based on mean decrease in accuracy from the final random forest prediction model trained on the training set (n = 272). ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BMI = body mass index, BP = blood pressure, LDH = lactate dehydrogenase, PT = prothrombin time, RT-PCR = reverse transcription polymerase chain reaction.

with severe COVID-19 admitted to the ICU. Tentative diagnosis and provisional prophylactic or therapeutic anticoagulation in patients with severe disease might have contributed to identification of a lower D-dimer threshold.

Previous studies have found that about half of the patients with PE have some degree of right ventricular compromise (25) and increased right-sided heart strain is associated with PE and syncope, as well as higher mortality (26). Among 31 PE-positive patients with COVID-19 with an available echocardiographic report, right-sided heart strain was associated with higher embolic burden. Because an estimated 25% of the pulmonary vasculature must be occluded to result in pulmonary hypertension and because acute right-sided heart failure requires more than 50% occlusion (27), it is not surprising to see higher rates of right ventricular strain in these patients, whose pulmonary vasculature is already compromised by infection. Right ventricular systolic dysfunction was previously reported in patients with COVID-19 without PE (28,29) due to the release of vasoactive mediators, such as serotonin, thromboxane, and histamine, in response to the acute hypoxic injury and platelet-rich clots (30), which may also contribute to right-sided heart strain in these patients.

The main limitation of this study was the retrospective data collection, which made it difficult to control for factors influencing the outcomes. These factors include severity of the disease, treatment protocols, and regular laboratory and clinical data collection. Furthermore, inclusion of only those patients undergoing imaging for suspected PE might not reflect the true incidence of PE in hospitalized patients with COVID-19. Several variables were excluded from the random forest analysis (including partial pressure of oxygen, erythrocyte sedimentation rate, and interleukin-6, C-reactive protein, brain natriuretic peptide, fibrinogen,

creatine kinase, and troponin I levels) for having more than 10% missing values; we used imputation for those with missing values below this threshold. Prophylactic anticoagulation may have influenced the D-dimer level in patients suspected of having PE. Furthermore, because of the limited data on prophylactic anticoagulation dosage and a lack of randomization in treatment assignment, our analysis of the effect of prophylactic anticoagulation dosage is limited. Finally, lack of echocardiography within 24 hours in all PE-positive patients prevented us from calculating incidence of right-sided heart strain among all patients.

In conclusion, our results indicate a high incidence of pulmonary embolism (PE) in hospitalized patients with COVID-19 undergoing CT pulmonary angiography or perfusion scintigraphy, which is even higher in men and smokers. A D-dimer level greater than 1600 ng/mL (8.761 nmol/L) is useful in the identification of patients likely to have PE. Right ventricular strain was associated with higher embolic burden.

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