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### Acute Pulmonary Embolism and COVID-19

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## Acute Pulmonary Embolism and COVID-19

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**Summary Statement:** Risk factors for pulmonary embolism in COVID-19 patients include obesity, an elevated D-dimer, elevated CRP and a rising D-dimer over time.

Thrombotic complications in patients diagnosed with COVID-19 are emerging as important sequelae that contribute to significant morbidity and mortality<sup>1,2</sup>. Pulmonary embolism (PE), deep vein thrombosis, ischemic stroke and myocardial infarction are examples of complications described in patients with increasing frequency<sup>1,2</sup>. Recent publications propose excessive inflammation, hypoxia, immobilization and diffuse intravascular coagulation in the setting of COVID-19 infection as contributors to a prothrombotic state<sup>2,4</sup>. The purpose of this study was to evaluate the clinical characteristics of COVID-19 patients that developed pulmonary embolism and compare their inflammatory markers, D-dimer values and outcomes.

## **Materials and Methods**

IRB approval and waived informed consent was obtained for this retrospective analysis. All chest exams performed in a single health system across multiple hospitals from March 16, 2020 to April 18, 2020 were obtained from the Picture Archiving and Communication System (PACS) database. From this list, patients with pulmonary CT angiography were identified; those who had positive Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) on nasopharyngeal swab formed the study population (Figure 1). The RT-PCR test was developed in-house by the Clinical Microbiology Laboratory with Federal Drug Agency's Emergency Use Authorization. All pulmonary CT angiography studies were initially read by fellowship trained thoracic or abdominal radiologists, or emergency radiologists, all with 2-40 years of experience. The radiology reports for these examinations were reviewed to determine the presence or absence of PE. CT studies that were limited by respiratory motion or poor contrast opacification were excluded. In addition, nine patients positive for COVID-19 had two pulmonary CT angiograms during their admission, and only the most recent CT and respective laboratory values were included in data analysis. Patient charts were reviewed for demographic, laboratory and clinical outcome variables. Laboratory values that were obtained within two days of the pulmonary CT angiogram were utilized in data analysis. If a patient was found to have a PE on a pulmonary CT angiogram performed greater than two days after admission, the admission values and values just prior to the CT were recorded to evaluate for absolute change. Simplified pulmonary embolism severity index (PESI) scores were calculated based upon clinical variables.

Wilcoxon two-sample test was utilized to analyze continuous variables and Pearson Chi-squared test was used for nominal variables. Logistic regression was used to generate AUC estimates. Sensitivity and specificity were chosen based on values that maximized sum over all possible cut points. A forward stepwise logistic regression with a 0.05 alpha value required for inclusion was used to determine a multivariate model. Demographic and laboratory values listed in the footnote of Table 2 were considered for inclusion. The final model included the smallest set of variables where each met the significance criteria and included hypertension, history of PE, BMI > 30 kg/m<sup>2</sup>, statin therapy and D-dimer prior to pulmonary CT angiography. Odds ratios were calculated for each variable while adjusting for other variables in the multivariate model.

## **Results**

During a one-month period, 328 patients positive on COVID-19 RT-PCR testing underwent pulmonary CT angiography. Of these, 72/328 (22%, 95%CI 18-27%) were found to have a PE (Figure 1). Demographic results are depicted in Table 1. Patients with a BMI greater than 30 kg/m<sup>2</sup> were seen more frequently in the PE group compared to the non-PE group (58% vs. 44%, p-value .05; example Figure 2). Fewer patients with PE were on statin therapy prior to

admission compared to the non-PE cohort (27% vs 46%, p-value 0.005). There was no significant difference in age, gender, ethnicity or history of cardiopulmonary disease, such as congestive heart failure (CHF) or chronic obstructive pulmonary disease (COPD). Laboratory values obtained prior to pulmonary CT angiography and absolute change in laboratory values from admission to just prior to pulmonary CT angiography within two days are depicted in Table 1. Mean D-dimer, obtained within two days of pulmonary CT angiography, was higher in the PE positive group relative to the PE negative group (9.33  $\mu\text{g/ml}$  vs. 2.54  $\mu\text{g/ml}$ , p-value 0.001). Mean C-reactive protein (CRP), obtained within two days of pulmonary CT angiography, was also higher in the PE positive group compared to the PE negative group (10.0 mg/dl vs. 7.4 mg/dl, p-value 0.01). Oxygen requirements, measured in liters/minute in non-intubated patients within four hours prior to pulmonary CT angiography, was higher in the PE group than the non-PE group (4.3 vs. 2.7, p-value 0.007).

In the pulmonary embolism group, the location of the PE was recorded with respect to the most proximal embolus. Distribution is as follows: 51% (37/72) segmental PE, 31% (22/72) lobar PE, 13% (9/72) central PE and 5.5% (4/72) subsegmental PE. CT evidence of right heart strain was documented in 11% (8/72) of patient reports. Average simplified pulmonary embolism severity index was  $1.2 \pm 0.70$ . Of the 72 patients that developed a PE, 51% were diagnosed in the emergency department. 28/122 (23%) of all patients that were on venous thromboprophylaxis developed a PE. Rate of intubation in patients admitted to the ICU was 65% in the PE group versus 67% in the non-PE group (p-value 0.89). Mean intubation time was  $10.2 \pm 6.6$  days in PE patients and  $10.1 \pm 7.9$  days in non-PE patients (p-value 0.73). No statistically significant difference in ICU admission or death was found between the PE and non-PE cohorts.

A multivariate model was developed to predict PE, and odds ratios for statistically significant results are depicted in Table 2. Patients taking statin therapy prior to admission had an adjusted multivariate odds ratio of 0.4 (CI 0.23, 0.75; p-value 0.005) for developing a PE. Patients with a BMI  $>30 \text{ kg/m}^2$  had an adjusted multivariate odds ratio of 2.7 (95% CI 1.3- 5.5; p-value 0.006) for developing a PE. An increase in D-dimer of 6  $\mu\text{g/ml}$  had an odds ratio of 4.8 (CI 3.2, 7.2; p-value 0.001) for developing a PE. The multivariate model had an AUC of 0.86 (0.81, 0.91). Sensitivity and specificity for a D-dimer of 3.11  $\mu\text{g/ml}$  was 78% and 81% respectively for development of PE with an AUC of 0.85.

## Discussion

Respiratory tract infection is a known risk factor in development of pulmonary embolism in hospitalized patients<sup>6</sup>. In recently published studies, the incidence of PE in COVID-19 patients who had pulmonary CT angiography performed was reported to be between 23-30%, which is similar to our rate of 22%<sup>7,8</sup>. Our patient population is unique when compared to recently published studies. There were a greater number of African Americans and obese patients in our demographic distribution. In our study, patients with a BMI  $>30 \text{ kg/m}^2$  were 2.7 times more likely to develop a PE, which has not been previously described. Recent literature suggests that obesity in COVID-19 is associated with more severe disease<sup>9</sup>. We found that COVID-19 patients on statin therapy prior to admission are less likely to develop a PE. Statins have been previously described to be associated with decreased rates of venous thromboembolism, as well as decrease the risk of recurrent PE<sup>10,11</sup>.

In our study, we found a significant difference in CRP and D-dimer between PE positive and PE negative groups, which may suggest that COVID-19 positive patients with higher levels of inflammation and D-dimer values are more susceptible to developing pulmonary embolism. In addition, we found that non-intubated patients who developed PE required more oxygen prior to pulmonary CT angiography evaluation than their non-PE counterparts.

We did not find a significant difference in ICU admissions, requirement for intubation or duration of intubation between patients who developed PE and those that did not. In fact, 72% of PEs were diagnosed in patients who did not require ICU level care. This is in sharp contrast to a recently published study highlighting PE to be associated with ICU admission and mechanical ventilation<sup>7</sup>. Our results suggest that even patients who do not have severe enough illness to qualify for ICU care can develop acute pulmonary embolism.

Limitations of our study include its retrospective nature and restriction to a single health system. Our study, in conjunction with recent and future studies, may prompt early evaluation with pulmonary CT angiography in COVID-19 patients who are at increased risk for developing pulmonary embolism based on demographic, clinical and laboratory variables<sup>8,9,13</sup>.

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**Table 1:** Demographic, outcome and laboratory variables

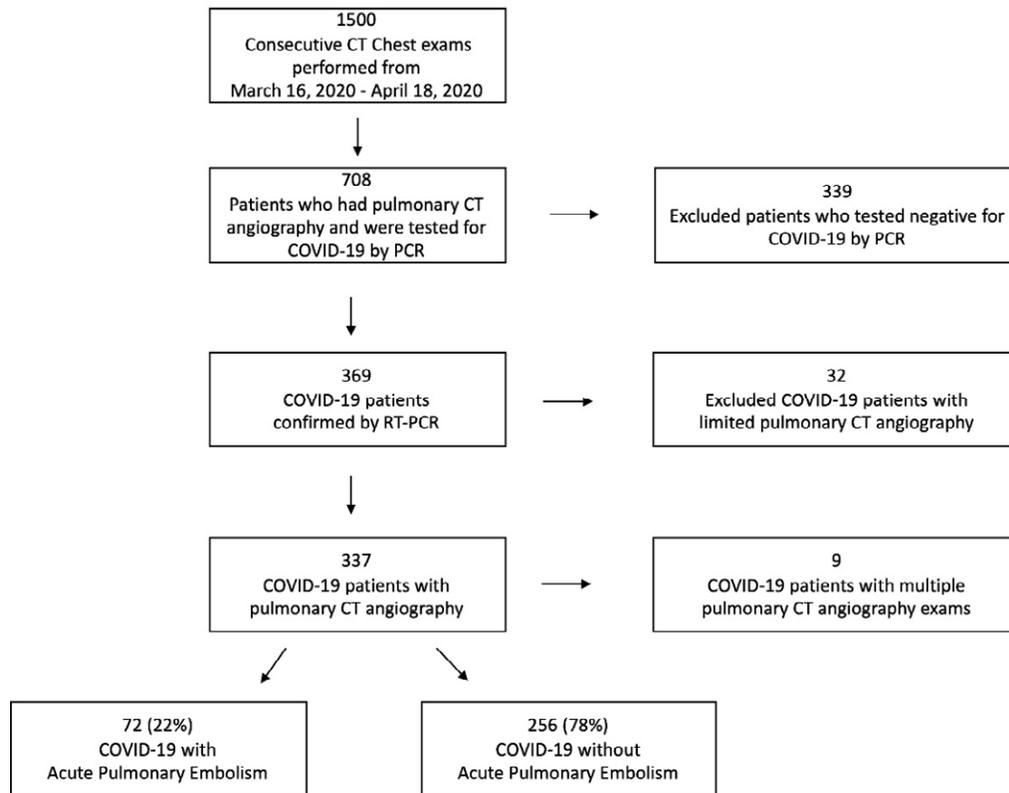
	No PE (N = 256)	PE (N=72)	P-value
Age in years (SD)	62 (16)	59 (15)	0.20
Male (%)	45	49	0.54
<b>BMI &gt; 30 kg/m<sup>2</sup> (%)</b>	<b>44</b>	<b>58</b>	<b>0.05</b>
African American (%)	58	56	0.60
Cancer History (%)	14	13	0.73
Surgery within 4 weeks (%)	1	3	0.20
PE/DVT History (%)	7	11	0.32
Smoking (%)	40	28	0.07
Diabetes (%)	38	40	0.76
Hypertension (%)	61	57	0.58
<b>Statin Therapy (%)</b>	<b>46</b>	<b>27</b>	<b>0.005</b>
COPD (%)	13	7	0.17
CHF (%)	9	4	0.19
<b>Oxygen Requirements average L/min (SD)</b>	<b>2.7 (3.5)</b>	<b>4.3 (5.4)</b>	<b>0.007</b>
Length of Stay in days (SD)	9.0 (8.0)	9.4 (7.5)	0.73
ICU Admission (%)	25	25	0.59
Required Intubation (%), (n)	67 (42/63)	65 (13/20)	0.89
Death (%)	10	6	0.23
<b>D-dimer mg/ml (SD) N=245</b>	<b>2.54 (3.67)</b>	<b>9.33 (7.00)</b>	<b>0.001</b>
Ferritin ng/ml (SD) N=224	781 (925)	676 (600)	0.38
LDH IU/L (SD) N=223	344 (121)	391 (189)	0.06
<b>CRP mg/dl (SD) N=225</b>	<b>7.4 (6.8)</b>	<b>10.0 (9.0)</b>	<b>0.01</b>
<b>Δ D-dimer mg/ml (SD) N=80</b>	<b>1.33 (4.22)</b>	<b>5.61 (7.49)</b>	<b>0.001</b>
Δ Ferritin ng/ml (SD) N=79	-108 (949)	-178 (496)	0.69
Δ LDH IU/L (SD) N=79	-50 (252)	-22 (173)	0.57
Δ CRP mg/dl (SD) N=78	-5.1 (9.6)	-13.1 (40.7)	0.23

Note.—Demographic, outcome and laboratory variables. D-dimer, ferritin, LDH and CRP laboratory values were obtained within two days of the pulmonary CT angiogram. Absolute change in laboratory values was calculated based on laboratory values obtained within two days of pulmonary CT angiography and laboratory values obtained on admission if these laboratory values were obtained at least two days apart. PE: Pulmonary Embolism, SD: Standard Deviation, DVT: Deep Venous Thrombosis, ICU: Intensive Care Unit.

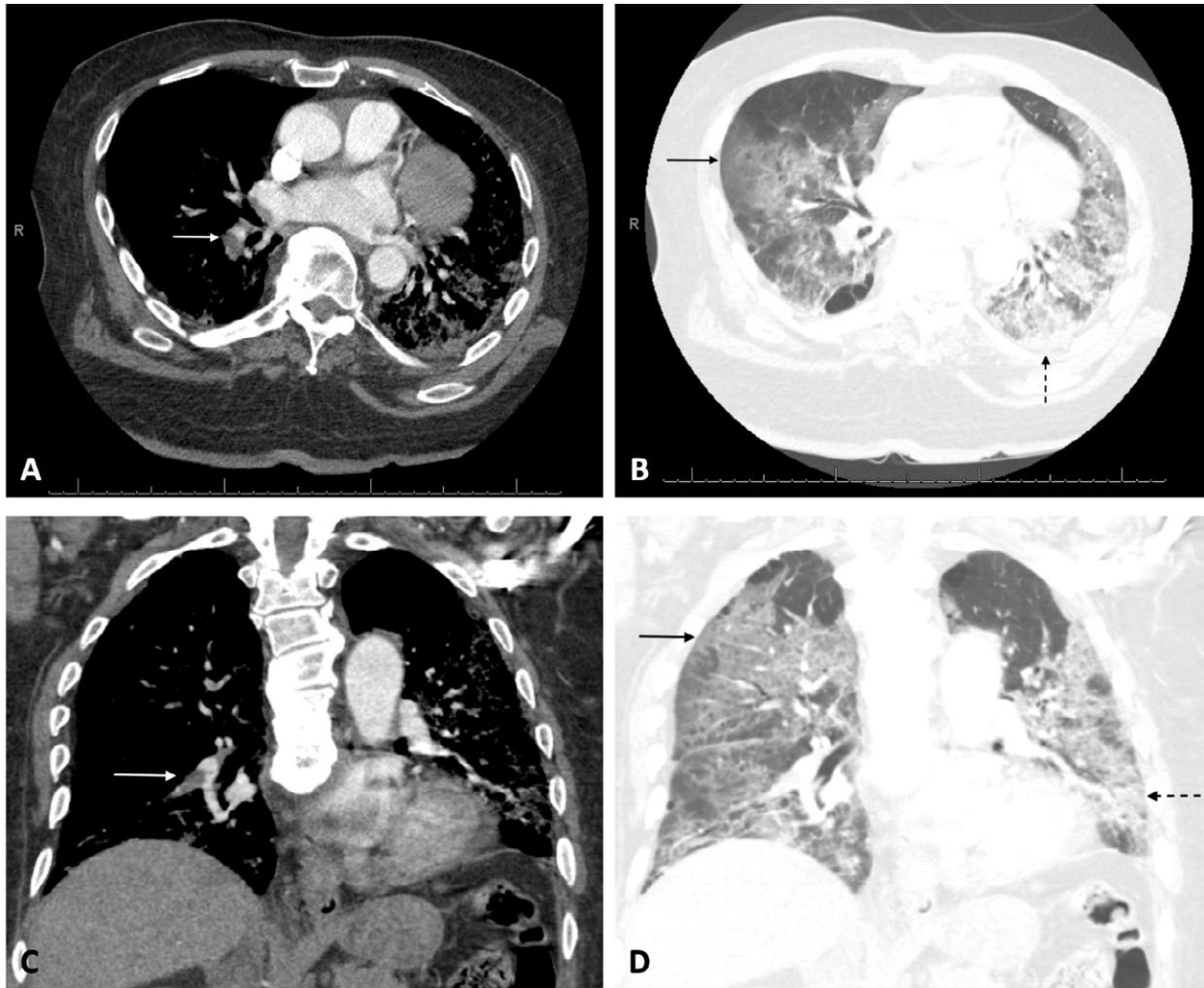
**Table 2:** Multivariate model demonstrating adjusted odds ratios of statistically significant variables with confidence intervals (CI).

	<b>Odds Ratio (95% CI)</b>	<b>P-value</b>
<b>BMI &gt; 30 kg/m<sup>2</sup></b>	<b>2.7 (1.3, 5.5)</b>	<b>0.006</b>
<b>D-dimer (increase by 6 mg/ml )</b>	<b>4.8 (3.2, 7.2)</b>	<b>0.001</b>
<b>Statin Therapy</b>	<b>0.4 (0.2, 0.8)</b>	<b>0.005</b>
<b>History of PE</b>	<b>3.5 (1.2, 10.5)</b>	<b>0.02</b>
<b>Hypertension</b>	<b>0.5 (0.2, 1.0)</b>	<b>0.04</b>

Note.—Multivariate model demonstrating adjusted odds ratios of statistically significant variables with confidence intervals (CI). Nonsignificant variables considered for inclusion included age, gender, race, previous history of cancer, previous surgery within 4 weeks, a prior PE, smoking history, presence of diabetes, COPD, CHF, oxygen requirements, ferritin, LDH, CRP, and platelets.



**Figure 1:** Flowchart depicting patient population. Limited pulmonary CT angiography was defined by respiratory motion and poor contrast opacification. Nine COVID-19 positive patients had multiple pulmonary CT angiograms and only the most recent study was utilized as a reference point in analysis.



**Figure 2:** Axial (A, B) and coronal (C, D) pulmonary CT angiography images of a 76-year-old African American male with a BMI of 37 kg/m<sup>2</sup> who required admission to the medical intensive care unit for acute respiratory failure secondary to COVID-19 confirmed by RT-PCR. Pulmonary CT angiography was obtained four days after admission and demonstrates acute pulmonary embolism in the right lower lobar pulmonary artery (white arrows), bilateral ground glass opacities (black arrows) and consolidation (dashed arrows).