Radiology: Cardiothoracic Imaging

ORIGINAL RESEARCH

Pulmonary Embolism at CT Pulmonary Angiography in Patients with COVID-19

Mark Kaminetzky, MD • William Moore, MD • Kush Fansiwala, BA • James S. Babb, PhD • David Kaminetzky, MD • Leora I. Horwitz, MD, MHS • Georgeann McGuinness, MD • Abraham Knoll, MD • Jane P. Ko, MD

From the Department of Radiology (M.K., W.M., K.F., J.S.B., G.M., J.P.K.), Department of Medicine, Division of Hematology and Medical Oncology, Laura and Isaac Perlmutter Cancer Center (D.K.), and Center for Healthcare Innovation and Delivery Science (L.I.H.), NYU Langone Health, 550 First Ave, New York, NY 10016; Division of Healthcare Delivery Science, Department of Population Health and Division of General Internal Medicine and Clinical Innovation, Department of Medicine, NYU Grossman School of Medicine, New York, NY (L.I.H.); and Garden State Urology, Wayne, NJ (A.K.). Received May 14, 2020; revision requested May 27; revision received June 5; accepted June 26. **Address correspondence to** M.K. (e-mail: *Mark.kaminetzky@nyumc.org*).

Conflicts of interest are listed at the end of this article.

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Purpose: To evaluate pulmonary embolism (PE) prevalence at CT pulmonary angiography in patients testing positive for coronavirus disease 2019 (COVID-19) and factors associated with PE severity.

Materials and Methods: A retrospective, single-center study evaluated 62 patients who tested positive for COVID-19 who underwent CT pulmonary angiography between March 13 and April 5, 2020. Another 62-patient cohort who underwent CT pulmonary angiography before the first reported local COVID-19 case was retrospectively selected. The relative rate of CT pulmonary angiography positivity was recorded. For the COVID-19 positive cohort, comorbidities, laboratory values, clinical outcome, and venous thrombosis of the patients were recorded. Two thoracic radiologists assessed embolic severity using the Mastora system and evaluated right heart strain. Factors associated with PE and arterial obstruction severity were evaluated by using statistical analysis. A P value $< .05$ was considered significant.

Results: Of the patients testing positive for COVID-19, 37.1% had PE, higher than 14.5% of pre-COVID-19 patients ($P = .007$). D-dimer levels closest to CT pulmonary angiography date correlated with the Mastora obstruction score. Receiver operating characteristic analysis identified optimal sensitivity (95%) and specificity (71%) for PE diagnosis at 1394 ng/mL D-dimer units. The mean D-dimer level was 1774 ng/mL and 6432 ng/mL D-dimer units in CT pulmonary angiography–negative and CT pulmonary angiography–positive subgroups, respectively ($P < .001$). One additional patient with negative results at CT pulmonary angiography had deep venous thrombosis, thus resulting in 38.7% with PE or deep venous thrombosis, despite 40% receiving prophylactic anticoagulation. Other factors did not demonstrate significant PE association.

Conclusion: A total of 37.1% of COVID-19 patients underwent CT pulmonary angiographic examinations diagnosing PE. PE can be a cause of decompensation in patients testing positive for COVID-19, and D-dimer can be used to stratify patients in terms of PE risk and severity.

Supplemental material is available for this article.

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2, began to spread in December 2019 and reached pandemic levels by March 2020 (1). Current guidelines from the American College of Radiology and the Centers for Disease Control do not support routine screening for COVID-19 with imaging; rather, nasopharyngeal or oropharyngeal swab for viral RNA testing is the recommended confirmatory test. This perspective is based on the literature that demonstrates that chest CT may be falsely negative in the early stages of the disease, with chest CT reserved for the evaluation of complications (2,3).

Hypercoagulability has been reported in patients who have COVID-19, with increased mortality associated with elevated serum thrombogenic proteins such as D-dimer (4). In fact, patients with severe COVID-19 who were empirically treated with low-molecular weight heparin had a lower 28-day mortality compared with similarly ill patients who were not treated with low-molecular weight heparin (5,6). This raises the question of whether thrombotic and embolic events worsen the patient's clinical status.

In particular, there is a heightened awareness of pulmonary embolism (PE) in patients who have COVID-19, which would diminish the already compromised pulmonary function and capacity. Currently, a few case series (7–11), clinical reports (12,13), and recent radiology research report letters in European cohorts have been published on PE, which is diagnosed using CT pulmonary angiography (14,15). Many acutely ill and hospitalized patients who have COVID-19 have multiorgan failure and possibly acute kidney injury (16), and decisions as to whether CT pulmonary angiography is performed take into consideration both the potential risk of nephrotoxicity from intravenous contrast material administration and the benefit of diagnosing PE.

Therefore, an understanding of the frequency of PE and the relationship between D-dimer levels and the degree of pulmonary artery obstruction may aid in the diagnosis and

Abbreviations

COVID-19 = coronavirus disease 2019, DDU = D-dimer units, DVT = deep venous thrombosis, ESR = erythrocyte sedimentation rate, ICU = intensive care unit, LV = left ventricular, PE = pulmonary embolism, RV = right ventricular

Summary

Patients with confirmed COVID-19 had pulmonary embolism diagnosed in 37% of CT pulmonary angiographic examinations with D-dimer levels associated with the presence of pulmonary embolism and the degree of pulmonary artery obstruction.

Key Points

- CT pulmonary angiography was positive for pulmonary embolism in 37% of patients with COVID-19.
- D-dimer levels directly correlate with the presence and extent of pulmonary embolism as indicated by the Mastora index and can be used to risk stratify patients for pulmonary embolism work-up.

management of this disease in patients who have COVID-19. Our objective was to determine the prevalence of PE in CT pulmonary angiography studies in a U.S. cohort of patients who have COVID-19 and identify clinical features associated with a positive CT pulmonary angiography examination, pulmonary artery obstruction severity, and outcomes.

Materials and Methods

The study was approved for an exemption by the institutional review board. Written informed consent was waived by the institutional review board. The study was a Health Insurance Portability and Accountability Act–compliant retrospective review of pertinent clinical and imaging data on consecutive CT pulmonary angiography studies at NYU Langone Health and affiliated hospitals. Two cohorts are detailed below.

General Methods

This is a single-institution retrospective study in which the radiology information system was queried (Primordial; Nuance Communications, Burlington, Mass) by a radiology resident (M.K.) using the search terms "pulmonary embolism" to identify CT pulmonary angiography examinations performed between March 13 and April 5, 2020. The electronic medical record (Epic, Verona, Wis) for these patients was reviewed to identify those who had COVID-19 infection confirmed by coronavirus polymerase chain reaction of nasopharyngeal or oropharyngeal swab samples. Only the patients who tested positive for COVID-19 with polymerase chain reaction testing were included in the study sample. All patients included in the study were 18 years of age or older. Those with technically inadequate CT studies by review of radiology reports (Fig 1) were excluded. This resulted in a cohort that comprised 62 patients who had COVID-19 who had CT pulmonary angiography result of PE (CT pulmonary angiography positive) and without PE (CT pulmonary angiography negative).

In the COVID-19–positive confirmed patient cohort, sex, age, CT pulmonary angiography indication, and comorbidity parameters of preexisting hypertension, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, and smoking history were recorded by review of medical records. Pertinent laboratory values were collected, including D-dimer level at admission and on the date closest to the CT pulmonary angiography examination, erythrocyte sedimentation rate (ESR), C-reactive protein level, coagulation markers (prothrombin time, international normalized ratio, and partial thromboplastin time), and platelet count. D-dimer test was ordered at physician discretion. The time from symptom onset to admission/emergency department visit, need for ventilator support, and clinical outcome were documented for each patient. The time between the D-dimer test closest to CT pulmonary angiography study and the imaging examination was calculated, in addition to any change in D-dimer level between admission and that closest to the CT pulmonary angiography. The use of any prophylactic or therapeutic anticoagulation was collected, and the date of initiation was recorded if initiated during the current hospitalization. Prophylactic anticoagulation was typically either subcutaneous enoxaparin (40–60 mg according to body mass index) or subcutaneous heparin. Therapeutic anticoagulation was typically subcutaneous enoxaparin (1 mg/kg) twice daily or intravenous heparin. Clinical outcomes at the time of medical record review were identified: 1 = discharged, 2 = improved as indicated by decreasing oxygen requirement, 3 = not improved or clinically worsening as evidenced by increasing oxygen requirement, or 4 = expired. Any venous US examinations to evaluate deep venous thrombosis (DVT) in addition to echocardiograms obtained within 48 hours of the CT pulmonary angiography to assess right heart strain and pulmonary hypertension were identified. The presence of right heart strain on a pre-existing echocardiogram was assessed for patients who had COVID-19 and were CT pulmonary angiography positive. The presence of other thrombotic events was recorded for the same hospitalization or outpatient encounter: ischemic stroke, intracerebral venous and arterial thrombosis, abdominal thrombosis, and peripheral vascular arterial thrombosis. In addition, the clinical setting in which the CT pulmonary angiography was ordered was documented.

A second cohort of the same number of patients who underwent CT pulmonary angiography examinations just before March 1, 2020 (the date of the first documented case of COVID-19 infection in New York) was identified retrospectively and sequentially (pre–COVID-19) for comparison of CT pulmonary angiography positivity rate with our COVID-19 positive cohort. The same search term of "pulmonary embolism" was used, and all included patients were aged 18 years and older. Of the 62 patients, one CT pulmonary angiography was excluded given the study was reported as nondiagnostic. Sex, age, comorbidities, patient setting of CT pulmonary angiography, clinical indication for CT pulmonary angiography, DVT at US, and clinical outcomes were collected.

Image Data

Chest CT pulmonary angiography protocol at our institution entailed intravenous administration of 300 mg/mL of iodinated contrast material at 3–5 mL/sec with timing optimized for the pulmonary artery using bolus tracking and automatic triggering. Imaging was performed after a small suspended

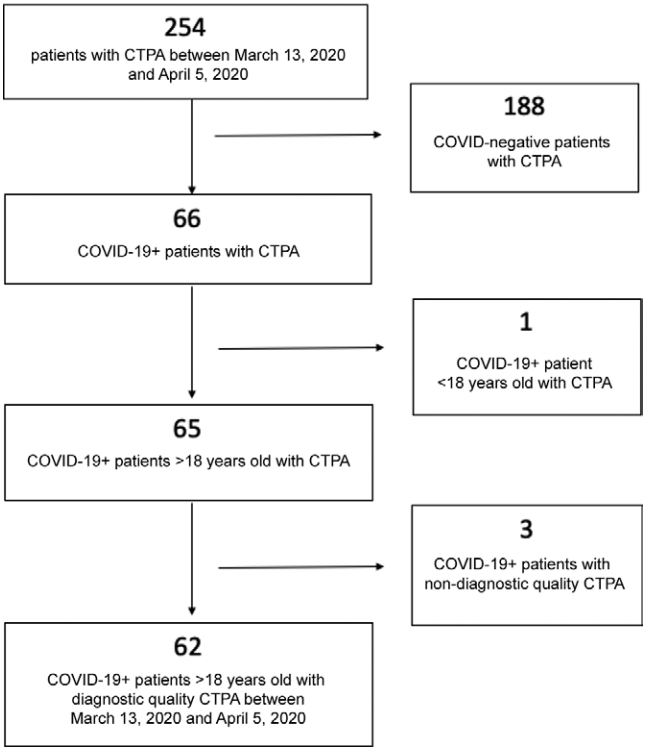


Figure 1: CT pulmonary angiographic cases in patients with COVID-19.

breath hold. Detector-row configuration of multidetector CT scanners ranged from 64 to 128 × 0.6. Dual-energy CT technique entailed dual-source configuration using 100 kVp (A tube)/150 kVp (B tube) and ref mAs of 130 (A tube)/100 (B tube), and single energy CT pulmonary angiography used either 100 or 120 kVp with ref mAs of 147 and 130 mAs, respectively. Gantry rotation times were 0.28–0.5 sec. Reconstructions included 1-mm and 2-mm axial soft-tissue sections and coronal and sagittal reformats.

Two board-certified thoracic radiologists with 16 (W.M.) and 22 (J.P.K.) years of experience in thoracic imaging independently reviewed the anonymized CT pulmonary angiography–positive examinations on clinical picture archive and communication system monitors. They graded the image quality of the CT pulmonary angiography examination that was scored ordinally as 1 = diagnostic optimal, 2 = diagnostic adequate, 3 = diagnostic limited, and 4 = nondiagnostic. The degree of pulmonary obstruction was assessed using the Mastora obstruction scoring system (17), grading each of the following vessels for the degree of obstruction (1 = <25%, 2 = 25%–49%, 3 = 50%–74%, 4 = 75%–99%, and 5 = 100%): main pulmonary artery, right pulmonary artery, left pulmonary artery, both interlobar arteries, lobar arteries, and segmental pulmonary arteries. Discrepancies were resolved by consensus between the two radiologists. For each patient, a total score was generated by summing the obstruction score of every vessel evaluated, and an obstruction ratio for all arteries was generated by dividing the total score for each patient by the maximum possible score of 155 (ObstTotRatio). An obstruction ratio for central arteries only (main pulmonary artery, right pulmonary artery, left pulmonary artery, interlobar arteries, and lobar arteries (ObstCenRatio) was achieved by dividing the sum of the scores for these vessels by the maximum possible score of 55. For all patients who had COVID-19, the extent of pulmonary opacities attributed to COVID-19 was assessed by the radiology readers using an adaptation of a scoring system (18); each of six lobes (left upper lobe, lingula, left lower lobe, and the right upper, middle, and right lower lobes) were scored in terms of the percentage of the lobe involved in COVID-19–related lung abnormalities (0 = 0%, 1 = <25%, 2 = 25% to < 50%, 3 = 50% to < 75%, 4 = 75%–100%). The proportion of the parenchyma involved in abnormalities (COVIDLungRatio) was achieved by dividing the sum of all scores by a maximal possible score of 24. The presence or absence of consolidation was recorded and confirmed by consensus.

The readers assessed the presence of a focally dilated subsegmental vessel (vascular enlargement) within an area of ground-glass or consolidative opacity in a lung region supplied by PE. This finding was defined as an area in which a vessel became focally dilated, in comparison with the area just proximal to the region and in comparison with other vessels at a similar branching level in the pulmonary arterial tree. Vascular enlargement was also assessed in ground-glass areas in the parenchyma not involved in PE. The presence of right heart strain at CT, as indicated by the right ventricular (RV)/left ventricular (LV) ratio > 1, contrast reflux into the inferior vena cava to the hepatic veins and coronary sinus, and the degree of septal bowing toward the LV, was recorded. For the RV/LV ratio, the maximal dimensions of the RV and LV chambers were obtained by measuring perpendicularly from the inner aspect of the free wall to the inner aspect of the interventricular septum (19). Consensus was obtained for discrepancies between the two readers. If either the CT pulmonary angiography or the echocardiography demonstrated right heart strain, the patient was considered as positive for right heart strain.

Statistical Analysis

Patients who were CT pulmonary angiography positive and those who were CT pulmonary angiography negative were compared in terms of binary factors using a Fisher exact test and in terms of ordinal and numeric factors using an exact Mann-Whitney test. For each binary feature including the presence of comorbidities, smoking history, mechanical ventilatory support, and DVT, the Fisher exact test compared the proportions within the CT pulmonary angiography–positive and CT pulmonary angiography–negative groups. For each numeric feature (age, laboratory values, time from symptoms to admission/emergency department visit, and COVIDLungRatio), the mean, standard deviation, median, and interquartile range for patients with positive CT pulmonary angiography and those with negative CT pulmonary angiography were compared using the exact Mann-Whitney test. A Fisher exact test was used to identify differences in CT pulmonary angiography and DVT positivity rate between the COVID-19–positive cohort and the pre-COVID-19 cohort. The cohorts were also compared in terms of clinical features with the Fisher exact test and Mann-Whitney test.

Table 1: Clinical Characteristics of Patients with COVID-19 Who Had Diagnostic Chest CT Pulmonary Angiography and Differences in Clinical Features Between Patients with Positive and Negative CT Pulmonary Angiography

Clinical Characteristic	All Patients (*n* = 62)	CT Pulmonary Angiography Negative (*n* = 39)	CT Pulmonary Angiography Positive (*n* = 23)	*P* Value*
Sex				
Female	35.5 (22/62)	35.9 (14/39)	34.8 (8/23)	>.99
Male	64.5 (40/62)	64.1 (25/39)	65.2 (15/23)	>.99
Comorbidities				
COPD	6.5 (4/62)	7.7 (3/39)	4.3 (1/23)	>.99
Diabetes	30.6 (19/62)	41.0 (16/39)	13.0 (3/23)	.025*
Hypertension	35.5 (22/62)	43.6 (17/39)	21.7 (5/23)	.104
CAD	3.2 (2/62)	5.1 (2/39)	0.0 (0/23)	.525
Smoking history	34.6 (18/52)	38.7 (12/31)	28.6 (6/21)	.558
DVT at US	53.3 (8/15)	25.0 (1/4)	63.6 (7/11)	.282
Clinical outcome				
Mechanical ventilation	12.9 (8/62)	12.8 (5/39)	13.0 (3/23)	>.99
Discharged	53.2 (33/62)	59.0 (23/39)	43.5 (10/23)	.296
Improved	17.7 (11/62)	15.4 (6/39)	21.7 (5/23)	.732
Worsened	17.7 (11/62)	12.8 (5/39)	26.1 (6/23)	.302
Died	11.3 (7/62)	12.8 (5/39)	8.7 (2/23)	>.99

Note.—Data are presented as percentages, with raw data in parentheses, unless otherwise specified. CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, DVT = deep venous thrombosis.
*$P < .05$ was considered significant.

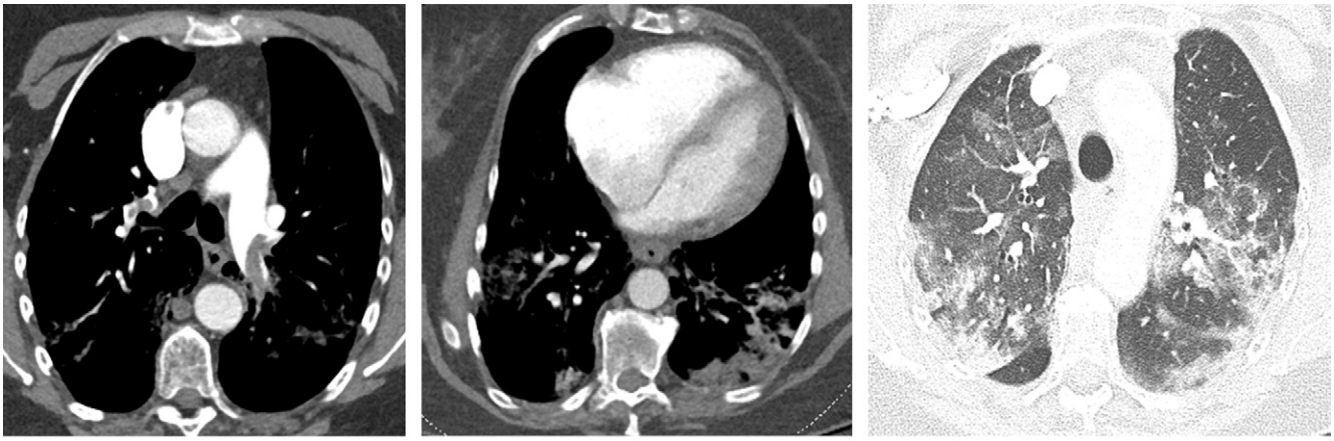
The association of numeric outcomes of RV/LV ratio (as an indicator of right heart strain), ObstCenRatio, and ObstTotRatio with numeric clinical features was performed using Spearman correlation. For binary factors, an exact Mann-Whitney test was used to compare those with and without the factor for numeric outcomes.

For significant numeric predictors of CT pulmonary angiography positivity, the Youden index from a receiver operating characteristic analysis was used to identify a threshold that was optimal for the detection of patients with positive CT pulmonary angiography with sensitivity and specificity calculated. Additional thresholds were investigated for significant factors, such as D-dimer level based on clinical knowledge of >500 and >2000 ng/mL D-dimer units (DDU). A *P* value of < .05 was considered statistically significant. Statistical analysis was performed using software (version 9.4, SAS Institute, Cary, NC).

Results

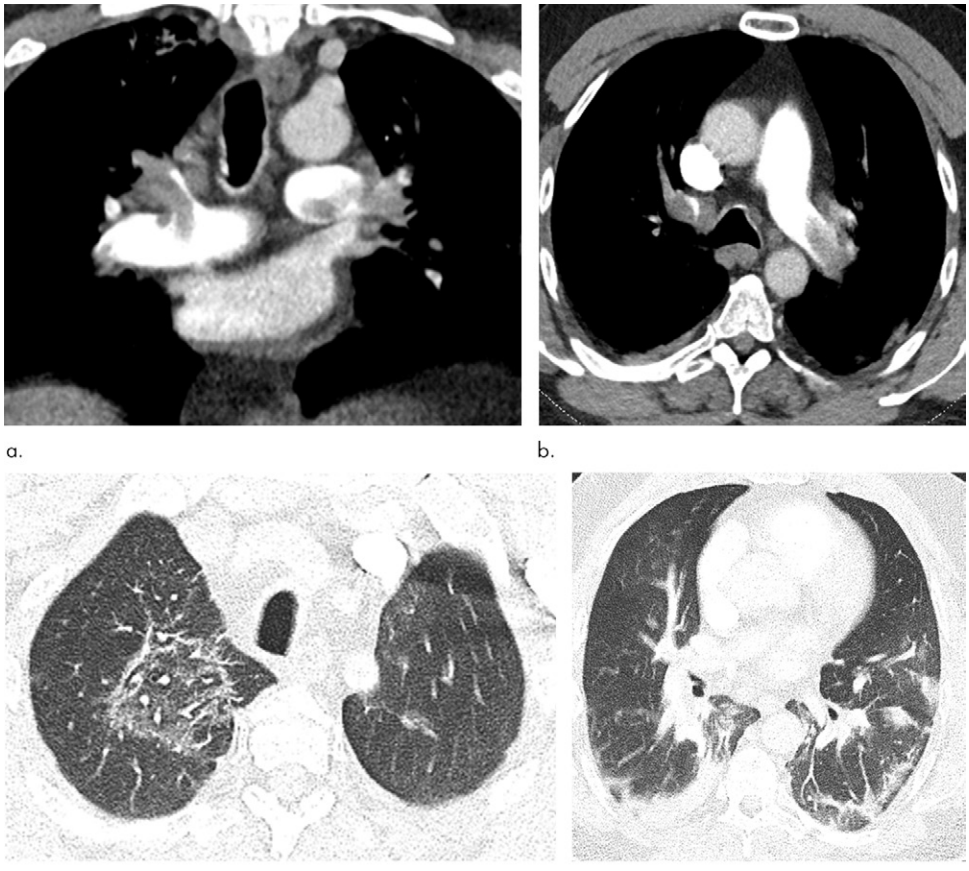
The COVID-19–positive cohort was composed of 62 patients with 40 men and 22 women, with a mean age of 57.8 years ± 13.9 (standard deviation) (range, 28–89 years) with men having a mean age of 55.5 years ±13.6 and women with a mean age of 61.9 years ± 13.8 (Table 1). In the COVID-19–positive cohort, 23 of 62 (37.1%) CT pulmonary angiography studies were positive for PE (Figs 2, 3). Diabetes, hypertension, and smoking history were identified in 30.6% (19/62), 35.5% (22/62), and 34.6% (18/52) of patients (Table 1), respectively. In terms of CT pulmonary angiography–positive and CT pulmonary angiography–negative COVID-19–positive cohorts (Table 1), patients with diabetes had a lower proportion of CT pulmonary angiography–positive examinations (*P* = .025). No significant difference was identified between sex, other investigated comorbidities, DVT at US, smoking history, and clinical outcome between CT pulmonary angiography–positive and CT pulmonary angiography–negative patients who had COVID-19 (Table 1). The first provided clinical indication for the CT pulmonary angiography study order or documented indication in the medical record for the 62 patients who had COVID-19 was as follows: hypoxia in 17 (27%), respiratory distress in 16 (26%), elevated D-dimer level in 14 (23%), tachycardia in seven (11%), chest pain in four (6.5%), extremity swelling in one (1.6%), and any other indication not specified above in three (4.8%). In the COVID-19–positive cohort, CT pulmonary angiography examinations were ordered in patients in the emergency department in 31 of 62 (50.0%) patients, as an inpatient in 27 of 62 (43.5%) patients, and in the intensive care unit (ICU) in four of 62 (6.5%) patients.

In the COVID-19–positive cohort, 25 of 62 (40%) patients had been receiving prophylactic dose anticoagulation at the time of CT pulmonary angiography for a mean of 4.6 days ± 3.1 of prophylaxis, and PE was diagnosed in 13 of 25 (52%) patients. Furthermore, five of 62 (8.1%) patients had been receiving therapeutic dose anticoagulation at the time of CT pulmonary angiography, secondary to underlying hypercoagulable or proembolic comorbid conditions including prior diagnosis of atrial fibrillation, past history of portal vein thrombosis, past history of PE (two patients), and current deep



a. b. c.

Figure 2: A patient with COVID-19 with bilateral pulmonary emboli had a D-dimer level of >10 000 ng/mL, 4 days after admission. **(a)** Axial CT pulmonary angiographic image shows bilateral pulmonary emboli in the left main pulmonary artery and right upper lobe proximal segmental vessels. **(b)** On an image in the lower thorax, the right ventricle is larger than the left ventricle indicating right heart strain. **(c)** Bilateral parenchymal consolidative and ground-glass opacities are present with a peripheral orientation in the right upper lobe and left lower lobe superior segments. Central and peripheral ground glass in the left-upper lobe is present. ObstTotRatio was 0.568.



a. b. c. d.

Figure 3: A patient with COVID-19 with bilateral pulmonary emboli had D-dimer level of >10 000 ng/mL. **(a)** Coronal CT pulmonary angiographic image identifies bilateral pulmonary emboli that involve the left main pulmonary artery, distal right main pulmonary artery, right upper lobe pulmonary artery, and proximal segmental vessels. **(b)** On an axial CT pulmonary angiographic image, there is an embolus present in the left main and right upper lobe pulmonary arteries extending into the bilateral anterior segmental artery. ObstTotRatio was 0.674. **(c)** A ground-glass opacity is present in the right upper lobe centrally with a reversed halo appearance, peripheral dense area, and central ground-glass opacity with prominent vessels attributed to lung involvement from COVID-19. **(d)** Axial image through the lung base demonstrates basilar consolidation compatible with COVID-19.

venous thrombosis; one of these five (20%) patients was CT pulmonary angiography positive. CT PE was diagnosed in 31% (10/32) of patients who had not been receiving anticoagulation.

In the CT pulmonary angiography–positive subgroup, 8.7% (2/23) of patients (Table 1) died, while in the CT pulmonary angiography–negative subgroup, 12.8% (5/39) of patients died. Six of 23 (26.1%) CT pulmonary angiography–positive patients clinically worsened in terms of increasing degree of supplemental oxygen requirement, compared with five of 39 (12.8%) worsening cases in the CT pulmonary angiography–negative group (Table 1). The review by the two readers did not yield additional studies deemed nondiagnostic, beyond those that had been initially excluded.

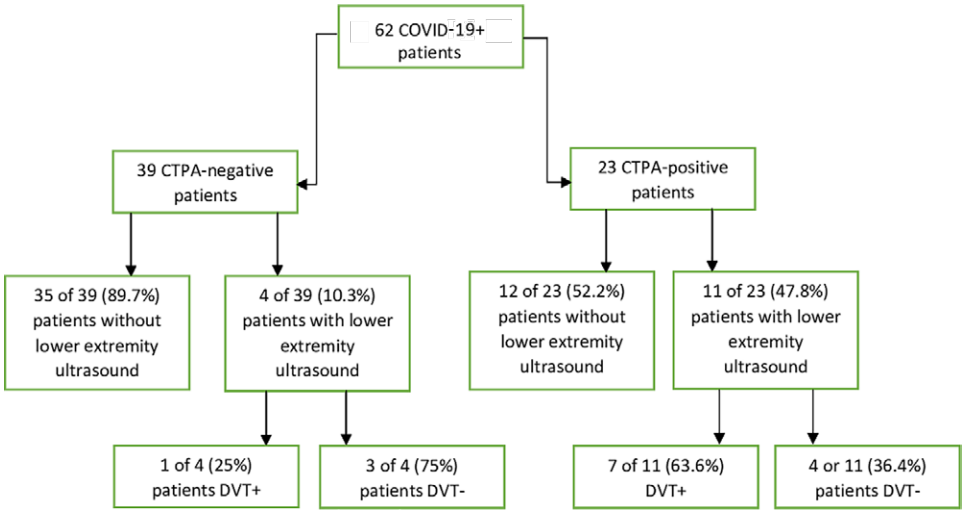


Figure 4: Patients with COVID-19 with deep venous US of the lower extremity and DVT. COVID-19+ = had COVID-19; DVT+ = Had deep venous thrombosis; DVT− = Did not have deep venous thrombosis.

In the patients who had COVID-19, 15 of 62 (24%) patients underwent venous US, and DVT was present in 53% (8/15) of the studies (Fig 4). Considering all patients who had COVID-19 with thromboembolic diagnoses (CT pulmonary angiography positive and/or DVT), 24 of 62 (38.7%) were positive, and 38 of 62 (61.3%) lacked thromboembolic diagnoses.

One of the 62 (1.6%) patients who were positive for CT pulmonary angiography in the COVID-19–positive cohort had a lower-extremity arterial thrombus demonstrated on arterial imaging during the current hospitalization. No additional thrombotic events were identified in the remaining COVID-19–positive cohort by review of the medical record including any neurologic, abdominopelvic, and extremity imaging.

The pre-COVID-19 cohort comprised 62 patients with 22 men and 40 women (mean age, 58.0 years ± 19.2; range, 21–94 years) with men having a mean age of 59.8 years ± 18.0 and women with a mean age of 57.1 years ± 20.0. In the pre-COVID-19 cohort, 41.8% (26/62) had hypertension; 27.4% (17/62) had diabetes; 17.7% (11/62) had coronary artery disease; 11.3% (7/62) had chronic obstructive pulmonary disease; and 41.8% (23/55 patients with known smoking status) had a reported smoking history (Table E1 [supplement]). Of these features, a greater percentage of patients were female (P = .002) and had coronary artery disease (P = .016) in the pre-COVID-19 cohort than the COVID-19–positive cohort (Table E1 [supplement]). Within the pre-COVID-19 cohort, CT pulmonary angiography studies were ordered in an outpatient setting in nine of 62 patients (21.4%), emergency department in 42 of 62 patients (67.7%), and an inpatient setting in 11 of 62 patients (17.7%). No patients were in the ICU at the time of CT pulmonary angiography. The indications listed first in the CT pulmonary angiography order or in the medical record for the 62 patients were respiratory distress in 23 (37%), tachycardia in 13 (21%), elevated D-dimer level in 11 (18%), lower extremity swelling in four (6.5%), hypoxia in three (4.8%), chest pain in three (4.8%), and nonspecified indication in three (4.8%) patients. Of the nine positive CT pulmonary angiography examinations in this cohort, 66.7% (6/9) were men; 55.6% (5/9) had hypertension; 33.3% (3/9) had diabetes; 11.1% (1/9) had coronary artery disease; 22.2% (2/9) had chronic obstructive pulmonary disease; and 71.4% (5/7 patients with known smoking status) had a reported smoking history. Two patients from the pre-COVID-19 cohort died, and one was CT pulmonary angiography positive. Lower-extremity US examinations were performed in 21 of 62 (34%) pre-COVID-19 patients. Six of these 21 (29%) patients had DVT at US, four of 21 (19%) patients were CT pulmonary angiography positive, and two of 21 (10%) patients were CT pulmonary angiography negative. Six of the 21 (29%) patients with DVT in the pre-COVID-19 cohort did not differ (P = .169) from the 53% (8/15) of patients who had DVT in the COVID-19–positive cohort. This pre-COVID-19 cohort had a 14.5% (9/62) positive CT pulmonary angiography rate, which was lower than that of the COVID-19–positive cohort (37.1%; P = .007). When accounting for all patients with PE and/or DVT, 17.7% (11/62) were positive in this pre-COVID-19 cohort, lower than that of the COVID-19–positive cohort (38.7%; P = .016).

In terms of the hematologic and coagulation laboratory values within the COVID-19–positive cohort, only the D-dimer level on the date closest to the CT pulmonary angiography demonstrated a statistically significant difference between CT pulmonary angiography–positive and CT pulmonary angiography–negative subgroups with mean 6432.3 ng/mL DDU ± 3675.9 for CT pulmonary angiography–positive (range, 368 to >10 000 ng/mL DDU) and 1774.6 ng/mL DDU ± 3003.8 for CT pulmonary angiography–negative patients (range, 100–13 109 ng/mL DDU; P < .001) (Table 2). The one patient with a negative CT pulmonary angiography who was diagnosed with a DVT had a D-dimer value of >10 000 ng/mL DDU. The time between D-dimer test and CT pulmonary angiography was mean 0.10 days ± 1.08, median 0, and range 3 days before 5 days after CT pulmonary angiography. Other laboratory values and the duration of symptoms before presentation to hospital/

Table 2: Comparison of Patients with Negative and Positive CT Pulmonary Angiography Studies in Terms of Quantitative Laboratory Values, Clinical Features, and Imaging Features

	CT Pulmonary Angiography Negative				CT Pulmonary Angiography Positive				
Feature	*n*	Mean ± SD	Median	IQR	*n*	Mean ± SD	Median	IQR	*P* Value*
Laboratory values									
Age (y)	39	59.5 ± 14.4	62.0	21.00	23	54.8 ± 13.0	54.0	14.0	.137
APTT (sec)	28	53.8 ± 112.1	30.8	9.6	17	32.5 ± 5.5	30.5	6.3	.842
PT (sec)	31	15.2 ± 4.9	13.7	3.6	18	15.3 ± 3.4	14.1	3.8	.410
Platelet count (1000/μL)	39	262.6 ± 130.5	227.0	183.0	23	325.2 ± 182.1	291.0	220.0	.163
INR	31	1.4 ± 0.4	1.2	0.4	18	1.4 ± 0.3	1.30	0.4	.499
CRP (mg/dL)	38	113.0 ± 84.9	90.5	129.8	23	118.1 ± 87.3	111.0	121.2	.869
D-dimer level (ng/mL DDU)	35	1774.6 ± 3003.8	624.0	1415.0	22	6432.3 ± 3675.9	7606.5	7978.3	<.001*
Change D-dimer (ng/mL DDU)	10	1871.6 ± 4546.4	204.5	4415.0	10	4863.4 ± 4745.6	4354.0	9401.8	.162
ESR (mm/hour)	15	81.6 ± 38.3	93.0	81.0	10	73.4 ± 28.7	74.0	37.8	.544
Ferritin (ng/mL)	38	1237.6 ± 1391.6	839.3	1352.3	23	1749.3 ± 3056.0	1009.0	1203.0	.354
Fibrinogen (mg/dL)	3	796.0 ± 83.1	843.0	145.0	5	567.2 ± 149.9	631.0	283.5	.075
CT pulmonary angiography features									
CT pulmonary angiography quality (scored 1–4)	39	1.49 ± 0.73	1.00	1.00	23	1.65 ± 0.71	2.00	1.00	.290
COVIDLungRatio	39	0.56 ± 0.27	0.58	0.48	22	0.66 ± 0.17	0.70	0.27	.182
Duration symptoms before hospital presentation (d)	39	6.77 ± 4.00	7.00	5.00	23	8.09 ± 4.85	7.00	6.00	.399

Note.—APTT = activated partial thromboplastin time, COVIDLungRatio: proportion of lung parenchyma affected by COVID-19, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, INR = international normalized ratio, IQR = interquartile range, PE = pulmonary embolism, PT = prothrombin time, SD = standard deviation.
*$P < .05$ was considered significant.

emergency department did not differ statistically, including the change in D-dimer level between admission and the date closest to CT pulmonary angiography. The time between the two D-dimer tests for CT pulmonary angiography–positive patients was 4.8 days ± 3.3 (range, 1–12 days) and that for CT pulmonary angiography–negative patients was 4.1 days ± 3.3 (range, 1–11 days) (Table 2). D-dimer test was ordered on 32 of 62 (51.6%) patients with a mean of 1095.2 ng/mL DDU ± 1122.4 in the pre-COVID-19 cohort and was lower than that in patients who had COVID-19 ($P = .008$). The pre-COVID-19 patients who were CT pulmonary angiography positive and had a D-dimer test had a mean value of 1293.5 ng/mL DDU ± 1372.8, which was significantly lower than that observed in the COVID-19–positive CT pulmonary angiography-positive cohort ($P = .013$).

In addition, the COVIDLungRatio, which reflects the degree of lung parenchyma affected by opacities, was not statistically different between CT pulmonary angiography–positive and CT pulmonary angiography–negative subgroups with a mean of 0.56 ± 0.27 for CT pulmonary angiography–positive patients and 0.66 ± 0.17 for CT pulmonary angiography–negative patients ($P > .05$) (Table 1). Consolidation was present in 55 of 62 (88.8%) patients, 23 of whom were CT pulmonary angiography positive and 32 of whom were CT pulmonary angiography negative. Only one of 62 (1.6%) patients had a dilated vessel in an area of consolidation and ground-glass opacity (vascular enlargement) observed in a CT pulmonary angiography positive patient with a segmental PE affecting the region (Fig 3). No vessel dilation within a COVID-19 lesion was identified in areas unaffected by PE.

The receiver operating characteristic analysis on the significant factor D-dimer level (at the date closest to the CT pulmonary angiography) identified that a value >1394 ng/mL DDU predicted CT pulmonary angiography positivity with an area under the curve of 0.857, with 94.5% (21 of 22) sensitivity and 71.4% (25 of 35) specificity. Use of a lower D-dimer threshold value of >500 ng/mL DDU resulted in a sensitivity of 95.5% (21 of 22) and a specificity of 42.9% (15 of 35) for a CT pulmonary angiography–positive result. For a D-dimer threshold level >2000 ng/mL DDU, CT pulmonary angiography–positive results would be indicated with a sensitivity of 77.3% (17 of 22) and a specificity of 82.9% (29/35). When grouping the one patient with DVT with those who were CT pulmonary

Table 3: Correlation of Laboratory Values, Imaging Measures, and Duration of Symptoms before Hospitalization with Indicators of Pulmonary Embolism Severity

Measure	RV/LV Ratio		Mastora Central Ratio (ObstCenRatio)		Mastora Total Ratio (ObstTotRatio)	
	r Value	*P* Value	*r* Value	*P* Value*	*r* Value	*P* Value*
Laboratory values						
APTT	−0.05	.837	−0.05	.720	−0.23	.378
PT	0.26	.295	0.07	.788	0.03	.906
Platelet count	−0.13	.562	−0.27	.211	−0.30	.165
INR	0.32	.200	0.05	.833	0.05	.834
CRP	0.12	.581	−0.03	.879	−0.02	.941
D-dimer	0.24	.279	0.56	.007*	0.61	.002*
Change D-dimer	0.24	.511	0.40	.254	0.55	.097
ESR	−0.50	.138	−0.85	.002*	−0.76	.011*
Ferritin	0.18	.406	0.20	.368	0.14	.517
Fibrinogen	−0.30	.624	−0.15	.805	0.00	>.99
CT pulmonary angiography features						
CT pulmonary angiography quality (scale of 1–4)	−0.19	.383	0.20	.354	0.16	.458
COVIDLungRatio	−0.49	.020*	−0.28	.205	−0.28	.200
Duration of symptoms prior to hospitalization (d)	0.45	.033*	0.32	.134	0.35	.104

Note.—APTT = activated partial thromboplastin time, COVIDLungRatio = proportion of lung parenchyma affected by COVID-19, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, INR = international normalized ratio, PT = prothrombin time.
*$P < .05$ was considered significant.

angiography positive, the threshold of 1394 ng/mL DDU predicted DVT and/or PE with an area under the curve of 0.880 and achieved a 95.7% (22/23) sensitivity and 73.5% (25/34) specificity. The sensitivities using thresholds of >500 and >2000 ng/mL DDU were 95.7% (22/23) and 78.3% (18/23), respectively, while specificities were 44.1% (15/34) and 85.3% (29/34), respectively.

PE Severity

For the CT pulmonary angiography–positive patients, 10 of 23 (43.5%) patients had evidence of right heart strain at either echocardiography or CT pulmonary angiography (Fig 2), with one of 10 (10%) with right heart strain (moderate) at echocardiography only, one of 10 (10%) had right heart strain at both echocardiography (mild) and CT pulmonary angiography, and eight of 10 (80%) had right heart strain only at CT pulmonary angiography. Of the eight patients who had CT pulmonary angiography right heart strain, five did not undergo echocardiography. No significant difference in clinical characteristics including laboratory values and clinical outcome was delineated based on the presence or absence of right heart strain ($P > .05$) (Table E2 [supplement]). Two of 10 (20.0%) patients who were CT pulmonary angiography positive and had right heart strain died, whereas none of the CT pulmonary angiography–positive patients who did not have right heart strain died (Table E2 [supplement]). None of the CT pulmonary angiography–positive patients with right heart strain at echocardiography and/or CT pulmonary angiography underwent pre-existing echocardiography within 1 year before the COVID-19–positive hospitalization.

ObstCenRatio, ObstTotRatio, and the RV/LV ratio did not differ significantly between the patient's sex, pre-existing conditions, and clinical outcome for each metric of PE severity ($P > .05$) (Table E3 [supplement]). Mean ObstCenRatio was 0.15 ± 0.20. Mean ObstTotRatio was 0.20 ± 0.21. Mean RV/LV ratio was 1.20 ± 0.55 (Fig 3) for CT pulmonary angiography positive patients, 1.55 ± 0.74 for those assessed by the radiologist consensus to have RV strain, and 0.95 ± 0.13 for those without RV strain.

There was a statistically significant and positive correlation between both ObstCenRatio ($P = .007$) and ObstTotRatio ($P = .002$) with D-dimer levels (Table 3). The ESR laboratory value negatively correlated with ObstCenRatio ($P = .002$) and ObstTotRatio ($P = .011$). COVIDLungRatio negatively correlated with RV/LV ratio ($P < .02$), but no significant correlation was identified with ObstCenRatio and ObstTotRatio. Duration of symptoms before hospital presentation positively correlated ($P = .033$) with the RV/LV ratio (Table 3).

Discussion

In this study of a U.S. cohort of patients who had COVID-19 who underwent CT pulmonary angiography, 37.1% of examinations were positive for PE. D-dimer levels significantly differed between patients who had positive CT pulmonary angiography and those with negative CT pulmonary angiography examinations. In addition, D-dimer levels correlated with the

degree of pulmonary artery obstruction as measured by the Mastora grading system (ObstCenRatio and ObstTotRatio).

The high prevalence of positive CT pulmonary angiography examinations in patients who had COVID-19 in our study supported the growing knowledge pertaining to the relationship between COVID-19 and hypercoagulable states including disseminated intravascular coagulation (6,20). The association of COVID-19 with thromboembolic disease has been indicated by a venous US study by Cui et al, which reported peripheral venous thromboembolism in 25% of patients with severe COVID-19 (21). PE in patients who had COVID-19 has been described only recently, beginning with single case and small-series reports (7–11). Our study findings supported two recently published radiology research letters describing 23% (14) and 30% (16) of CT pulmonary angiography examinations to be positive in European COVID-19–positive cohorts. The high rate of PE in our study occurred despite 40% of the patients receiving prophylactic anticoagulation, 52% who had a positive result at CT pulmonary angiography. In addition, a brief clinical report by Llitjos et al further reinforced the association of COVID-19 and PE, with a high rate of peripheral venous thrombosis in 56% and PE in 23% of their patients who had COVID-19 in the ICU, despite prophylaxis and therapeutic anticoagulation; their rate of PE was potentially underestimated, given that patients with peripheral thrombosis may not necessarily had undergone CT pulmonary angiography (12). The 37.1% with PE in our COVID-19–positive cohort was higher than the 10% rate (22) reported in the general population and 14.5% (9/62) in our comparison group imaged just before the first case of COVID-19 reported in the New York City area. When including patients who were CT pulmonary angiography positive and/or had DVT, 38.7% of our patients who had COVID-19 were CT pulmonary angiography positive. In addition, it is acknowledged that patient selection and the examination interpreter expertise can influence the proportion of positive CT pulmonary angiography examinations, as all of the patients who had COVID-19, were hospitalized or in the emergency department at the time of examination (23). Despite this, the heightened risk of PE in patients who had COVID-19 was supported by our elevated percentage of positive CT pulmonary angiography examinations in patients who had COVID-19, compared with the 22.7% and 30% rates reported in cohorts composed of only acutely ill patients in the ICU before COVID-19 (24,25). Furthermore, a majority of the emergency department CT pulmonary angiography examinations are interpreted by thoracic radiologists at our institution, and thus, the effect of interpreter expertise is minimized (23).

Recent literature in COVID-19 has reported thrombosis secondary to the COVID-19–associated vascular injury (26,27). It is difficult to reliably distinguish between thrombus formation and embolism at CT pulmonary angiography. We did not specifically evaluate whether the central CT pulmonary angiography intravascular defects extended to distal subsegmental vessels. Our COVID-19 cohort had a higher rate of DVT (53%) than the 29% in our pre-COVID-19 cohort, suggesting a thromboembolic component for the intravascular defects at CT pulmonary angiography, though this difference was not statistically significant, possibly because of small numbers. Given the association of COVID-19 with a hypercoagulable state, prophylactic anticoagulation has been studied and shown to decrease mortality (6), and the role of empirical prophylactic and therapeutic anticoagulation needs elucidation (28).

Some imaging studies reported vascular enlargement or dilatation in areas of lung opacity as a feature of COVID-19 (29,30), which we observed in only one patient in our study who had PE, who had vessel dilation in an area of consolidation, and ground-glass opacity with a "reversed-halo" sign. The significance and cause of the finding of vessel enlargement in COVID-19 is therefore not clarified by our study. Vascular enlargement in lung opacities in COVID-19 has been increasingly reported at chest CT; some have defined vessel enlargement as a subsegmental vessel >3 mm in diameter. It has been proposed that vessel enlargement relates to hyperemia and inflammation from infection or other vascular disease, although the etiology is unclear at this time (31). The lack of vascular enlargement reported in this study may well relate to the severity of diseased lung parenchyma, given that 0.56 and 0.66 of the lungs were involved by opacities in our CT pulmonary angiography–positive and CT pulmonary angiography–negative subsets, respectively. The finding has mainly been reported in chest CT in scenarios in which CT may have been performed as a method of COVID-19 diagnosis and thus potentially may be seen in milder and earlier presentations of pulmonary COVID-19 than in our cohort (29–31). A higher threshold for this finding, given the use of visual qualitative assessment rather than a quantitative size definition, may account for a small amount of this finding reported.

Our results indicate that D-dimer, a fibrin degradation product, was associated with a higher prevalence of thromboembolic events and correlated with the degree of pulmonary artery obstruction as shown by the Mastora score, which has been used as an indicator of PE severity. The D-dimer level was significantly elevated in positive CT pulmonary angiography patients with COVID-19, with a mean of 6432.3 ng/mL, compared with 1774.6 ng/mL in COVID-19 patients with negative CT pulmonary angiography and 1293.5 ng/mL DDU in patients who were pre-COVID-19 CT pulmonary angiography positive. The mean D-dimer level for the COVID-19–positive cohort of 3572.3 ng/mL DDU was significantly higher than the mean D-dimer value of 1095.2 ng/mL DDU for the entire pre-COVID-19 cohort. The particularly high D-dimer levels in the COVID-19–positive cohort may relate to the proinflammatory and hypercoagulable COVID-19–positive state. The D-dimer level positively correlated with the degree of PE obstruction as measured by ObstCenRatio and ObstTotRatio, for the central and for both central and segmental pulmonary arteries, respectively. This correlation between D-dimer and PE is well supported by the existing literature (32,33), although a number of causes for D-dimer elevation exist that we did not specifically analyze, including disseminated intravascular coagulation from multiple etiologies, pregnancy, age, and cancer (34). However, our investigation raises the possibility of risk stratification according to the D-dimer value for PE in patients who had COVID-19. A 500 ng/mL value is used as a threshold for D-dimer positivity in the general population (32). Our study demonstrated that a D-dimer value of 1394 ng/mL provided a sensitivity of 95% and a specificity of 71% for PE

in our COVID-19–positive cohort. When including the patient who had DVT but a negative CT pulmonary angiography, the rate of thromboembolic disease increased to 38.7%. This may aid in identifying those patients with higher likelihood of PE and determining those who should be considered for CT pulmonary angiography, particularly given the need to minimize the hospital transmission of COVID-19 to other patients and staff.

Most of the other demographic, comorbid, laboratory, clinical, and imaging features did not differ significantly between the CT pulmonary angiography–positive and CT pulmonary angiography–negative subgroups. A history of diabetes was the only comorbidity that was significantly less frequently observed in the CT pulmonary angiography–positive cohort, which may possibly be attributed to our relatively small sample size (only 3/23 patients with PE had diabetes). In addition, the inflammatory marker ESR was inversely associated with the severity of PE as evidenced by ObstCenRatio and ObstTotRatio. This may reflect our small sample size of 10 CT pulmonary angiography positive patients whose ESR values were known. The proportion of abnormal lung parenchyma thought to be related to COVID-19 (COVIDLungRatio) was inversely proportional to the presence of RV/LV ratio. An explanation for this association is not clear, and this finding may also be related to our small numbers. In terms of outcome, we did not identify a significant mortality difference between the CT pulmonary angiography–positive and CT pulmonary angiography–negative cohorts (8.7% vs 12.8%), which could reflect the diagnosis and treatment of PE although it is unclear given our small numbers. Compared with our pre-COVID-19 cohort, patients who had COVID-19 comprised a significantly higher fraction of men, which may result from men associated with worse prognosis and higher mortality. It is unclear why a lower proportion of coronary artery disease was seen in the patients who had COVID-19 compared with the pre-COVID-19 group. Possibly more pre-COVID-19 patients who had coronary artery disease and chest pain may have undergone CT pulmonary angiography because of overlapping clinical presentations than patients in the COVID-19–positive cohort.

There has been an association of better outcomes of COVID-19–positive patients treated with anticoagulation prophylaxis, such as low molecular weight heparin in sepsis-induced coagulopathy and high D-dimer levels (5,28). Awareness and identification of thromboembolic complications such as PE may aid in improving outcomes as diagnosed patients would be treated with anticoagulation.

As discussed, a major limitation of our study was the relatively small sample size. In addition, COVID-19 in our cohort may have raised the threshold of health care professionals for ordering CT pulmonary angiography, given concerns pertaining to the contamination of CT scanners and in-hospital transmission of disease, thus elevating the proportion of positive examinations. Conversely, critically ill patients with PE may not have undergone CT pulmonary angiography because they were being ventilated and had unstable clinical status. Furthermore, many patients with US-confirmed peripheral venous thrombosis may not have undergone CT pulmonary angiography. In addition, we compared the CT pulmonary angiography positivity rate in patients who had COVID-19 with that of a cohort before COVID-19 that was not specifically matched for demographic, comorbidity, or laboratory data, including D-dimer values, which may serve as a basis for future investigations. This may entail correlation of D-dimer levels with pulmonary artery obstruction severity. We cannot exclude the possibility that undetected COVID-19 was present in the geographic population before March 1, 2020. Despite these aspects, an increased rate of thromboembolic events, PE, and derangements in coagulation factors in patients who had COVID-19 has been supported by recent literature and is higher than that reported in ICU patient cohorts (12–15,24). In addition, due to the retrospective design of our study, many patients lacked laboratory testing of coagulation and inflammatory markers during their work-up, limiting our evaluation of values such as fibrinogen, ferritin, and ESR; echocardiography; and understanding for ordering CT pulmonary angiography. In addition, echocardiography is subject to observer variation (35). Another limitation was that we cannot ascertain whether right heart strain was acute or preceded the current clinical presentation. None of the investigated COVID-19 patients with positive CT pulmonary angiograms and right heart strain had undergone echocardiography in the year before the COVID-19–positive hospitalization; therefore, right heart strain chronicity cannot be reliably ascertained. Some of the patients' final clinical outcomes have not been established because of the short time frame between CT pulmonary angiography and data collection for this study. Nasopharyngeal polymerase chain reaction testing was used as the standard of reference for determining COVID-19 infection; however, the test is not 100% sensitive (36). Thus, the true rate of PE may be higher in our network as there may have been patients with positive CT pulmonary angiography studies who were not identified to be COVID-19 positive. In addition, as mentioned previously, chest CT was not performed routinely for the initial diagnosis of COVID-19, and our patient population may have reflected those with more severe lung involvement. Thus, we were unable to address vascular enlargement proposed by other investigators (29,30) as a sign in early COVID-19 infection. Future investigation with a larger cohort may elucidate influencing factors for PE.

In conclusion, 37.1% of the CT pulmonary angiography examinations were positive for PE in a U.S. cohort of patients who had COVID-19. We have demonstrated that D-dimer levels differed significantly between CT pulmonary angiography–positive and CT pulmonary angiography–negative studies and correlated with the severity of pulmonary artery obstruction. This supports the growing understanding that hypercoagulable events are elevated in patients who had COVID-19, and these patients are at increased risk for PE. PE should remain to be a primary differential consideration for all patients with COVID-19 exhibiting acute or subacute respiratory distress. D-dimer levels can potentially be used to risk stratify patients in terms of suspicion for PE and severity.

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