

Arterial and Venous Thromboembolic Complications of COVID-19 Detected by CT Angiogram and Venous Duplex Ultrasound

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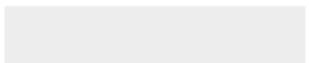
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Abstract:	<p>OBJECTIVE. To investigate the incidence of thromboembolic events, specifically pulmonary embolism (PE), deep vein thrombosis (DVT), and cerebrovascular accidents (CVA), in patients tested positive for COVID-19 through RT-PCR in a regional healthcare system in Connecticut.</p> <p>MATERIALS AND METHODS. All CT angiogram (CTA) and venous duplex extremity ultrasound (US) examinations performed on 192 consecutively documented cases of COVID-19 were retrospectively reviewed at a multi-centered healthcare system. Clinical characteristics and patient outcomes were evaluated and compared between two groups based on the presence or absence of acute thromboembolic events.</p> <p>RESULTS. Of the 16,264 patients tested for COVID-19, 3,727 (23%) were positive. Out of those, 192 patients underwent 245 vascular imaging studies including chest CTA (86), venous duplex ultrasound (134), and CTA head and neck (25). Among those who underwent imaging, 49 (26%) demonstrated acute thromboembolic events which included 13/86 (15%) with PE, 34/134 (25%) with DVT, and 6/25 (24%) with CVA. One patient had positive results on all 3 examinations and 2 patients had positive results on both chest CTA and venous duplex US. Males were more likely to have a thromboembolic event than females (33/103 (34%) vs. 14/89 (16%), $p=0.009$). No significant difference was observed with respect to age, cardiopulmonary comorbidities, malignancy history, diabetes, or dialysis.</p>

CONCLUSION. Approximately 26% of COVID-19 patients with positive testing who underwent vascular imaging with CTA or venous duplex ultrasound had thromboembolic events including PE, DVT, and CVA. This indicates that COVID-19 patients are at increased risk for thromboembolic complications.



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Abstract

OBJECTIVE. To investigate the incidence of thromboembolic events, specifically pulmonary embolism (PE), deep vein thrombosis (DVT), and cerebrovascular accidents (CVA), in patients tested positive for COVID-19 through RT-PCR in a regional healthcare system in Connecticut.

MATERIALS AND METHODS. All CT angiogram (CTA) and venous duplex extremity ultrasound (US) examinations performed on 192 consecutively documented cases of COVID-19 were retrospectively reviewed at a multi-centered healthcare system. Clinical characteristics and patient outcomes were evaluated and compared between two groups based on the presence or absence of acute thromboembolic events.

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Introduction

The novel coronavirus pandemic in the United States has been difficult to manage due to rapid dissemination and ease of transmission. COVID-19 has been causing death primarily due to pneumonia and respiratory failure, which was the initial focus of investigation and treatment. However, as the disease spread and more cases were recognized, it became apparent that the disease affects multiple organs and can cause severe complications resulting in subsequent morbidity and mortality.

While pulmonary embolism was an unexpected finding among preliminary studies in COVID-19 patients [1-4], one of the complications which has since been described in COVID-19 infection is the increased systemic inflammatory response from the virus which leads to a higher risk of hypercoagulability and associated thromboembolic disease [5-8]. Prevention and/or treatment of the thrombo-inflammatory state such as therapeutic or prophylactic anticoagulants can be effective [5, 9]. However, providers must first recognize the increased risk of vascular complications and deploy intense surveillance measures.

Initial recognition of coronavirus-related venous and arterial thromboembolic complications prompted expanded use of vascular imaging studies such as CT angiograms and venous duplex ultrasounds at our institution. This study investigates the incidence of thromboembolic events of COVID-19 patients who underwent dedicated imaging for systemic or pulmonary thrombosis or emboli.

Materials and Method

This study received approval from the Hartford HealthCare Institutional Review Board (HHC-2020-0110).

Patients

This study was conducted as a retrospective review. All patients who underwent COVID-19 testing at the inpatient and outpatient settings of the campuses of a regional healthcare system anchored by a large (>700 bed) urban teaching hospital in the northeast US were eligible.

A retrospective review of certain vascular imaging studies performed on patients tested positive for COVID-19 was performed via electronic medical record (EPIC Systems, Verona, WI, USA) and a system wide PACS (Inteleviewer, Montreal, QC, Canada). Specifically, these are all chest and head/neck CT angiograms (CTA) and venous duplex ultrasound (US) studies performed from 3/20/2020 - 5/3/2020, inclusive, on patients diagnosed with COVID-19.

Images and patient information were collected from the EPIC electronic medical record system as well as the picture archiving and communication system (PACS). All patients were confirmed positive for COVID-19 on reverse transcriptase – polymerase chain reaction (RT-PCR). All patients who underwent a CTA examination, which included CTA pulmonary embolism protocol, CTA chest/abdomen/pelvis, CTA head and neck, and all venous duplex ultrasound examinations of the upper and lower extremities, were included in the study. Abdominal ultrasounds were excluded.

The study reports were examined by one of 5 diagnostic radiologists to assess the presence or absence of acute thromboembolic events. Patients were considered to be positive for vascular events based upon the presence of acute filling defects in a vein or artery on CTA or the presence of echoes in a non-compressible vessel on ultrasound with absence of color signal or Doppler signal.

Comorbidities such as cardiopulmonary and vascular diseases were recorded for analysis. Cardiovascular diseases included hypertension, coronary artery disease, prior myocardial infarction (MI), and history of cardiac surgery. Chronic respiratory disease included chronic obstructive pulmonary disease (COPD), asthma, current or previous tobacco use, and history of previous pulmonary embolism (PE). The maximum D-dimer, fibrinogen, C-reactive protein (CRP), lactate dehydrogenase (LDH) values, and leukocyte count were also recorded, if available. The use of systemic and mechanical VTE prophylaxis was included.

Imaging studies included were:

- Patients with CTA and US up to 7 days prior to positive COVID-19 results on RT-PCR
- Patients at least 18 years of age
- Studies reviewed until the censoring of data collection on 5/3/2020

Statistical Analysis

Comparison of continuous variables was performed with a Student's t-test or Mann-Whitney U test (depending on distribution), and comparison of categorical variables was performed with Pearson's chi-square

test. A p-value of < 0.05 is considered statistically significant. SPSS v. 26 (IBM: Armonk, NY 2019) was used for all analyses.

Results

Incidence

A total of 16,264 people were tested for COVID-19 between March 20, 2020 and May 3, 2020 of which 3,727 had positive results. Testing sites included drive-up testing centers, urgent care centers, and acute care hospitals at a multi-centered healthcare system in Connecticut. During the study period, 192 patients who tested positive for COVID-19 underwent imaging as depicted in the Prisma flow diagram (Fig. 1).

The median age was 62 years old (interquartile range 52-74) and 54% were male. Out of the imaging done in males, 33% were positive for thromboembolism, while 16% of the tests performed in females were positive.

Of the 86 patients who underwent chest CT angiography, 13 (15%) were positive for pulmonary embolism (Table 1). A total of 134 venous duplex ultrasound studies were performed, and 34 (25%), were positive for deep vein thrombosis. 25 patients underwent CTA head and neck, and 6 (24%) were positive for cerebral vascular accident. Of the total 192 COVID-19 patients who had imaging, 26% showed evidence of thromboembolic events. Of note, 42 patients had multiple imaging examinations including a combination of CTAs and lower or upper extremity venous duplex examinations. Two patients had positive results on both chest CTA and venous duplex US and one patient had positive results on all 3 examinations.

Patient characteristics

Statistically significant difference was demonstrated between males and females (70% vs. 30%, $p=0.009$) in thromboembolic events among all the cardiovascular events that occurred.

The median hospital length of stay was longer in the event group than in the non-event group (10 days [range 8-18.5] vs. 7 days [range 3-14], respectively; $p=0.008$). The rate of ICU admission was 70% in the thromboembolic event group compared to 46% in the non-event group ($p=0.007$). Patients in the event group were more likely to be intubated (57% vs. 34%, $p=0.004$). Nearly all inpatients and those admitted to the ICU received at least systemic and mechanical thromboembolic prophylaxis, although regimens varied. In the event group, 100% of patients were anticoagulated, and 92% were put on sequential compression devices.

Patient characteristic and laboratory values are listed in Table 2. There was no significant difference between event and non-event groups with respect to age, BMI, history of cardiovascular disease, chronic respiratory disease, diabetes, dialysis, malignancy, and death.

Discussion

Until recently, hypercoagulability associated with COVID-19 infections and thromboembolic complications were unexpected and likely underestimated. Early radiologic investigations understandably focused primarily on lung parenchymal findings in chest CT. However, since then several papers ranging from case reports and small cohort studies reported elevated incidence of pulmonary thromboembolic events. There is now growing awareness of COVID-19 related to multi-system complications secondary to thromboembolism leading to increasing numbers of angiographic imaging studies ordered by providers. In our review, out of 245

angiographic imaging studies that were obtained on COVID-19 patients, we found 26% of patients with thromboembolic events. These include pulmonary embolism, cerebral vascular accidents, and deep vein thrombosis from CT angiography of the chest or head/neck, or venous duplex ultrasounds of the upper or lower extremities. This is significantly higher than expected. Although there are no literature references reporting the incidence of thromboembolism in patients with viral illnesses, a frame of reference by comparing to White's estimates in 2003 reported venous thromboembolism occurs for the first time in approximately 100 persons per 100,000 each year in the United States, and rises exponentially from <5 cases per 100,000 persons for <15 years old to approximately 500 cases (0.5%) per 100,000 persons at age 80 years [10]. Approximately one-third of patients with symptomatic VTE manifest as pulmonary embolism, whereas two-thirds manifest as deep vein thrombosis alone [10]. This indicates that our rate of VTE during COVID-19 is significantly higher compared to pre-COVID. Moreover, the Spanish registry for both DVT and PE reports incidence of VTE at 1.6 per 1000 ED visits [11]. Numbers published by Singer et al. estimated a 0.17% incidence for DVT and PE over a 5-year period in the ED in the US [12].

Comparing results of this study with other reports of thromboembolic events in COVID-19 patients, our data is comparable to the study by Grillet *et al.* from France, in which 23% of thromboembolic events were found [13]. However, that paper only had contrast-enhanced CT exams and did not include venous duplex studies. Similarly, Spiezia *et al.* from Italy found 5 out of 22 (23%) ICU patients with COVID-19 developed in-hospital deep vein thrombosis despite anticoagulant prophylaxis [8]. On the contrary, Cavagna *et al.* and Helms *et al.* reported a higher level of pulmonary thromboembolic events – 41% and 43%, respectively [6, 14]. Cavagna *et al.* also looked at DVT and reported a 12% prevalence of DVT compared to 25% from our study [14]. These reports indicate a higher rate of thromboembolism due to coronavirus infection, and providers caring for patients with or under investigation for COVID -19 need to be hypervigilant about thromboembolic complications and may want to have a low threshold for performing imaging tests to look for thrombus and emboli. There should be considerations for prophylaxis using mechanical and medical anticoagulation in COVID-19 patients early in their management.

One issue to consider with regards to CT angiography exams is the administration of intravenous contrast. Some COVID-19 patients have multi-organ failure including acute kidney injury predisposing them to contrast nephropathy [15]. Consequently, the need for angiographic studies to rule out PE and CVA is balanced by preserving kidney function. However, with a lower threshold to obtain venous duplex ultrasound studies, physicians can detect DVTs earlier, ideally before the evolution to PE.

In our series it was interesting to observe that COVID-19 patients with more comorbidities did not have a statistically higher risk of thromboembolism. Despite this finding, Wu *et al.* reported that risk factors associated with severe infection and death include male sex and comorbidities such as hypertension and diabetes [16]. Furthermore, our study revealed that men were more likely than women to have thromboembolic events. Perhaps physicians may also want to have a higher level of suspicion for thromboembolism in men.

The limitations to our study include a relatively small sample size in which we collected data for a limited time period. Moreover, we only collected data on patients with confirmed positive COVID-19 diagnoses. Another limitation was that there were inconsistencies in reporting lab values; not every patient had data for all of the lab collections. It would be helpful to know if the patients who tested positive for COVID-19 later

developed thromboembolism outside of our study's date range for inclusion. There is limited data on those who tested negative for COVID-19 during the time period, and it may be valuable to collect data on them to determine their rate of thromboembolism as a point of comparison. As a future direction it would also be interesting to see if there is a higher rate of thromboembolism during the traditional influenza season compared to the beginning of the COVID-19 pandemic.

Conclusion

This study reports the incidence of arterial and venous thromboembolic events detected by CTA and venous duplex ultrasound occurring in patients who tested positive for COVID-19 in a multi-centered healthcare system, including a large regional tertiary care urban teaching hospital, in the Northeast during the peak period of the novel coronavirus pandemic. Similar to other recent studies, our results showed that COVID-19 patients are at increased risk of thromboembolic complications. Specifically, we report 26% of COVID-19 patients had thromboembolism. Increased hypercoagulability in patients with COVID-19 may decrease the threshold for clinicians to order angiographic imaging studies when there is clinical suspicion for PE, stroke or DVT.

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TABLE 1: Imaging results

Imaging Modality (<i>n</i> = 245)	No Event (<i>n</i> = 192) (%)	Event (<i>n</i> = 53) (%)
CTA (<i>n</i> = 86)	73 (85)	13 (15)
Venous duplex US (<i>n</i> = 134)	100 (75)	34 (25)
CTA head and neck (<i>n</i> = 25)	19 (76)	6 (24)

TABLE 2: Clinical Characteristics and Outcomes

Characteristics (<i>n</i> = 192)	No Event (<i>n</i> = 145) (%)	Event (<i>n</i> = 47) (%)	<i>p</i>
Sex			0.009
Male, n=103	70 (48)	33 (70)	
Female, n=89	75 (52)	14 (30)	
Age (y)			
Mean ± SD	63.0 ± 15.7	59.5 ± 13.7	0.171
Range	24 - 91	18 - 89	
BMI (kg/m ²), mean ± SD	31.1 ± 8.70	30.3 ± 8.8	0.580
Cardiovascular disease	95 (66)	31 (66)	0.956
Chronic respiratory disease	47 (32)	13 (28)	0.541
Diabetes	64 (44)	25 (53)	0.427
Dialysis	13 (9)	3 (6)	0.578
Malignancy	29 (20)	8 (17)	0.653
Anticoagulation	131 (90)	47 (100)	0.027
Mechanical VTE prophylaxis	131 (90)	43 (92)	0.815
Length of stay (days), median (IQR)	7 (3-14)	10 (8-18.5)	0.008
Care Status			0.007
ICU	66 (46)	33 (70)	
Inpatient	70 (48)	14 (30)	
ED	9 (6)	0 (0)	
Requiring intubation	49 (34)	27 (57)	0.004
Death	16 (11)	8 (17)	0.281
D-dimer ng/mL (<250), n=176	121 (83)	42 (89)	0.144
Fibrinogen ng/mL, n=67	651.0 ± 209.0	596.9 ± 244.9	0.337
CRP mg/dL, n=164	14.5 ± 11.5	19.3 ± 12.1	0.024
LDH IU/L, n=163	455.6 ± 235.9	525.3 ± 259.6	0.103
Lymphocyte count, n=192	13.0 ± 7.3	18.2 ± 8.7	<0.001

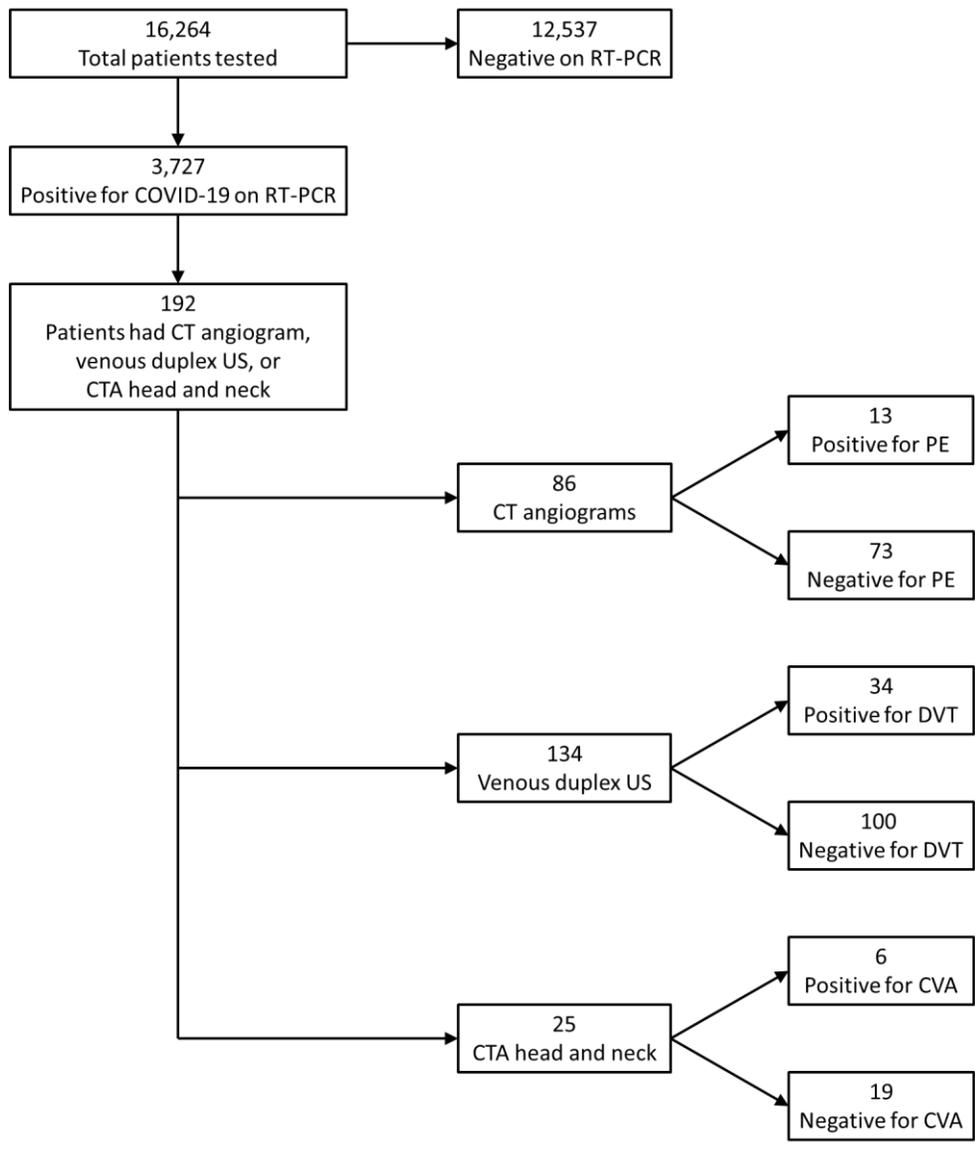


Fig. 1 Prisma Flow Diagram

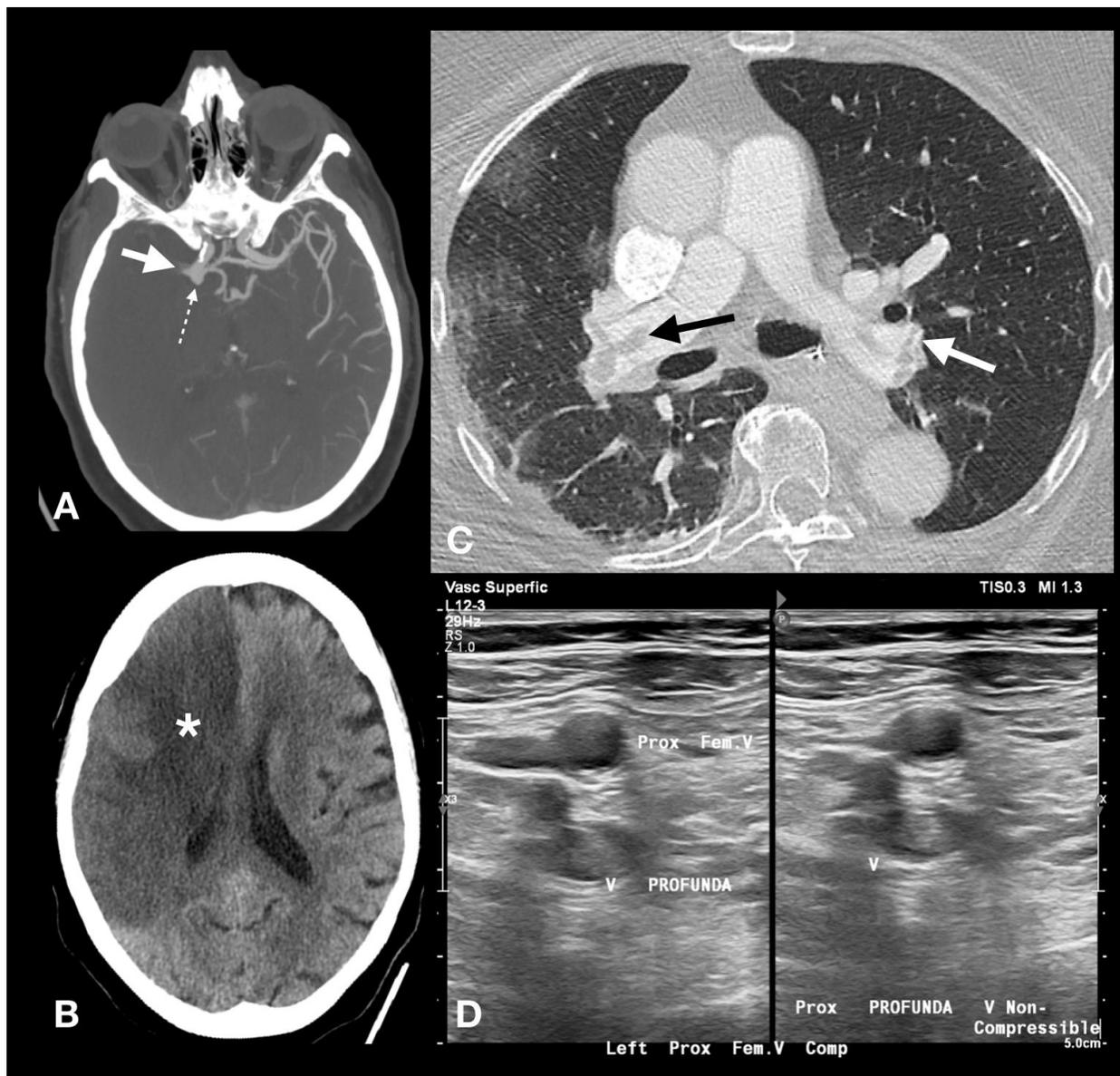


Fig. 2 74 year-old female who presented to the emergency department with acute stroke symptoms and respiratory distress. Images A, B and C were obtained for evaluation of infarct and pulmonary embolism. (a) Axial MIP CTA at the level of the Circle of Willis showed occlusive thrombus filling the M1 segment of the right middle cerebral artery (solid arrow) with no substantial filling of the distal branches of the right anterior and middle cerebral arteries. Incidental 1 cm bilobed saccular aneurysm of the right internal carotid artery near the origin of the right posterior communicating artery (dotted arrow). (b) Axial CT at the level of the body of the lateral ventricles 2 days after demonstrated continued evolution of large right anterior and middle cerebral artery territorial infarcts with cytotoxic edema (asterisk) and effacement of the right lateral ventricle. (c) Axial CTA at the level of the hila shows pulmonary emboli in the right main pulmonary artery (black arrow) and multiple left lower lobe subsegmental pulmonary arteries (white arrow) with right upper and lower lobe peripheral subpleural groundglass opacities. (d) 56 year-old male with respiratory failure and positive for COVID-19. Left lower extremity duplex US demonstrated low echogenicity in distended non-compressible veins suggesting acute thrombus involving the distal common femoral and proximal profunda veins.

Figures

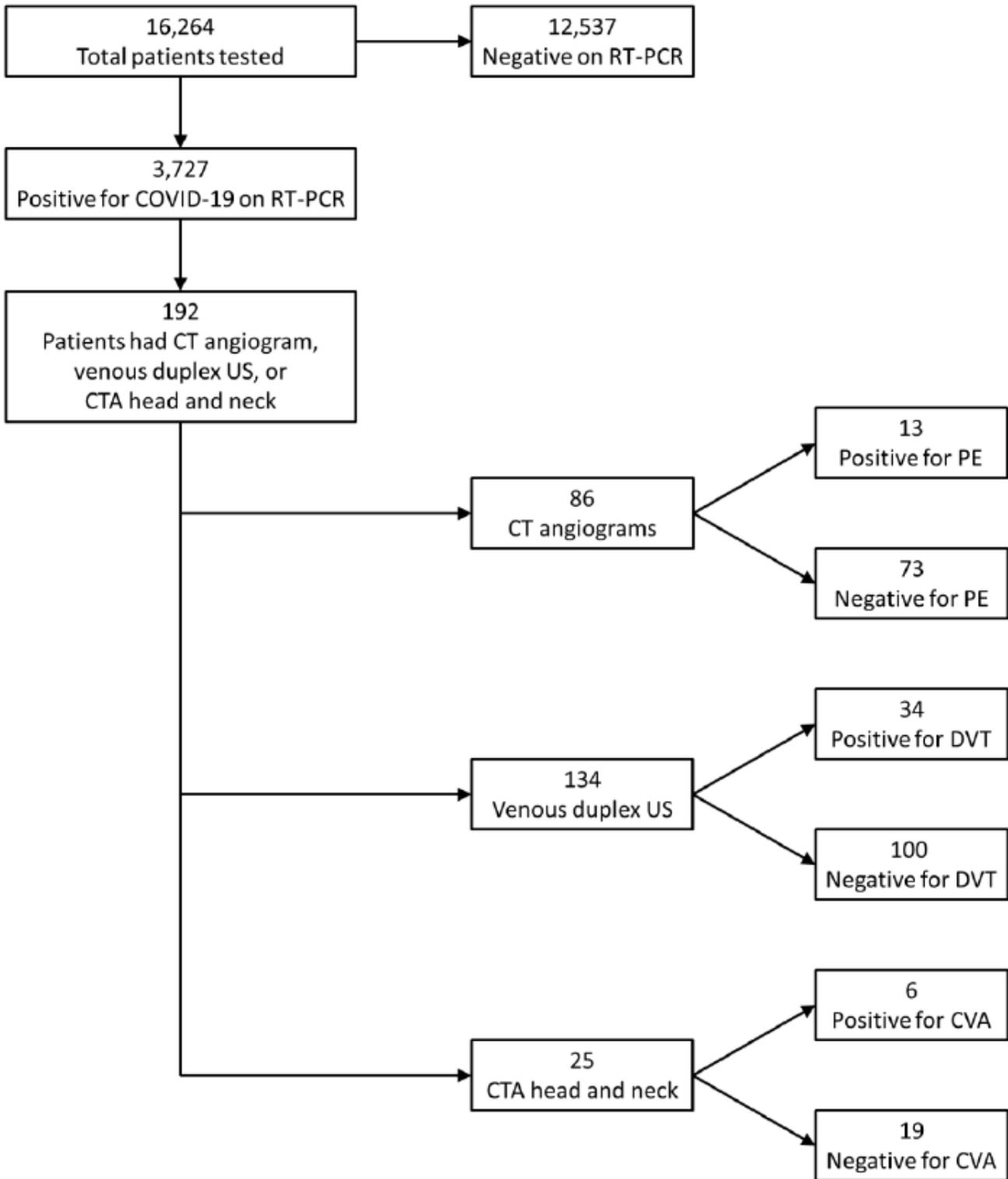


Figure 1

Prisma Flow Diagram

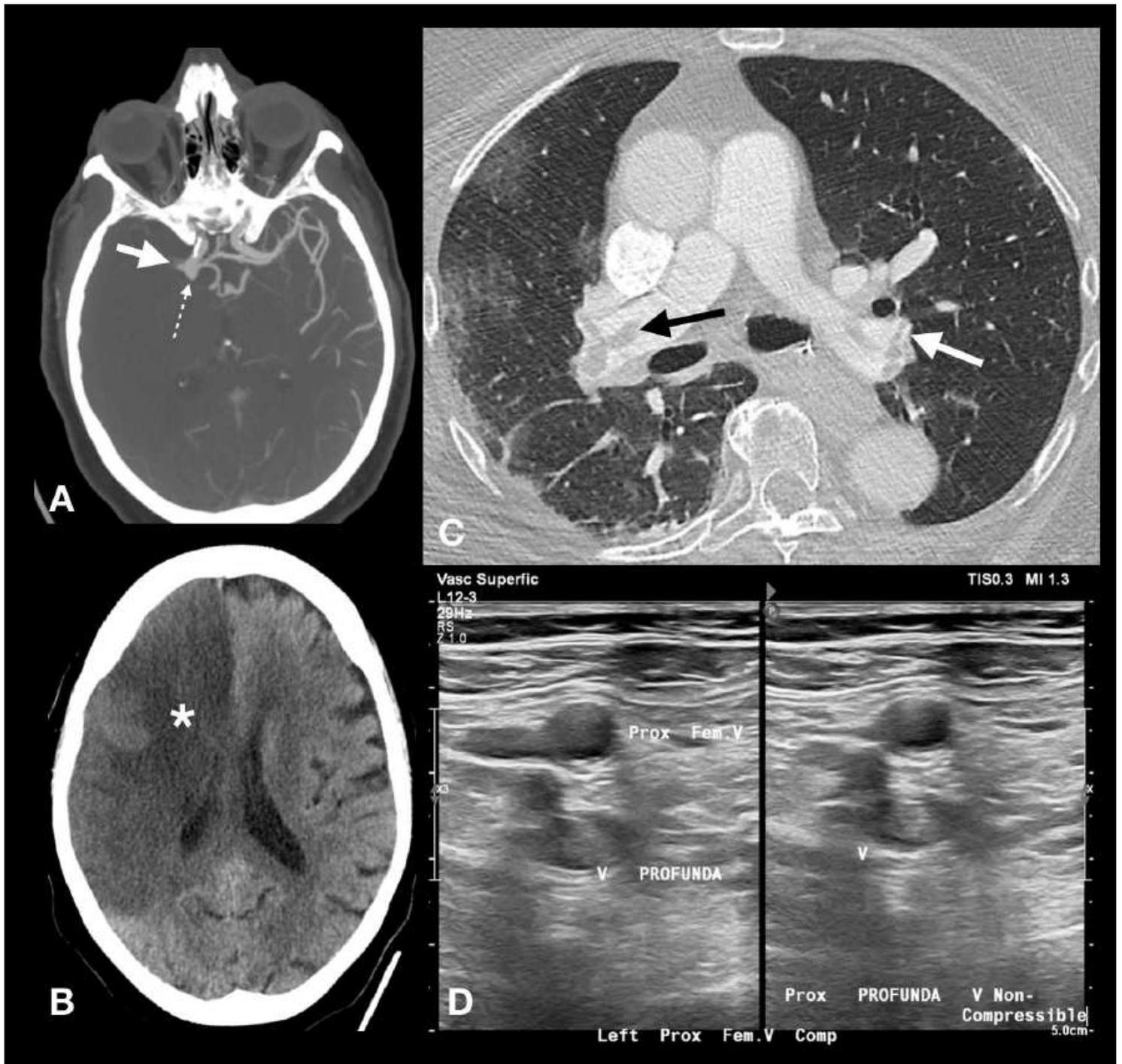


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