Advanced International Journal for Research (AIJFR)
E-ISSN: 3048-7641 ● Website: www.aijfr.com ● Email: editor@aijfr.com

Multimodality Imaging for Vascular Complications of COVID-19 Patients

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Provisional Regd No :140-46105-201-228306

1. Introduction

Emergence of The Covid-19 Disease

On December 31, 2019, the WHO China Country Office received notification of cases of pneumonia of unknown aetiology (unknown cause) in Wuhan City, Hubei Province, China. Authorities claim that some of the patients worked as dealers or vendors in the Huanan Seafood market.(1) On 7 January 2020, Chinese scientists were able to isolate a 2019-nCoV (Novel corona-virus) from a patient and perform genome sequencing on the 2019-nCoV (Novel corona-virus). On January 12, 2020, the WHO received the genetic sequence of the 2019-nCoV, which aided laboratories in various countries in developing specific diagnostic PCR tests for detecting this novel infection.(2)

Corona-virus disease 2019 (COVID-19) has emerged as a pandemic with unprecedented levels of mortality and morbidity caused by a novel enveloped single-stranded RNA virus, SARS-CoV-2.(3,4) The viral surface spike proteins bind to the ACE2 receptor, which is expressed in alveolar cells, vascular endothelium, and enterocytes of the intestine.(5,6)

Clinical Spectrum of Covid-19

Based on symptoms, clinical signs, laboratory results, and imaging, COVID-19 patients were classified as mild, moderate, severe, or critical, according to WHO guidelines (7). The clinical spectrum of COVID-19 ranges from asymptomatic carriers who can transmit the virus to mild clinical upper respiratory infection, which can progress to acute respiratory distress syndrome (ARDS) in critically ill patients.(8)

In hospitalized patients, the most common symptoms were fever, dry cough, shortness of breath, nausea/vomiting, and diarrhoea. Anosmia, dysgeusia, and gastrointestinal symptoms have also been reported among hospitalized patients.(9) Approximately one- quarter of hospitalized patients require intensive care, most often due to hypoxemic respiratory failure.(10) Mechanical ventilation is

required for more than half of the ICU patients.

COVID-19 clinical characteristics and complications include myocardial, renal, liver, thrombo-embolic manifestations, and neurological events in addition to pulmonary symptoms.[9]

It is stated that SARS-CoV-2 causes direct viral tissue damage to extra-pulmonary organs by attaching to ACE2 receptors. Endothelial damage, thrombotic-inflammation, and immune response dysregulation all played a role in the disease's extra-pulmonary manifestations.[11]

DIAGNOSIS OF COVID-19 INFECTION

Early detection and disease management are challenging because of the non-specific nature of the clinical symptoms and the rapidity with which the disease progresses.[10] The first-line COVID-19 diagnostic test is a real-time reverse-transcriptase PCR (RT-PCR) test from a nasopharyngeal swab, which has high specificity but low sensitivity ranging from 80 to 90% due to insufficient viral load or nucleic acid extraction failure. [12, 13]

In addition to the RT-PCR test, radiological imaging acts as an adjunct in determining the disease severity and risk stratification of COVID-19 patients. Multi-modal imaging can aid in characterizing organ injury and dysfunction in COVID-19 patients as we learn more about the disease's effects on systemic inflammation and pro-coagulant activity. Therefore, it is essential to have a thorough understanding of the imaging characteristics of COVID- 19 in order to effectively treat patients and identify any potential sequelae of this infection.

LIMITATIONS IN IMAGING OF COVID-19 PATIENTS

Due to the stringent safety precautions, such as patient transfer and infection control measures, that are required in COVID-19 patients, multi-modality imaging for thrombo- embolic complications is practically impossible for all COVID-19 patients. The purpose of our study is to know the importance and role of multi-modality imaging in these COVID- 19 patients.

REVIEW OF LITERATURE

COVID-19 AND ITS MECHANISM IN VASCULAR COMPLICATIONS

Studies by **Hoffmann et al. s**uggested that SARS-CoV-2 infection occurs first in the lung where the viral entry is mediated through ACE 2 receptor. Serine proteases like trans- membrane protease serine 2 (TMPRSS2), cathepsin B, and cathepsin L1 facilitates the viral entry. From the lung, SARS-Cov-2 enters into systemic circulation and affects the organs that express ACE 2 receptor.[14]

The vascular endothelial cells are the main target for the SARS-CoV-2, and damage to the endothelial cells are the reason for COVID-19 related vasculopathies. Many studies suggested that there is an increased prevalence of COVID-19 related vascular complications. Studies by **Tang et**

al, reported that patients who died of COVID-19 are found to have elevated laboratory parameters of D-dimer and fibrinogen.[15]

Histological studies conducted by **Varga et al.,** found that endothelial cell involvement across multiple organs (e.g., lungs, heart, intestines, kidneys, and liver) in three patients, of which two of them died (multi-system organ failure; myocardial infarction, and subsequent cardiac arrest, respectively) and one survived. Their study suggested that endothelial inflammation occurred due to direct invasion by the virus.[16]

Study conducted by **Ackermann et al**, found severe endothelial injury, viral infection, and disrupted cell membranes in the lungs that are obtained from seven post-mortem specimens of COVID-19 patients. They also found that micro-thrombi was observed to be nine times more prevalent in the lungs of COVID-19 patients than in the lungs of influenza patients.[17]

Histopathological examination of post-mortem renal specimens by **Su and his colleagues,** found endothelial cell swelling with foamy degeneration in 19% of patients, with 12% demonstrating few areas of segmental fibrin thrombus in glomerular capillary loops, which is associated with severe endothelial injury.[18]

Potential Mechanisms of Endothelial Dysfunction in COVID-19

Angiotensin-Converting Enzyme 2 (ACE2)

Mahmoud gheblawi and Kaiming wang et al. (2020) reported that ACE2 is the key receptor facilitating SARS-COV-2 viral entry along with key serine proteases to prime the spike glycoprotein of the virus, most notably TMPRSS2 expressed by endothelial cells. Since, ACE2 is expressed in many organs, the virus can cause multi-organ dysfunction.[19,20]

Cheng et al (2020) suggested that when virus enters the endothelial cells, the ACE2 receptors in them decrease, resulting in an increase in the circulating levels of angiotensin
II. As circulating levels of angiotensin II is increased, they cause endothelial cells to release von-willibrand factor and result in subsequent platelet activation. Thus, angiotensin II initiates the vascular inflammation and coagulation in COVID-19 patients.[21]

Qing Ye et al (2020), reported that, once SARS-CoV-2 mediated endothelial damage occurs, these cells release various inflammatory response regulators such as cytokines and chemokines which is responsible for the cytokine storm in COVID-19 patients.[22]

Hiba Alsaffar et al.(2018) and Tina R. Desai et al.(2002) documented that pro- inflammatory markers particularly, IL-6, is associated with increased vascular permeability, a hallmark of the inflammatory response. IL-6, with other cytokines such as IL-1, activates endothelial cells increasing the adhesion molecules, resulting in leukocyte tethering to the vascular bed, platelet aggregation, and coagulation derangements.[23,24] **Chen G et al and Ruan Q et al.** observed elevated IL-2R , IL-6, TNF-α, and IL-10 in severely ill COVID-19 patients, which might be

responsible for cytokine storm in these patients.[25,26]

Victor W.M.Van Hinsbergh (2012) described the importance of endothelium in the prevention of thromboembolic events, since it regulates the coagulation cascade by inhibiting various tissue factors with a Kunitz-type protease inhibitor known as the tissue factor pathway inhibitor (TFPI), that is found on the endothelial cell surface.[27] **Tang et al. (2020)** in their retrospective study analyzed that patients who died of COVID-19 had abnormal coagulation profile such as elevated D-dimer, prolonged prothrombin time and activated partial thromboplastin time.[15] All these above studies tells us about COVID-19 mediated endothelial damage, cytokine storm and abnormal coagulation in diseased patients.

In a study conducted by **Lodigiani et al.,** they found that hospitalised COVID-19 patients had the greatest risk of thrombo-embolic consequences. [28]

Epidemiological Burden of Thrombo-embolism in COVID-19

Mao et al. from Wuhan, China, conducted retrospective studies which reported that the prevalence of neurological manifestations, including cerebrovascular diseases, was 36.4%.[29] In patients who presented with confirmed or suspected COVID-19, the prevalence of thrombo-embolism was 20.4%.[30] In the study conducted by **Vogrig et al.,** it was found that six of the patients with laboratory findings of elevated D-dimer levels (>7,000 mg/L) and 40% of the patients had pulmonary thrombo-embolism. Another series showed that 67% of thrombo-embolic complications are ischemic in origin, while 33% are hemorrhagic.[31] **Elizabeth Whittaker et al. and in one of the large, multi-centre European cohort studies** found that thrombo-embolic complications did not occur in pediatric population with COVID-19.[32,33]

F. A. Klok, et al. conducted studies on COVID-19 patients admitted to ICU and found the cumulative incidence of thrombo-embolic complications was about 31%, with the majority of the patients were found to have pulmonary thrombo-embolism.[34] **Chuan Qin et al.** in their conducted cohort studies, found that there was an increased severity and related thrombo-embolic complications in COVID-19 patients with a prior history of stroke, in which many of them were elderly with other associated co-morbidities.[35] In support of the **Chuan Qin et al.** studies, another retrospective cohort study conducted by **Fei Zhou et al.** found that increased hospital mortality was among patients who were elderly, patients those with high SOFA (sequential organ failure assessment) score and patients with elevated D-dimer values.[36]

Choudry et al. found that vascular complications are more common in COVID-19 patients with existing cardiac comorbidities.[37] To support the above evidence, there were studies by **S.E.Janus et al and Sethi et al.,** both demonstrating the presence of right ventricular clots on echocardiography in COVID-19 patients.[38,39]

Dominic Wichmann et al. conducted a prospective cohort study on 12 deceased COVID- 19 patients, found that 7 out of 12 patients (58%) had deep venous thrombosis, with pulmonary embolism being the direct cause of death in 4 patients.[40]

Louise Bowles et al. did coagulation screening in patients with COVID-19 and found the presence of auto-antibodies, such as lupus anticoagulant, in the majority of the patients, concluding that lupus anticoagulant may activate the coagulation pathways and increase the thrombo-embolic risk.[41]

In their prospective study of COVID-19 patients, **Hottz et al.** found that there was increased platelet activation and the formation of platelet-monocyte aggregates in patients with severe COVID-19 infections but not in patients with mild COVID-19 infections. They stated the reason to be increased expression of tissue factor(TF) caused by the platelets in monocytes, which in turn activates the extrinsic coagulation pathways, causing the hypercoagulability in severely ill COVID-19 patients.[42]

Younes Zaid et al. found the presence of SARS-CoV-2 RNA in the platelets of COVID- 19 patients, which results in their degranulation and release of cytokines.[43] From the above two studies by **Hottz etal. and Younes Zaid et al.,** we can infer that platelets also have a role in the thrombo-inflammatory process that occurs in the COVID-19 patients.

Leo Nicolai et al. conducted histopathological and immunofluorescent studies in the autopsy specimens of COVID-19 patients and concluded that there is excessive platelet and neutrophil activation, neutrophil-platelet aggregate formation, and neutrophil extracellular traps in the COVID-19 patients.[44] These above-conducted studies show us that SARS-Cov 2 causes thrombo-inflammatory changes in the affected individuals through several mechanisms.

NERVOUS SYSTEM INVOLVEMENT IN COVID-19 INFECTION

Giacomelli et al., 2020 and Lechien et al., 2020[45,46] in their cross-sectional studies reported gustatory and olfactory symptoms in COVID-19 patients. Their hypothesis also suggested that early neurological symptoms in these patients, which appeared before respiratory symptoms, may have been caused by an early viral invasion of the nervous system through the olfactory bulbs. In support of the above studies, **Politi et al. (2020)**[47] reported a patient with SARS-CoV-2 infection with acute anosmia and only mild respiratory symptoms. This patient's MRI revealed hyper-intense right gyrus rectus and both olfactory bulbs on the fluid-attenuated inversion recovery (FLAIR) sequence, providing additional evidence that the olfactory pathway is engaged. In contrast to the studies mentioned above, **D. Fumagalli et al.**[48] observed that mice exposed to SARS- CoV 2 by aerosols, experienced anosmia and respiratory illness. However, only on intra- nasal inoculation it resulted in lethal neuroinvasion. They concluded that aerosol exposure did not cause neurological symptoms, i.e., anosmia might be the only symptom of COVID-19 without neuroinvasion. As mentioned earlier, **Mao et al.(2020)**[29] in their retrospective observational study of cases from 3 hospitals in China found out that 36.4% of COVID-19 patients had neurological manifestations. Among them, the majority of the patients had severe respiratory illness. They concluded that if a COVID-19 patient had neurological manifestations, severe ARDS should be suspected.

In a retrospective analysis, **Kandemirli et al.(2020)**[49] included 749 COVID-19 patients who had

MRI of the brain. Out of the 57 patients who underwent brain MRI, 12 had positive imaging results for leptomeningeal enhancement and FLAIR cortical signal anomalies, raising the probability of encephalitis**. Alireza Radmanesh et al.**[50] in their retrospective analysis of MR brain imaging of COVID-19 patients found that the majority of these patients had diffuse leukoencephalopathy changes and juxta-cortical/callosal micro-hemorrhages. Massive hemorrhages did not occur among study subjects.

Mahammedi and Gasparotti et al.(2020)[51] conducted a multicentric retrospective observational study in Italy with RT-PCR confirmed hospitalised COVID-19 patients who had acute neurological symptoms and underwent neuroimaging. They found out that the majority of the patients had acute ischemic infarctions and intra-cerebral haemorrhage. It was observed that patients with acute ischemic infarctions predominated over those with intracerebral hemorrhage.

Neo Poyiadji et al.[52] reported a COVID-19 patient with altered mental status and MR neuroimaging revealed hemorrhagic rim enhancing lesions in both thalami, medial temporal lobes, and subinsular areas, suggesting acute necrotizing encephalopathy.

Princiotta Cariddi L et al.[53] reported a case of COVID-19 with altered mental status, and brain imaging revealed features of posterior reversible encephalopathy syndrome (PRES). They hypothesised that it was caused by SARS-CoV-2-induced cerebrovascular endothelial dysfunction, which disrupts the blood-brain barrier.

In their retrospective, single-center cohort study, **Alberto Benussi et al.**[54] evaluated COVID-19 vs. non-COVID-19 hospitalised patients in the neuro ICU. When compared to patients without COVID-19, patients with COVID-19 had a greater incidence of strokes with poorer outcomes.

Syahrul S et al.[55] did a comprehensive review and meta-analysis to analyse the global prevalence of ischemic and hemorrhagic stroke in COVID-19 patients. They reviewed several studies and found that the combined prevalence of ischemic stroke was 1.11% among 58,104 COVID-19 patients and 0.46% among 67,155 COVID-19 patients. Hemorrhagic stroke was less prevalent (incidence: 28.42%) than ischemic stroke (incidence: 71.58%) among COVID-19 patients.

Abdalkader et al.,[56] in their multi-center, cross-sectional, retrospective study of patients, they found 8 COVID-19 patients with cortical venous sinus thrombosis who underwent imaging at 7 of 31 participating centers. The majority of patients (87.5%) were females who presented with focal neurological deficits or decreased consciousness. The most common sites for acute cerebral venous sinus thrombosis formation were found to be the superior sagittal and transverse sinuses.

ABDOMINAL INVOLVEMENT IN COVID-19 PATIENTS

Xiao et al.[57] evaluated 73 SARS-CoV-2-infected hospitalised patient's serum, nasopharyngeal and oropharyngeal swabs, urine, faeces, and tissues. 39 of the 73 SARS- CoV-2 hospitalised patients were positive for SARS-CoV-2 RNA in stool sample, comprising 25 males and 14 females. They hypothesised that viruses may spread via the feco-oral route.

The possible four mechanisms of Acute mesenteric ischemia in severe COVID-19 were described by **Parry AH et al.**[58] One is that COVID-19's hypercoagulable state itself may result in mesenteric vascular thrombosis. Vascular endothelium expresses angiotensin converting enzyme 2, the target receptor for severe acute respiratory syndrome 2 (SARS-CoV-2), resulting in endothelial dysfunction or damage and vascular thrombosis. Third, angiotensin converting enzyme 2 is expressed on small bowel enterocytes, the target receptor for SARS-Cov-2, may result in intestinal tropism and direct bowel damage. Finally, shock or hemodynamic compromise, which is common in severe COVID-19 pneumonia, can result in non-occlusive mesenteric ischemia.

A retrospective cross-sectional analysis was carried out by **Bhayana R et al.**[59] on COVID-19 patients who received abdominal imaging at single quaternary care centre between March 27 and April 10, 2020. A total of 224 patients underwent abdominal imaging. Abnormalities in the bowel wall were seen on 31% of CT images and were linked to ICU admission. Pneumatosis or portal venous gas was found in 20% of CT images obtained from ICU patients. A bowel infarction was found during the surgical correlation. Pathological findings revealed ischemic enteritis with patchy necrosis and fibrin thrombi in arterioles, implying a small vessel thrombosis mechanism. They suggested that the presence of pneumatosis should be interpreted with caution since it could be caused by mechanical ventilation in patients with severe COVID-19 or by an extension of air in the thorax (pneumothorax, pneumopericardium, or pneumomediastinum).

Several studies have found that portal vein thrombosis is less common than other thrombo-embolic complications. **Kushala WM Abeysekera et al. (2020)**[60] from Bristol haematology and oncology centre reported a chronic hepatitis B patient with controlled viral load and prior COVID-19 infection who presented with right upper quadrant pain in whom imaging revealed portal and superior mesenteric vein thrombosis. **Rahimian S et al.(2021)**[61] reported a case of an acute portal venous thrombosis following recovery from COVID-19 infection.

Similarly, **Neeraj Sharma et al.(2021)**[62] reported a case of portal vein thrombosis caused by COVID-19 infection. In a systematic review of case report studies, **Setare Kheyrandish et al.(2021)**[63] found up to 40 cases of portal vein thrombosis from approximately 34 studies.

The prevalence of portal vein thrombosis was found to be higher in men, and 50 percent of the 40 case studies had associated co-morbidities.

Besutti G et al.[64] reported three cases of COVID-19 patients in Italy who developed abdominal pain and underwent a CT abdominal angiogram. The first patient had renal artery thrombi as well as renal and splenic infarctions. The second patient had large infarcted areas in the spleen and left kidney. The third patient had small bowel ischemia associated with massive splenic infarction and was treated with heparin in continuous infusion after resection of the ischemic bowel loop and splenectomy. They concluded that if COVID-19 patients experience abdominal pain, visceral infarction should be suspected and further work up should be performed. From the above studies, we came to know that COVID-19 patients had acute mesenteric ischemia due to splanchnic vessel thrombosis, portal vein thrombosis, and solid organ infarcts due to their respective vessel occlusion.

DEEP VENOUS AND PULMONARY THROMBOEMBOLISM IN COVID-19 PATIENTS

Several studies show that deep venous thrombosis and acute pulmonary thrombo- embolism are more common than other vasculopathies in COVID-19 patients. In a comprehensive review and meta-analysis of 27 studies from January to June 2021, **Suh et al.** found that the cumulative incidence of deep vein thrombosis and pulmonary thrombo- embolism in COVID-19 patients was 16.5 and 14.8%, respectively.[65]

A) PULMONARY THROMBOEMBOLISM

Buen et al. conducted a study on thrombo-embolic events and apparent heparin resistance in hospitalised SARS-CoV 2 patients over a period of 1 month. Of the 75 patients who were admitted in ICU, 35 patients had clinical suspicion of thrombo-embolic events and underwent imaging studies. 16(21.3%) patients had pulmonary embolism involving segmental arteries while 4(2.7%) patients had central artery involvement. 2(2.7%) patients had ischemic cerebrovascular events and 3(4%) had DVT. So a total of 25(33.3%) patients among the admitted 75 COVID patients had thrombo-embolic events.[66]

Desborough et al. conducted a study on 66 patients admitted to ICU over a period of 1 month. They found that 10(15%) patients had at-least one episode of image proven thrombo-embolism, 6(9%) patients had DVT, and 5(8%) had changes in CTPA. Among the 5 image-proven pulmonary thrombosis patients, 3 had lobar involvement, and the other two had segmental and subsegmental involvement.[67]

F.A.Klok et al. evaluated the incidence of symptomatic acute pulmonary embolism, DVT, ischemic stroke, myocardial infarction, or systemic arterial embolism in 184 COVID-19 pneumonia patients admitted to the intensive care unit. They found that the cumulative incidence of composite outcomes was 31%, of which 27% had CTPA/USG proven VTE and 3.7% had arterial thrombotic events. They concluded that there is an unusually high incidence of thrombotic complications in the ICU patients.[34]

M.W.X.Ooi et al. conducted a study to define the prevalence of thrombo-embolic disease diagnosed on CTPA in COVID-19 patients. A total of 974 patients were included in the study, and 84 patients underwent CTPA. PTE was present in 38% (32/84) of the cases, with an overall prevalence of 3.3% (32/974). In patients with PTE, 75 % of thrombo- embolism was observed within small vessels (sub-segmental or smaller vessels) and 25% had thrombo-embolism within both small and larger vessels. PTE occurred in 50% of patients with moderate, severe, and very severe COVID-19 infections, while it occurred in 17% of patients with normal lung or mild disease. As a result, they found that PTE is more common in individuals with severe COVID-19 disease.[68]

J A Hippensteel et al. performed a one-month retrospective cohort study on the prevalence of venous thrombo-embolism in 91 critically ill COVID-19 patients admitted to ICU. 24 (26.1%) patients were found to have VTE, of which 21% were found to have lower extremity DVT, 25% had upper extremity DVT, 33% had internal jugular vein thrombus, and 21% had pulmonary emboli. They concluded that there is a high prevalence of VTE in critically ill patients with SARS

CoV-2 infection.[69]

B) DEEP VENOUS THROMBOSIS

Anna Maria et al. studied the prevalence of DVT in COVID-19 patients admitted to the ward using Lower Extremity Duplex Ultrasound (LEDUS). Of the 263 patients screened, DVT was detected in 67(25.5%) patients, of which 22 had bilateral DVT. In 21(31.3%) patients, DVT was found in femoral veins, 18(26.9%) in the popliteal vein, and 28 (41.8%) in calf veins. They concluded that DVT has a 25.5% prevalence in COVID-19 patients and it is reasonable to screen COVID patients for the same.[70]

Li Zhang et al. evaluated the prevalence, risk factors, and prognosis of DVT in COVID- 19 patients. The study was conducted among the 143 confirmed COVID-19 patients admitted to the hospital. From those, 66(46.1%) developed DVT, of which 23(34.8%) had proximal DVT and the rest, 43 (65.2%), had distal DVT. They concluded that there was a 43% prevalence of DVT in confirmed COVID-19 patients.[71]

Chuanqi Cai et al. conducted a retrospective cohort study to determine the prevalence and risk factors of DVT in COVID-19 patients. Among the screening of a total of 121 patients, 58(48%)patients were identified with DVT. At least 83% of DVT's were unilateral, and 17% had bilateral leg involvement. The overall prevalence of DVT among COVID-19 patients was found to be 48%, which was obviously higher than that in patients of general medicine wards (9–27%) and patients of ICUs (26–32%) before COVID - 19.[72]

Oleg Kerbikov et al. conducted a study to investigate the incidence of DVT in moderate to severe COVID-19. Among the 75 consecutive patients admitted with moderate to severe COVID-19 infection who were evaluated with duplex ultrasound, 53(70.7%) were detected to have markedly decreased venous flow velocity and blood stasis. DVT was found in 15 (20%) patients, of which 13 (86.7%) were found to have calf vein thrombus and 2 (13.3%) had ilio-femoral thrombosis. Hence, their study found a relatively high incidence of DVT in moderate to severe COVID-19 patients, and most of them had signs of decreased venous velocity and blood stasis.[73]

Voicu et al. conducted a prospective cohort study to determine the DVT characteristics in 55 COVID-19 adults who were mechanically ventilated. DVT was diagnosed in 19(35%) patients, including 5 (9%)femoral, 2(4%) popliteal, and 12(22%) below the knee sites. They concluded that there is an overall prevalence of about 33% DVT in critically ill COVID-19 patients, with a 9% DVT occurrence in the common femoral vein.[74]

PERIPHERAL ARTERIAL THROMBOSIS IN COVID-19 PATIENTS

Makoto Ogawa et al. conducted a retrospective study on patients who had a CT lower limb angiogram with a positive peripheral arterial occlusion as well as analysed their COVID-19 status. During their investigation, they found nine such patients. These patients also had high levels of inflammatory markers, d-dimers, and a history of hypertension or obesity. These patients, however, did not have a hypercoagulable disorder. Therefore, they hypothesised that COVID-19 patients with

co-morbidities are at an increased risk of peripheral arterial thrombosis.[75]

In their retrospective cohort study, comparing COVID-19 patients with propensity score- matched control patients, **Inessa A. Goldman et al.** found that the majority of COVID-19 patients had peripheral arterial thrombosis involving arteries such as the common iliac arteries, external iliac arteries, superficial femoral arteries, and popliteal arteries. Therefore, they concluded that COVID-19 patients are more likely to develop peripheral arterial thrombosis.[76]

AIM AND OBJECTIVES

1. To determine the incidence of vascular systemic complications in hospitalised COVID-19 positive patients.
2. To evaluate the total number of COVID-19 hospitalised patients who had multi- modality vascular imaging.
3. To know the usage status of multi-modality radiological imaging for vascular pathologies among them.
4. To determine the major vascular complications that have occurred in these COVID-19 patients.
5. To ascertain the systemic distribution of vascular complications in hospitalised COVID-19 patients who underwent vascular imaging.

MATERIAL & METHODS

The present study was conducted at CARE Hospital, Banjara Hills after taking informed consent waiver from the institutional ethics committee. Ethical committee approval was obtained prior to starting the study.

• **STUDY SITE:** This study was conducted in the department of radio-diagnosis, CARE Hospital, Banjara hills, Hyderabad, Telangana.

• **STUDY POPULATION**: COVID -19 positive patients (both symptomatic and asymptomatic) who were subjected to vascular imaging in our care inpatient, Radiology department.

• **STUDY DESIGN:** A retrospective cross sectional observational study.

• **SAMPLE SIZE JUSTIFICATION:-**

Since there is no evidence of previous literature showing the combined incidence of all the vascular systemic complications, sample size was calculated from a study **Grillet F et al.** [143]

Sample size is calculated using the formula

$$n \geq \frac{Z^2_{1-\alpha/2} \times p(1-p)}{d^2}$$

where n : Desired sample size Alpha (α) : Type 1 error rate p : Prevalence

d : Absolute error Substituting
$Z_{\alpha/2}$: 1.96 (from z table) at Type 1 error of 5 %

Prevalence (p) = 23 % (Prevalence of Pulmonary Embolism Detected by Pulmonary CT Angiography was 23 % In Patients With Severe COVID-19 Infection according to previous study [32])

Absolute error (d) = 15 % We get n = 31

Therefore, a minimum of 31 subjects was included as sample size in the present study.

STUDY PERIOD: MAY 1 2020 TO MAY 1 2021.

INCLUSION CRITERIA:

1. Patients with laboratory confirmed SARS-COV-2 infection on RT-PCR/TRUENAT/CBNAAT/RAT.
2. Patients of either sex from all age groups.
3. Both symptomatic and asymptomatic COVID-19 patients who came for imaging modalities.
4. All patients who could be imaged that is, who did not have contraindications to imaging.

EXCLUSION CRITERIA:

1. Pregnant patients.
2. Patients with known vasculitis due to any cause.
3. Our study excludes acute coronary syndromes since many COVID-19 patients did not undergo coronary imaging in our hospital during the study period.

METHODOLOGY

EQUIPMENTS USED:

- PHILIPS AFFINITI 70 ULTRASOUND MACHINE
- PHILIPS INCISIVE CT SCANNER 128 SLICE
- SIEMENS MAGNETOM AVANTO 1.5 T
  ERLANGEN, GERMANY.

Peripheral vascular imaging analysis in our study subjects

Duplex studies and CT/MR peripheral angiography of the upper and lower limbs underwent by our study group were evaluated for presence and extent of acute venous thrombosis and presence and extent of acute arterial occlusion. Philips affiniti 70 ultrasound machine was used for Doppler examination in our study subjects. Linear probes L12-5 and L12-3 were utilized for duplex assessment in these patients.

Neurological imaging analysis in our study subjects

For neurovascular complications, our study subjects had either CT neck and brain angiogram or MRI brain with MRA/MRV using time of flight (TOF) technique. The location and extent of acute

arterial thrombosis and venous sinus thrombosis, as well as the extent and presence of ischemic and hemorrhagic cerebral infarctions, were determined using CT angiogram images. Patients with evidence of diffusion restriction in MRI but no definite vascular occlusion on magnetic resonance angiography are also considered.

CT Pulmonary angiogram imaging analysis in our study subjects

The location and extent of the thrombus and the presence of lung infarcts in our hospitalised COVID-19 patients were all assessed using pulmonary CT angiography images done in our hospital using Philips incisive ct scanner 128 slice.

Gastro-intestinal contrast CT imaging analysis in our study subjects

The images of CECT abdomen/ CT abdominal angiogram were examined for evidence of arterial /venous thrombus (location and extent) like involvement of the IVC, portal, mesenteric and iliac vessels and associated manifestations of bowel ischemia or intestinal obstruction. The presence of evidence of solid organ infarction with respective vessel thrombosis was assessed.

Data of our study patients who underwent vascular imaging in our department will be reviewed from previous images and reports stored in PACS and analysed.

STATISTICAL ANALYSIS:

All the qualitative factors like sex, complications, etc. was represented by the frequencies and percentages. All quantitative parameters like Age,decrease in hematocrit value (%), etc., was represented by means and standard deviation.

To compare the mean difference between 2 groups for quantitative variables, t –test was used for independent samples. To find the association between qualitative factors, Chi- Square test is used.

All the data was entered and maintained in MS. Excel and analyzed by using SPSS 23.0 A p- value less than 0.05 was considered as significant for all statistical tests and comparison between the two study groups.

OPERATIONAL ALGORITHMS OF STUDY SUBJECTS

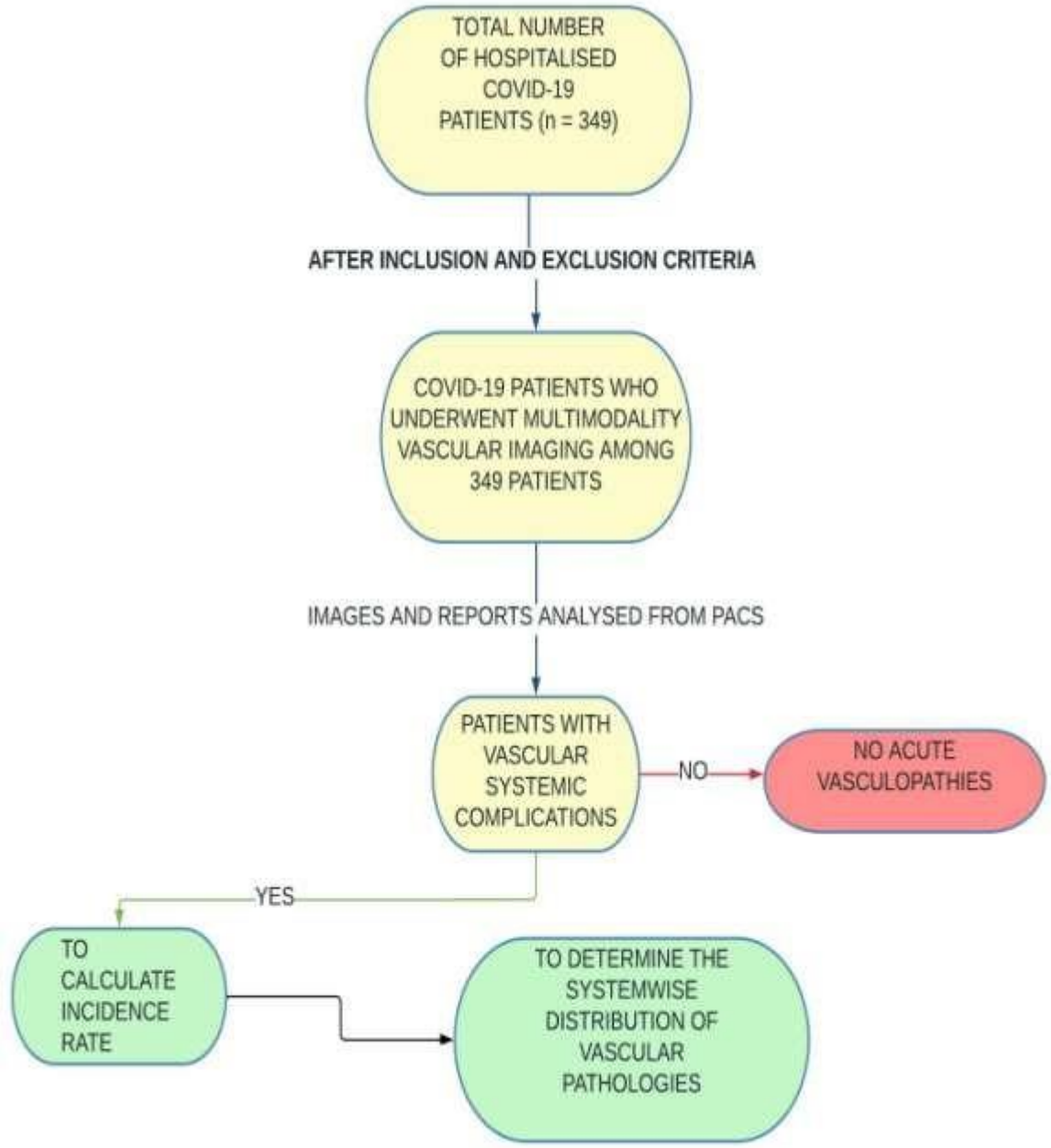


FIGURE 1

RESULTS & OBSERVATIONS

The present retrospective study was conducted in CARE Hospitals, Banjara hills, Hyderabad to know the incidence of vascular complications in the hospitalised COVID-19 patients who underwent various modalities of radiological imaging from May 1 2020 to May 1 2021.

TABLE-1: INCIDENCE RATE OF VASCULAR COMPLICATIONS IN OUR HOSPITALISED COVID-19 PATIENTS

No of COVID-19 patients admitted to wards	162
No of COVID-19 patients admitted to ICU	187
Total number of hospitalised COVID-19 patients including ICU and other ward admissions (162 + 187)	349
The total number of patients who underwent vascular imaging in our radiology department	33
Total positive cases for vascular thrombo-embolic complications	16
Total negative cases for vascular thrombo-embolic complications	17

In our hospital, there were 349 COVID-19 patients admitted during the study duration and 33 patients among them underwent vascular imaging in our radiology department. In these 33 patients, 16 patients were diagnosed with vascular systemic complications.

In the present study, the incidence of vascular complications in hospitalised COVID-19 patients who underwent radiological imaging was 4.58%.

TABLE-2: DISTRIBUTION OF AGE AMONG COVID-19 PATIENTS WHO UNDERWENT VASCULAR IMAGING

Statistics	**Age**
Mean	58.2424
Median	57.0000
Std. Deviation	14.41577
Minimum	37.00
Maximum	83.00

TABLE-3: DISTRIBUTION OF STUDY SUBJECTS WHO UNDERWENT VASCULAR IMAGING ACCORDING TO AGE GROUP

Age	Frequency	Percent
30-40	4	12.1
40-50	8	24.2
50-60	10	30.3
60-70	2	6.1
70-80	4	12.1
80-90	5	15.2
Total	**33**	**100.0**

FIGURE 2: GRAPHICAL REPRESENTATION OF AGE DISTRIBUTION OF STUDY SUBJECTS WHO UNDERWENT VASCULAR IMAGING

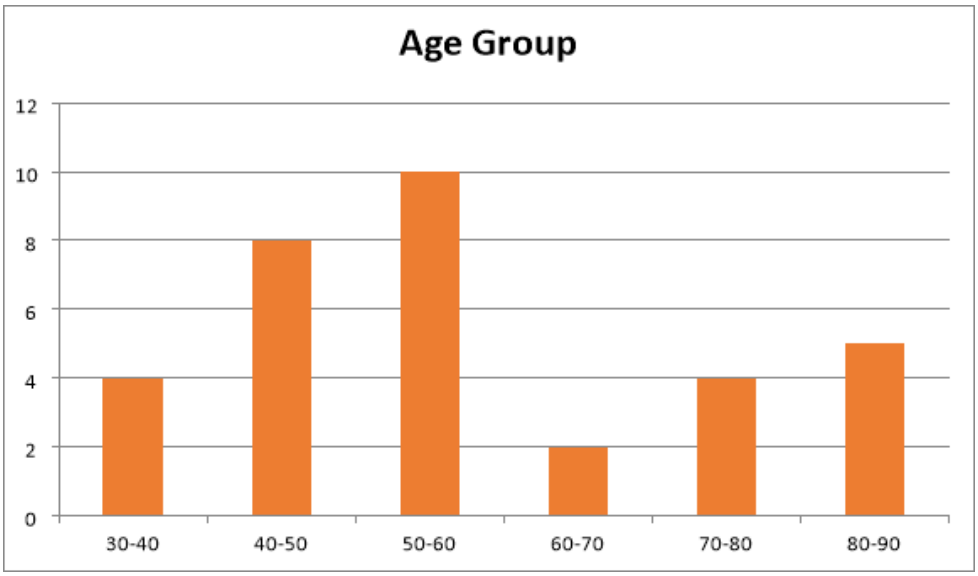
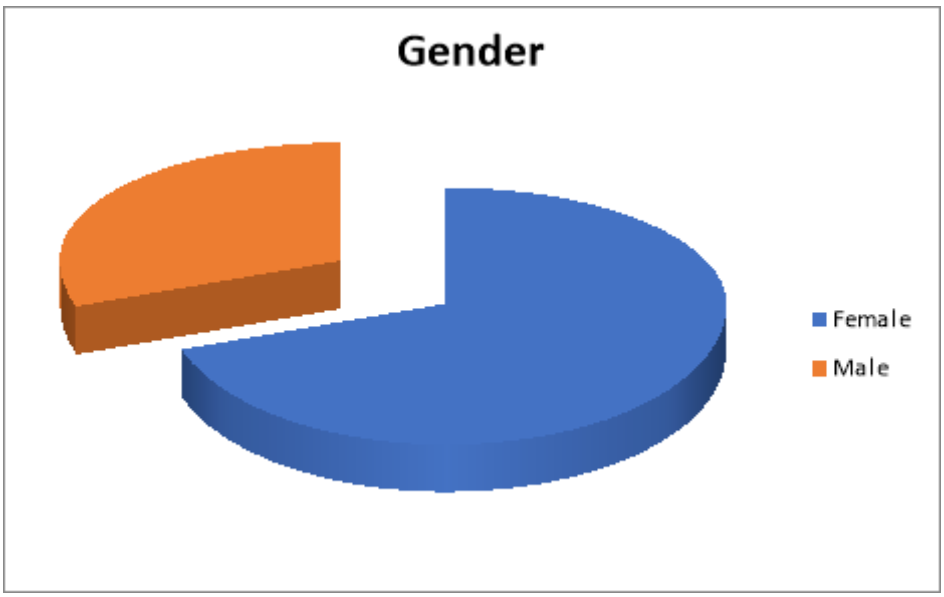


TABLE-4: GENDER DISTRIBUTION IN COVID-19 PATIENTS IN WHOM VASCULAR IMAGING WAS DONE IN OUR HOSPITAL

Gender	Frequency	Percent
Female	23	69.7
Male	10	30.3
Total	**33**	**100.0**

FIGURE 3: GRAPHICAL REPRESENTATION OF GENDER DISTRIBUTION IN COVID-19 PATIENTS IN WHOM VASCULAR IMAGING WAS DONE IN OUR HOSPITAL



Among the 33 COVID-19 patients who underwent radiological imaging for vascular complications in our study, majority were females and was between age group 50-60 years of age.

TABLE-5: DISTRIBUTION OF RESULTS RELATED TO ACUTE VASCULAR PATHOLOGY

RESULTS RELATED TO ACUTE VASCULAR PATHOLOGY	Frequency	Percent
NO	17	51.5
YES	16	48.5
Total	**33**	**100.0**

FIGURE 4: GRAPHICAL REPRESENTATION OF RESULTS RELATED TO ACUTE VASCULAR PATHOLOGY

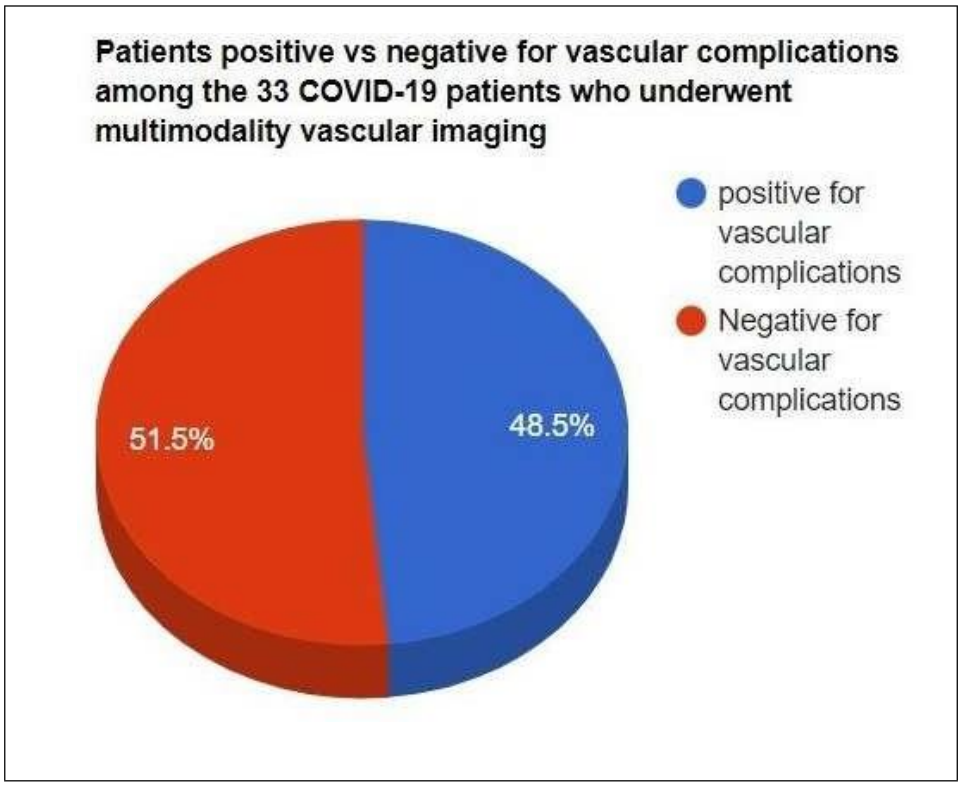


TABLE-6: DISTRIBUTION OF VASCULAR COMPLICATIONS IN OUR COVID- 19 PATIENTS ACCORDING TO AGE

AGE GROUP	FREQUENCY	%
30-40	2	12.5
40-50	4	25
50-60	3	18.7
60-70	2	12.5
70-80	2	12.5
80-90	3	18.8
TOTAL	**16**	**100**

FIGURE 5: PIE CHART REPRESENTATION AGE DISTRIBUTION OF VASCULAR COMPLICATIONS IN OUR COVID-19 PATIENTS

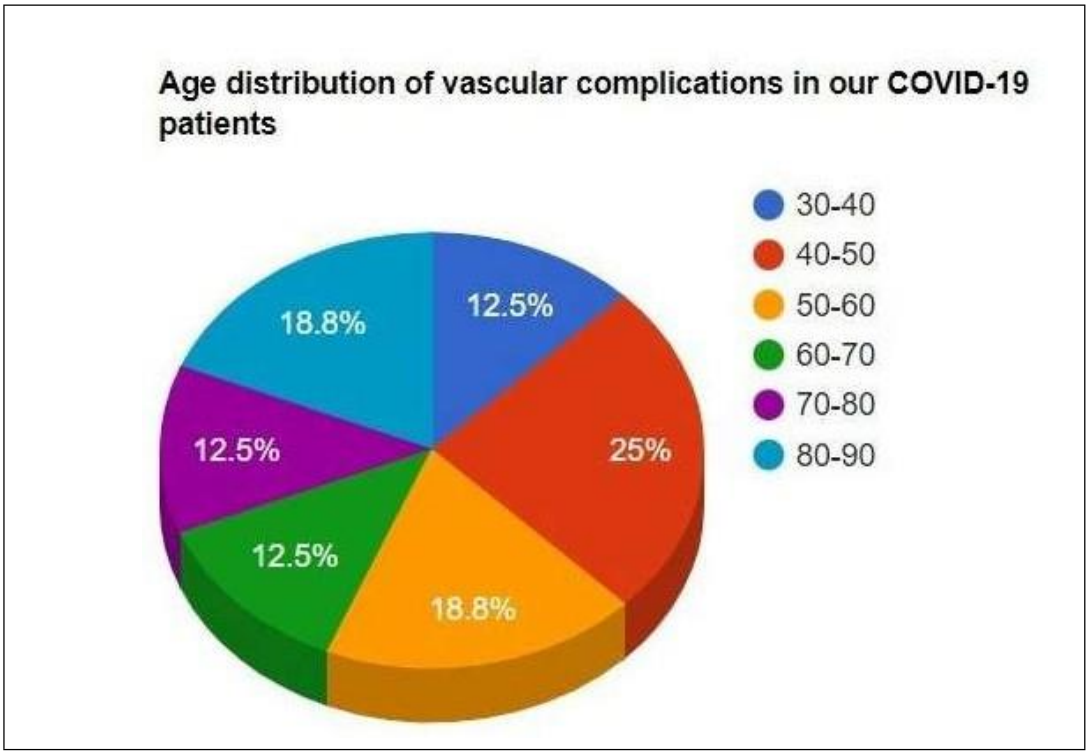
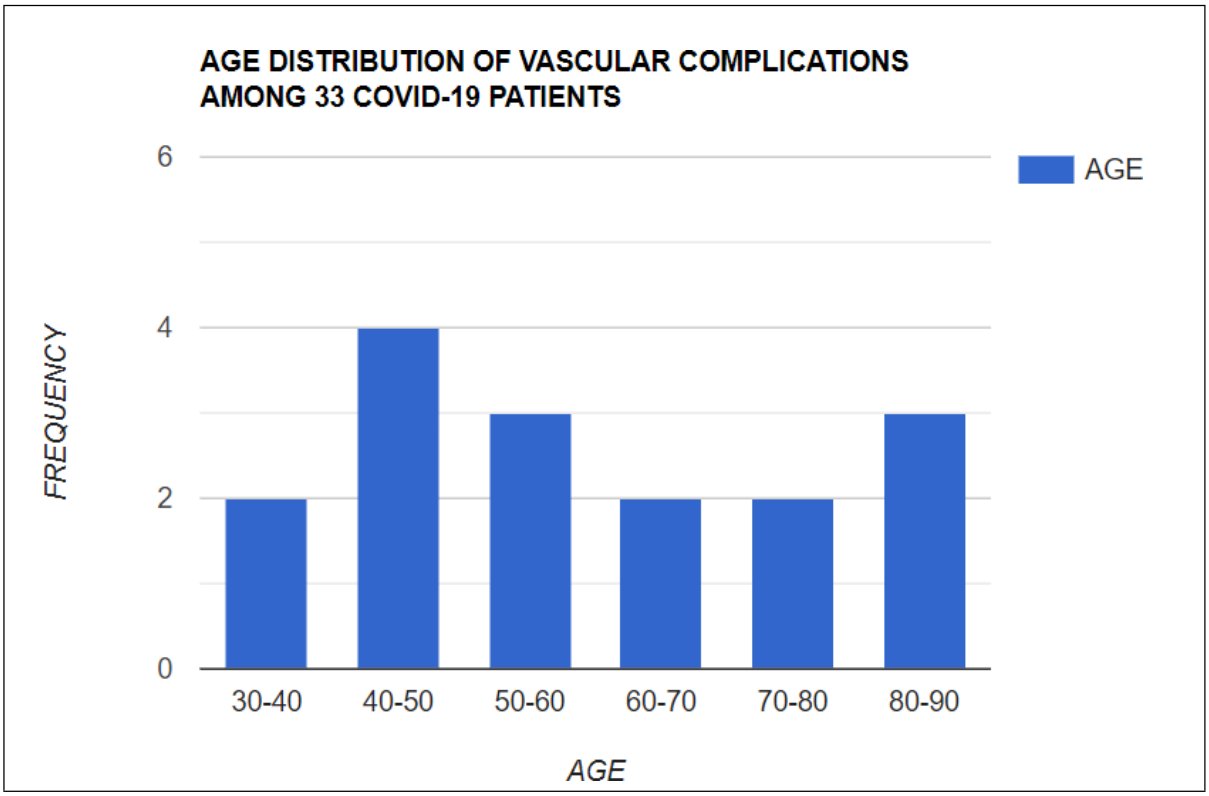


TABLE-7: DISTRIBUTION OF VASCULAR COMPLICATIONS IN OUR COVID-19 PATIENTS ACCORDING TO AGE

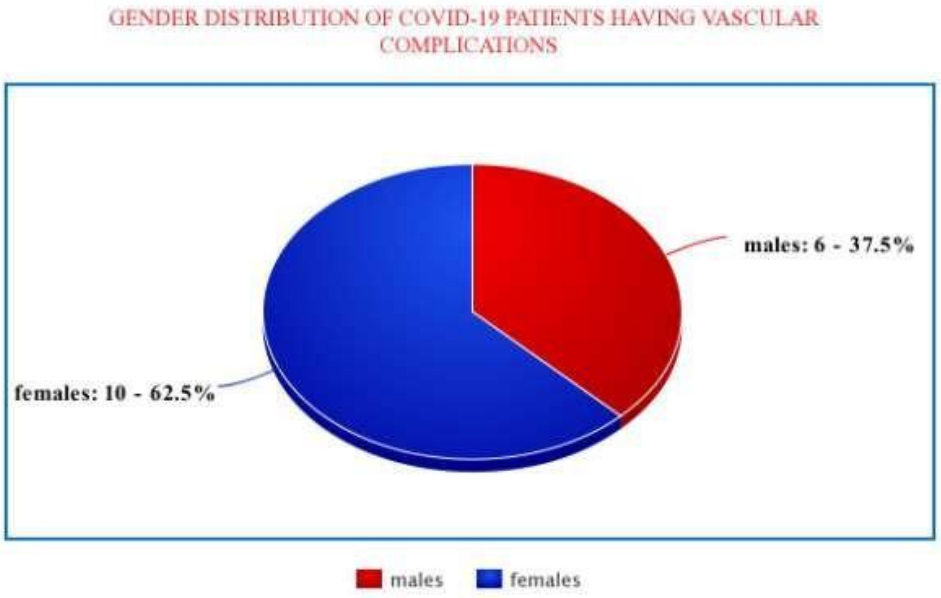
Statistics	Age
Mean	59.75
Median	58
Std. Deviation	15.56
Minimum	37.00
Maximum	84.00

FIGURE 6: BAR CHART REPRESENTATION AGE DISTRIBUTION OF VASCULAR COMPLICATIONS IN OUR COVID-19 PATIENTS



Patients with middle and elderly age groups were affected more with thrombo-embolic complications i.e, between the age group of 40 - 50 and 80-90.

FIGURE 7: GENDER DISTRIBUTION IN HOSPITALISED COVID-19 PATIENTS WITH VASCULAR COMPLICATIONS IN OUR STUDY.

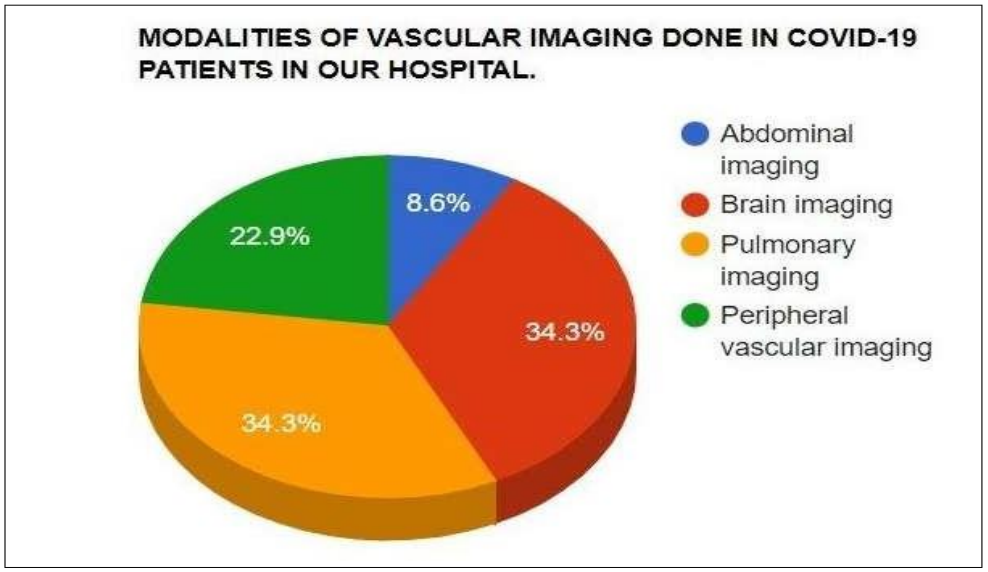


Number of females who underwent vascular imaging were more than males, and they had more thrombo-embolic complications.

TABLE-8: MODALITIES OF VASCULAR IMAGING DONE IN COVID-19 PATIENTS IN OUR HOSPITAL

1. ABDOMINAL VASCULAR IMAGING	**3**
CECT of abdomen (oral + IV contrast)/ CT abdominal angiogram (only IV contrast)	
2. VASCULAR IMAGING FOR INTRACRANIAL VESSELS	**12**
A) CT neck and brain angiogram	**5**
B) MRI brain with TOF (MRA or MRV)	**2**
C) MRI brain including CT brain angiogram	**3**
D) MRI brain (TOF imaging) done along with CT pulmonary angiogram	**2**
3.PERIPHERAL VASCULAR IMAGING	**8**
A) Lower limb venous Doppler	**4**
B) Arterial and venous Doppler of left upper limb	**1**
C) CT lower limb angiogram	**3**
4. PULMONARY VASCULAR IMAGING	**12**
A) CT pulmonary angiogram	

FIGURE 8: GRAPHICAL REPRESENTATION OF MODALITIES OF VASCULAR IMAGING DONE IN COVID-19 PATIENTS IN OUR HOSPITAL.



The majority of COVID-19 patients had a CT-pulmonary angiogram and MRI brain (+/- TOF) or a CT neck and brain angiogram. The reason for this is that the majority of patients were admitted to the ICU with worsening dyspnea or altered mental status, most likely due to respiratory distress and hypoxemia.

TABLE-9: DISTRIBUTION OF COVID-19 RELATED VASCULAR PATHOLOGIES (INTRA-CRANIAL VS ABDOMINAL VS PERIPHERAL (LIMBS) VS PULMONARY VASCULOPATHIES)

vascular pathologies	Positive (n=17)	Negative(n=19)	p-value
intra-cranial	6(35.29%)	7(36.84%)	0.92
abdominal	4(23.52%)	0	0.02
peripheral (Limbs)	3(17.64%)	5(26.31%)	0.53
pulmonary vasculopathies	4(23.52%)	7(36.84%)	0.39

Fisher exact test is used. P-value is insignificant, Expect abdominal.

Among the 33 patients, only 3 patients underwent CECT of abdomen that had thrombo- embolic problems. All three patients had thrombo-emobolic complications. One reason for relatively less imaging studies (MR/CT abdominal angiogram) was possibly due to the reason that not all patients had considerable gastrointestinal symptoms, which could be one reason why fewer imaging studies were performed.

FIGURE 9: COMPOUND BAR DIAGRAM OF SYSTEM-WISE DISTRIBUTION OF VASCULAR COMPLICATIONS AMONG OUR SUBJECTS

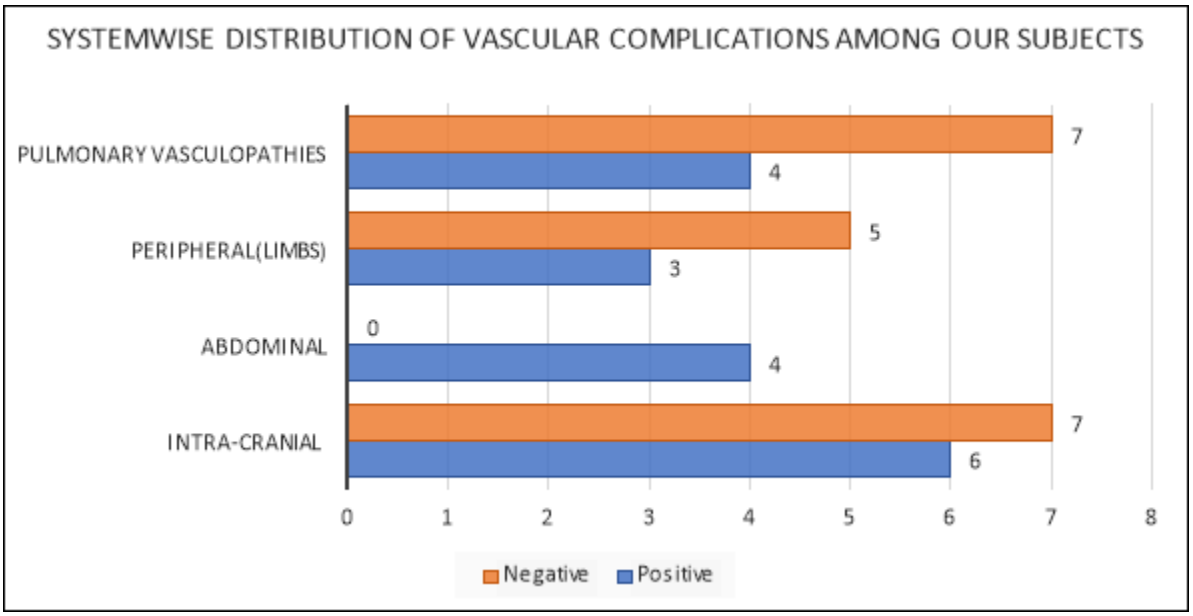


FIGURE 10: PIE CHART OF SYSTEM-WISE DISTRIBUTION OF VASCULAR COMPLICATIONS AMONG OUR SUBJECTS

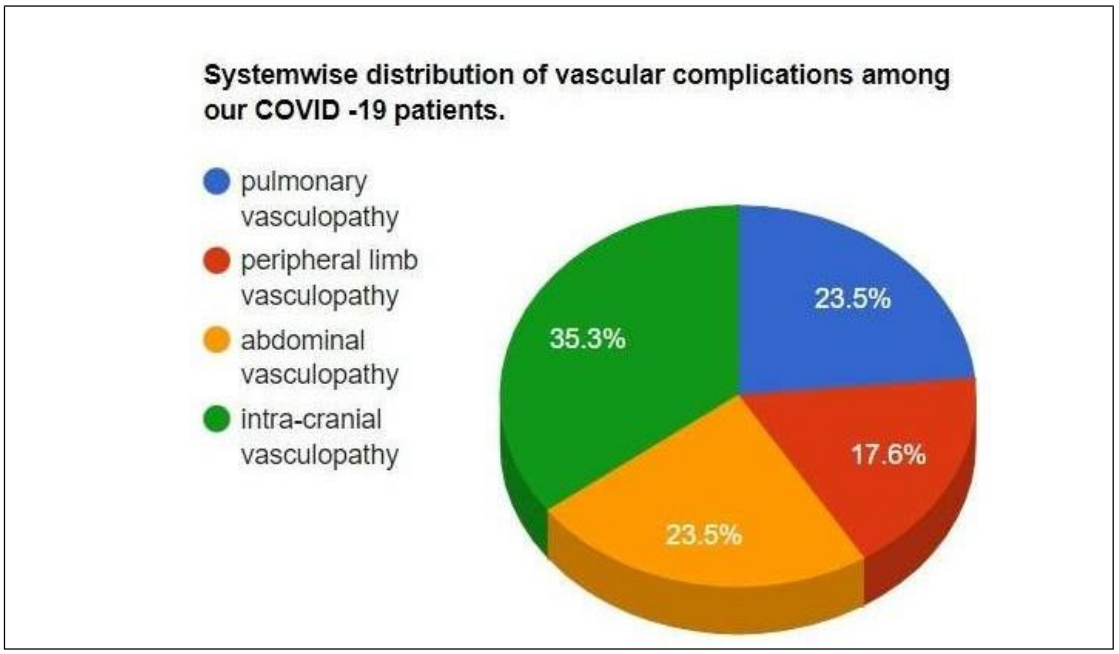


FIGURE 11: BAR CHART REPRESENTATION OF INCIDENCE OF VASCULAR COMPLICATIONS AMONG OUR SUBJECTS

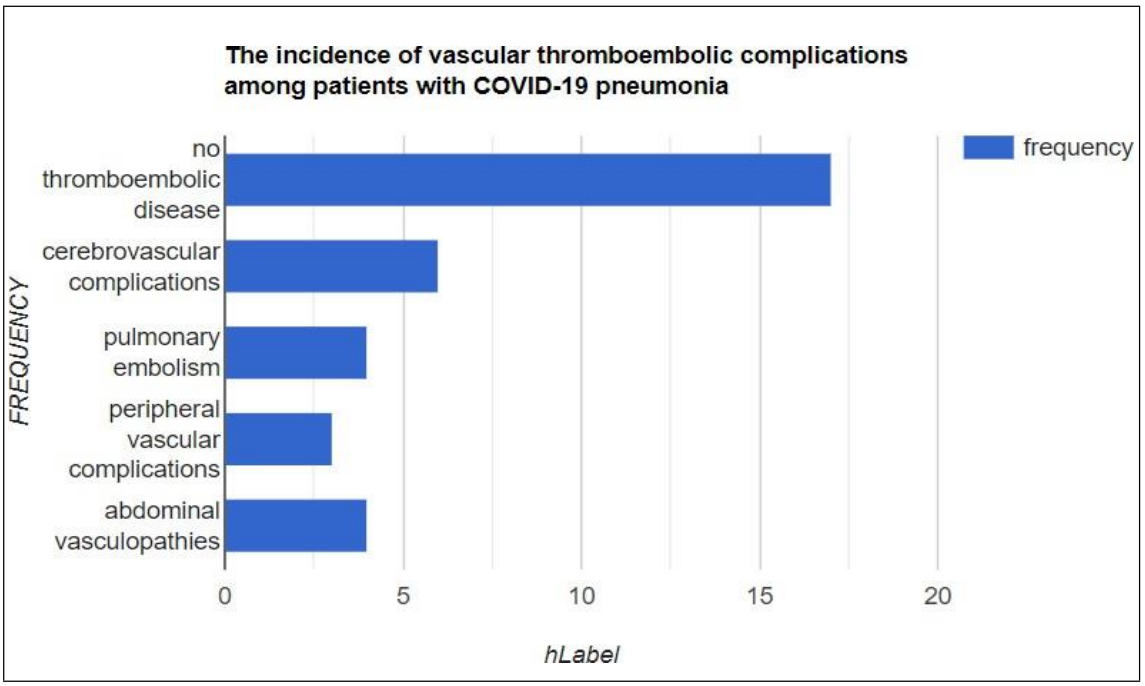


TABLE-10: SYSTEMWISE SPECIFICATION OF THE VASCULAR PATHOLOGIES IN THE HOSPITALISED COVID-19 PATIENTS

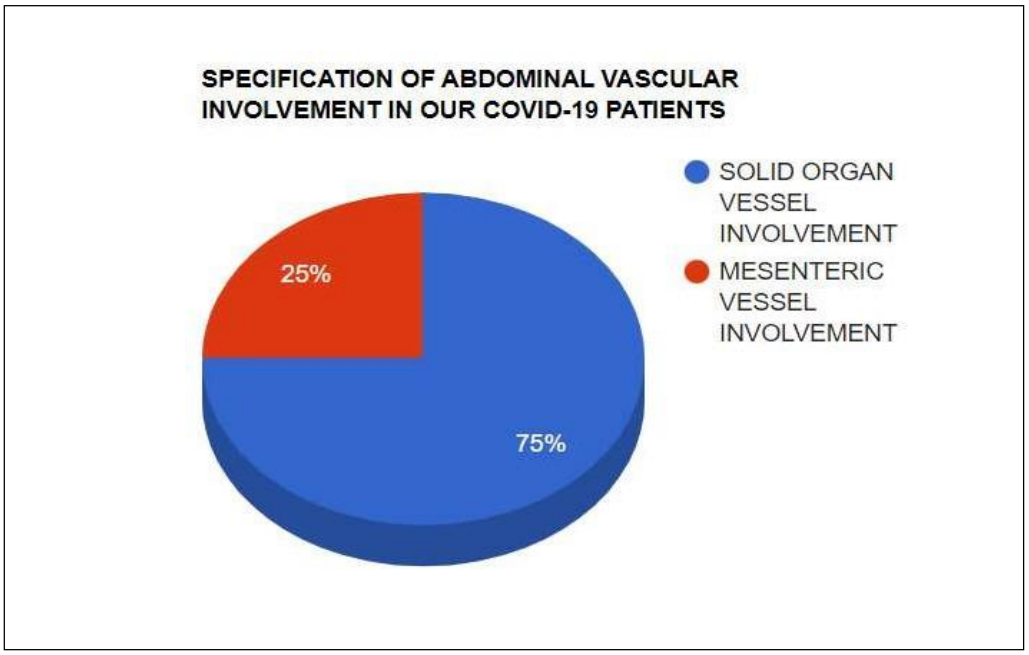
ABDOMINAL VASCULOPATHIES	
Involvement of splenic vessels (arterial/venous thrombosis)	**2**
Superior mesenteric artery thrombosis	**1**
Portal vein thrombosis	**1**
INTRACRANIAL VASCULOPATHIES	
Acute brain infarcts with internal carotid/middle cerebral arterial occlusion (thrombosis)	**4**
Acute brain infarct (hemorrhagic) with thrombosis of left transverse and sigmoid sinuses.	**1**
PERIPHERAL VASCULOPATHIES	
Lower limb Involvement	
Thrombosis of tibio-peroneal arteries	**1**
Deep venous thrombosis involving common femoral vein	**1**
Upper limb Involvement	**1**
Radial artery thrombosis	
PULMONARY VASCULOPATHIES	**4**
Acute pulmonary thrombo-embolism involving the right pulmonary artery (interlobar/ its segmental branches)	

ONE PATIENT WAS FOUND TO HAVE PULMONARY AS WELL AS CEREBRAL VASCULAR INVOLVEMENT

TABLE-11: DISTRIBUTION OF POSITIVE VS NEGATIVE CASES FOR VASCULOPATHIES IN EACH SYSTEM MENTIONED ABOVE.

A) **ABDOMINAL VASCULOPATHIES**	**Frequency**
Splenic infarcts due to splenic artery thrombosis	1
superior mesenteric artery thrombosis	1
Splenic vein thrombosis	1
Portal vein thrombosis	1

FIGURE 12: PIE CHART OF SPECIFICATION OF ABDOMINAL VASCULAR COMPLICATIONS AMONG OUR SUBJECTS



We had cases of splenic infarct, splenic vessel thrombosis, portal vein thrombosis and superior mesenteric artery thrombosis. However, there were no cases of acute bowel pathologies such as mesenteric ischemia with bowel infarcts. We did not encounter cases of renal infarcts due to renal arterial occlusion.

B) **INTRACRANIAL VASCULOPATHIES**	**Positive**	**Negative**
Acute ischemic infarcts due to arterial occlusion.	3	0
Acute infarct with hemorrhagic transformation due to arterial occlusion	1	0
Acute hemorrhagic infarcts with dural sinus venous thrombosis	1	0
Negative for acute infarct/intracranial vasculopathies	0	7
case of acute sub-arachnoid and sub-dural hemorrhage without further vascular imaging	1	0

FIGURE 13: PIE CHART OF POSITIVE VS NEGATIVE STUDY FOR CEREBROVASCULAR COMPLICATIONS AMONG OUR SUBJECTS

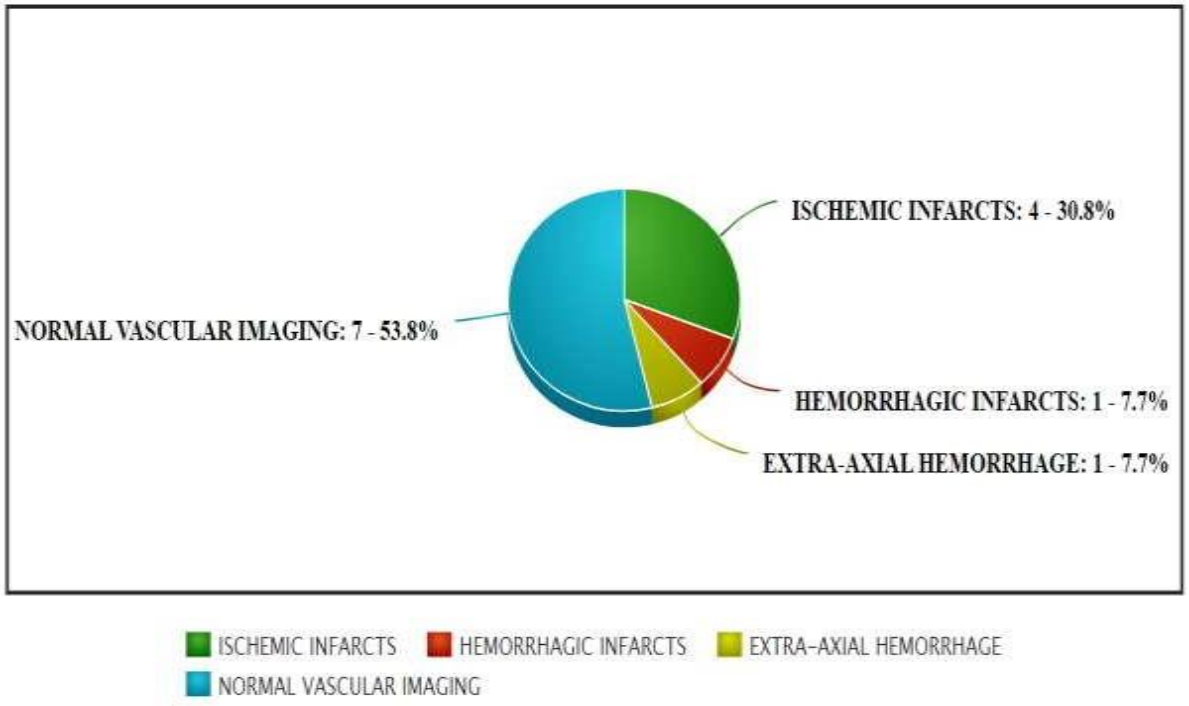
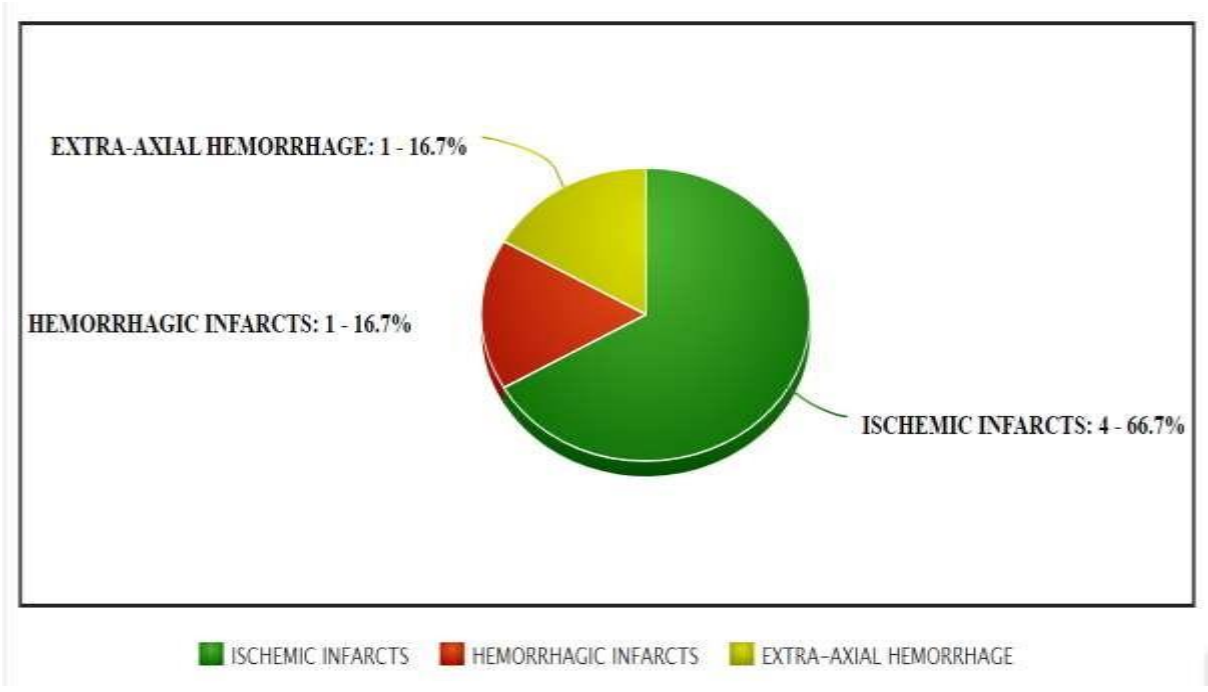


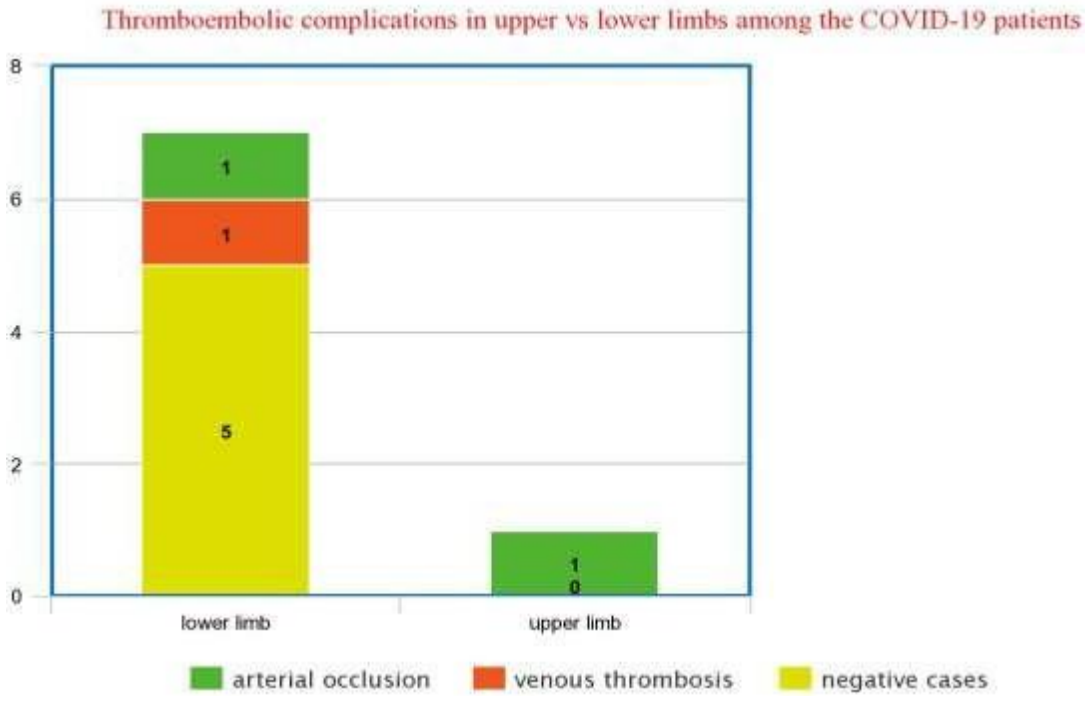
FIGURE 14: PIE CHART OF DISTRIBUTION AND SPECIFICATION OF CEREBROVASCULAR COMPLICATIONS AMONG OUR SUBJECTS



Acute ischemic brain infarcts predominated in our cases more than the hemorrhagic brain infarcts. The majority of the ischemic infarcts were due to internal carotid and middle cerebral arterial thrombosis. Hemorrhagic infarct with dural sinus thrombosis involving the transverse and sigmoid sinuses.

C) **PERIPHERAL VASCULAR COMPLICATIONS**	**Positive**	**Negative**
Lower limb arterial occlusion/thrombosis	1	2
Deep Venous Thrombosis of Lower Limbs	1	3
Upper limb arterial occlusion	1	0

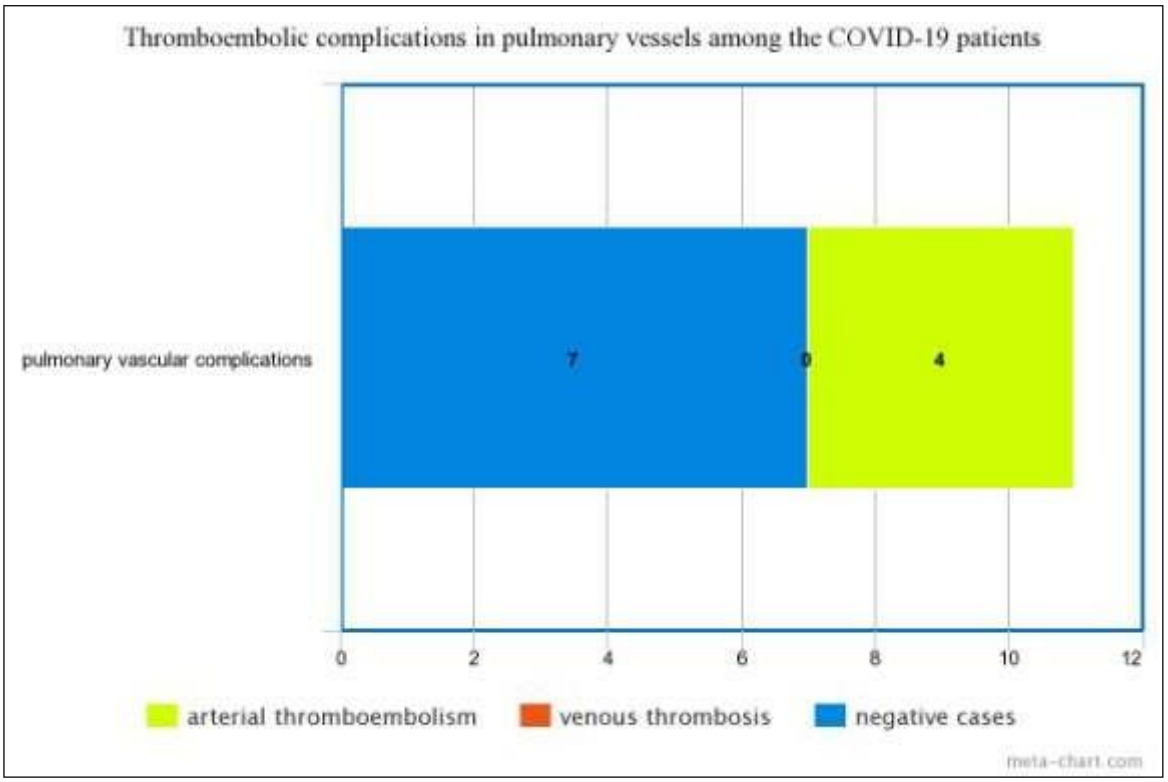
FIGURE 15: STACKED BAR CHART REPRESENTATION OF DISTRIBUTION AND SPECIFICATION OF PERIPHERAL VASCULAR COMPLICATIONS AMONG OUR SUBJECTS



In the peripheral vascular system, there was an equal proportion of cases with arterial thrombus involving both lower and upper limbs (1:1). There was one case of lower limb deep venous thrombosis. In our studies, there was no involvement of upper limb venous system.

D) **PULMONARY VASCULOPATHIES**	**Positive**	**Negative**
Acute pulmonary thrombo-embolism	4	7

FIGURE 16: STACKED BAR CHART REPRESENTATION OF DISTRIBUTION AND SPECIFICATION OF PULMONARY VASCULAR COMPLICATIONS AMONG OUR SUBJECTS

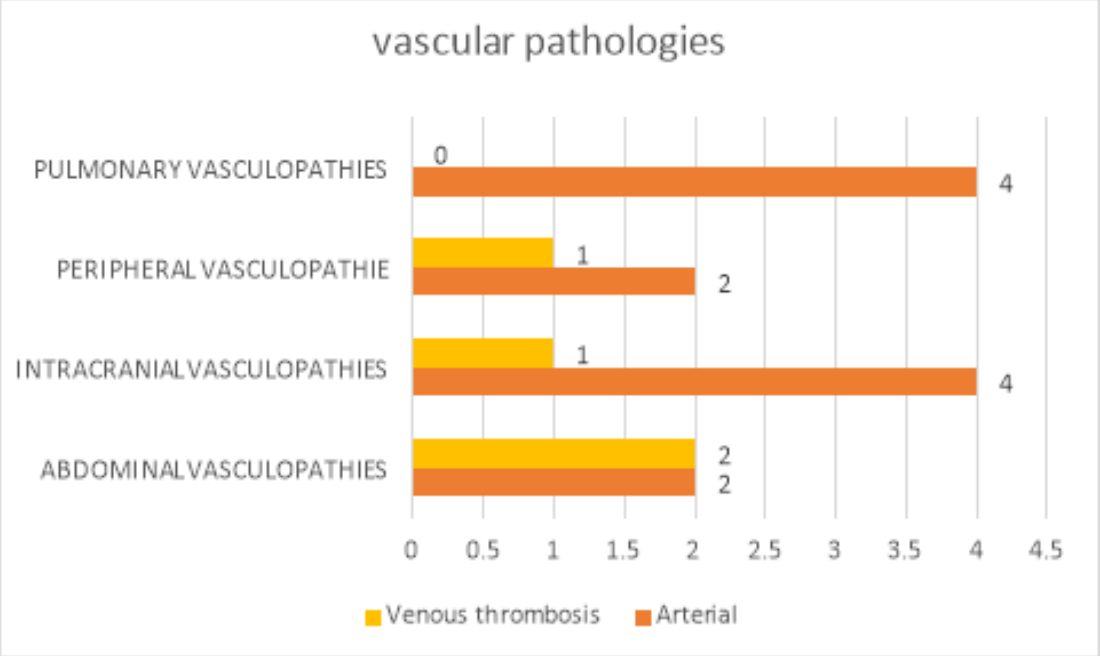


Among the 4 cases of acute pulmonary thrombo-embolism, all of these patients had involvement of the inter-lobar and segmental branches of right pulmonary artery.

TABLE 12: SYSTEMWISE DISTRIBUTION OF ARTERIAL AND VENOUS VASCULAR PATHOLOGY AMONG THE COVID-19 PATIENTS IN OUR STUDY

VASCULAR PATHOLOGIES	ARTERIAL OCCLUSION	VENOUS OCCLUSION
ABDOMINAL VASCULOPATHIES	2	2
INTRACRANIAL VASCULOPATHIES	4	1
PERIPHERAL VASCULAR COMPLICATIONS	2	1
PULMONARY VASCULAR COMPLICATIONS	4	0

FIGURE 17: COMPOUND BAR CHART OF SYSTEMWISE DISTRIBUTION OF ARTERIAL AND VENOUS VASCULAR PATHOLOGY AMONG OUR STUDY GROUP.



With the exception of abdominal vasculopathies, all systemic vasculopathies had more arterial involvement than venous occlusion.

DISCUSSION

SARS-CoV-2 first emerged in December 2019 in Wuhan, China, and has since spread throughout the world. In March 2020, the World Health Organization declared the corona- virus outbreak a pandemic. COVID-19 severe forms primarily manifest as acute pulmonary respiratory syndrome. Several studies have found that patients with severe COVID-19 infections are more likely to develop cytokine storms and thrombo-embolic states.

The present study is a retrospective, observational study to determine the incidence of vascular complications among the COVID-19 patients admitted to our hospital during the study period of May 1 2020 to May 1 2021, who underwent multi-modality imaging in the Department of Radiology, Care Hospital, Banjara Hills. Out of 349 COVID- 19 patients admitted to our hospital, 33 patients, including ICU and ward admissions, had vascular imaging in our radiology department. In imaging, 16 (48.5%) of the 33 patients had vascular systemic complications, whereas 17 (51.5%) had no vascular pathologies. The incidence rate of thrombo-embolic complications among the hospitalised COVID-19 patients in our study group was found to be 4.58%.

Piazza et al.[77] found in their retrospective cohort study on COVID-19 patients in Boston hospital, USA that major arterial or venous thrombotic episodes occurred in approximately 5.9% of the hospitalised patients. **Hanif et al**. [78] in their retrospective study of 921 COVD-19 patients in New York city hospital reported 16 patients (1.7%) had venous thrombo-embolism (VTE) confirmed with imaging, 11 patients had an ischemic stroke, and 2 patients developed limb ischemia.

In our study group, the minimum age of COVID-19 patients with vascular complications was 37 years and the maximum of 84 years. The mean age was 58.2±14.4 years. Maximum number of systemic thrombo-embolic complications were found in 40-50 years (25%), followed by 50-60 years (18.7%), and the 80-90 years age group (18.8%). In the present study, among 16 COVID-19 cases with vascular complications, 62.5% were female and 37.5% were male patients.

In retrospective observational study by **M.F. Yusuf Mohamud and M.S. Mukhtar**[79] in COVID-19 patients, thrombo-embolic events occurred in patients with age group more than 65-year-old. In contrast to our study, where females appear to be affected more than males, there was no significant gender difference in the appearance of thrombo-embolic complications among COVID-19 patients in this study. In a single center cohort study for the incidence of venous thrombo-embolism (VTE) in 198 hospitalized COVID-19 patients, conducted by **Middeldorp S et al. (2020)**,[80] they found the mean age of thromboembolism was 61 years and the majority of them with thrombo-embolic complications (66%) were male. In another retrospective study by **B.Tholin et al.,**[81] to determine the 90-day incidence of venous and arterial thrombo-embolic complications in hospitalized COVID-19 patients in ten Norwegian hospitals, found the mean age of COVID-19 patients with thromboembolic complications was 61.5 years and the majority of them (52%) were males.

RADIOLOGICAL IMAGING MODALITIES USAGE AMONG STUDY GROUP

CT-Pulmonary Angiogram (34.3%) and cerebral imaging including MRI Brain with MRA/MRV using time of flight technique /CT neck and Brain Angiogram (34.3%) was most common imaging modality in present study group followed by peripheral vascular imaging including CT-Lower Limb Angiogram and arterial/venous Doppler of peripheries (22.9%) and CECT/CT abdominal angiogram (8.6%).

VASCULAR COMPLICATIONS AMONG HOSPITALISED COVID-19 PATIENTS

Acute cerebrovascular events predominated in our study group compared to other systemic vascular complications. The patterns of brain ischemia in patients with COVID-19 may include large vessel occlusion with territorial infarct and hypoxic-ischemic injury related to hypoxemia or cardiopulmonary arrest. Severe hypoxic-ischemic injury manifests in regions of greater metabolic demand, such as the cortex, basal ganglia, and thalamus.The presence of severe hypoxic-ischemic injury may be implicated in a longer hospital stay, larger neurological sequelae, and a dismal prognosis. In the present study, among 349 hospitalised COVID-19 patients, brain imaging was done in 12 hospitalised COVID-19 patients.

It was found that the distribution of vascular pathologies were as follows - Majority of the COVID-19 patients who underwent radiological imaging had cerebrovascular complications (35.3%) such as acute ischemic brain infarcts (30.8%), acute hemorrhagic infarcts (7.7%) and extra-axial hemorrhage (7.7%). 53.8% of patients did not have any acute cerebrovascular events. In retrospective observational cohort study by **Siegler JE et al.**[82] in hospitalised COVID-19 patients treated at 31 hospitals in four countries, they found that 1.13% of patients had acute cerebrovascular events in which the majority of patients had acute ischemic stroke (1.08%), about 0.19% had intra-cranial hemorrhage and 0.02% had cortical venous sinus thrombosis. They also concluded that, although the incidence rate of acute cerebrovascular events was lower among hospitalised COVID-19 patients, their prognosis was worse when compared to the general population with cerebrovascular events.

Several studies have reported an increase in the incidence of ischemic strokes secondary to occlusion of large vessels in patients infected with SARS-CoV-2. They concluded that vascular occlusion could be connected to a pro-thrombotic state related to angiotensin- converting enzyme 2 (ACE2) down-regulation and inflammation induced coagulopathy in COVID-19. Additionally, changes in coagulation with increased D-dimer level and fibrin/fibrinogen degradation products may be seen in these patients. Such abnormalities may be related to a higher incidence of thrombotic events, including ischemic stroke related to large vessel occlusions, as well as pulmonary thrombo-embolism related to venous thrombosis in these patients.

In 33 COVID-19 patients who underwent imaging, 11 patients had CT-Pulmonary angiogram. Out of 11 patients, 4 patients had acute pulmonary thrombo-embolism. Next to acute cerebrovascular events, acute pulmonary thrombo-embolism (23.5%) predominated in patients of our study group.

One patient who underwent both brain imaging and CT pulmonary angiography had both acute cerebrovascular complication as well as acute pulmonary thrombo-embolism. **B.Tholin et al.**[81] in their retrospective study among hospitalized COVID-19 patients, reported that among a total of 38 patients with thrombo- embolic events in their study 23 patients had acute pulmonary thrombo-embolism.

Similar to acute pulmonary thrombo-embolism, there was equal incidence of abdominal vascular complications (23.5%) in our study group. There was 3 patients who underwent CECT/CT abdominal angiography. We had totally 4 cases of acute vascular events in which one patient had splenic vein thrombosis incidentally found during CT pulmonary angiogram. There was one case of solid organ infarct involving the spleen due to splenic artery thrombosis and a case of superior mesenteric artery thrombosis without any imaging features of mesenteric ischemia/bowel infarcts. One patient had portal venous thrombosis in our study group. In their observational cross-sectional study of COVID-19 patients, **Omar et al.**[83] found 124 patients with thrombo-embolic complications. 19 of them (15.3%) had gastrointestinal thrombo-embolic complications. Isolated superior mesenteric vein thrombosis was found in 4 patients (21%), isolated portal vein thrombosis in 3 patients (15.8%), isolated inferior vein thrombosis in 1 patient (5.3%), and combined vein thrombosis in 9 patients (47.4%). Arterial thrombosis in the superior mesenteric artery was found in two patients (10.5%), both of whom had bowel ischemia and intestinal obstruction.

In our study, three (16.9%) of the 33 COVID-19 patients who underwent vascular imaging had peripheral vascular complications. There was one case of acute lower limb arterial thrombosis involving the tibio-peroneal arteries among three patients who had a CT lower limb angiogram. One COVID-19 patient had acute deep venous thrombosis of the left common femoral vein, and three patients were negative for acute deep venous thrombosis on bedside Doppler evaluation. One patient in our study group underwent an arterial and venous Doppler of the left upper limb and was found to have left radial artery thrombosis.

In a recent Dutch paper, symptomatic VTE was diagnosed in 28 (15% of total; cumulative rate 27%) of 184 patients receiving thromboprophylaxis during intensive care and mainly consisted of PE (n = 25).[34] In the Dutch study, only a minority of patients experienced arterial thrombotic events (n = 3).[34] According to a Chinese study, the prevalence of VTE was 25% with routine VTE screening, although details on the type and timing of screening were not provided. These values appear much higher than the rate of symptomatic VTE events observed in thromboprophylaxis trials, not exceeding 3% in patients not receiving anticoagulant therapy and < 1% on thromboprophylaxis,[85] but in line with what observed in patients with sepsis or shock.[86,87] A recent analysis from a French group showed that the rate of thrombo-embolic complications in 150 COVID-19 patients with ARDS was much higher (11.7%) than what observed in a historical control group of non-COVID-19 ARDS patients (2.1%) despite anti-coagulation. **Omar et al.**[83] reported 17 (13.7%) patients with peripheral thrombo-embolic manifestations in their observational cross-sectional study of COVID-19 patients. The majority of the patients had lower limb deep venous thrombosis. In their study, 9 patients (52.9%) had lower limb deep venous thrombosis, 2 patients (11.8%) had upper limb deep venous thrombosis, 5 patients (29.4%) had lower limb ischemia, and one patient (5.9%) had upper limb ischemia.

The possible reason for less incidence of peripheral vascular complications in our study group, is that bedside ultrasound Doppler of the limbs is the most preferred modality of imaging to detect arterial and venous thrombosis. Generally, CT/MR angiography is less preferred among majority of the hospitalized COVID-19 patients due to several restrictive measures and precautions needed in mobilizing these patients to the radiology department. Not many of the COVID-19 patients underwent Doppler studies during the study period.

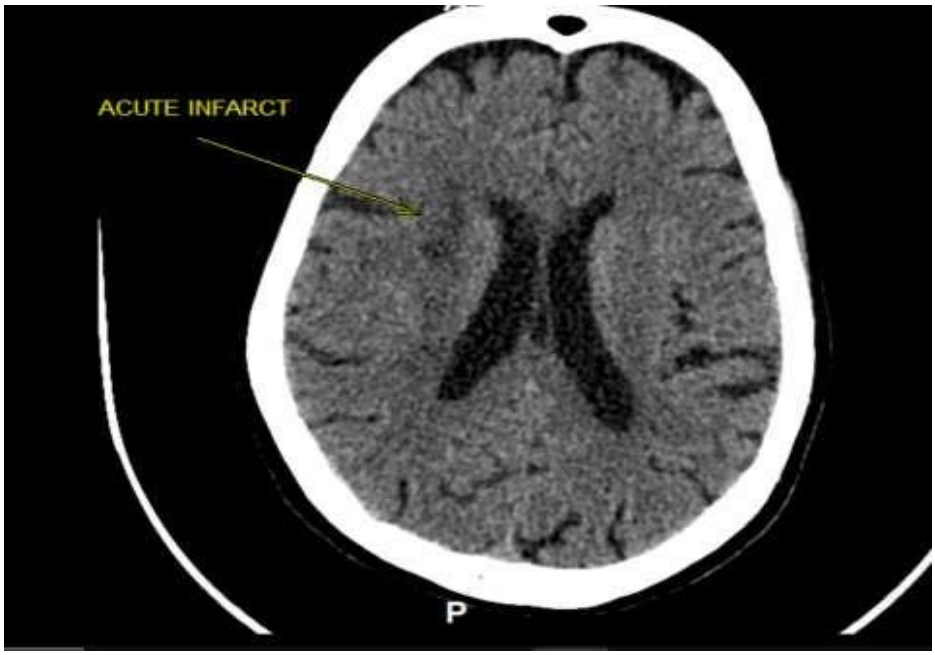
Apart from thrombo-embolic complications, hemorrhagic manifestations has also been reported in COVID-19 patients. **Ignacio Boira et al.**[88] reported that hemorrhagic manifestations occurred in COVID-19 patients, particularly in the second and third weeks of admission, and were more common in those on therapeutic anticoagulant therapy. Females were among the most affected.

Fewer hospitalised COVID-19 patients in our study group had radiological imaging techniques other than HRCT chest to identify thrombo-embolic complications. Though the incidence of vascular complications is relatively less among the COVID-19 patients, they are of great therapeutic importance. Cerebral infarction due to thrombosis of large vessels requires the implementation of immediate re-canalization therapy, if the patient is eligible. In addition, other approaches that may still be required are full anti-coagulation therapy for venous thrombo-embolism as well as surgical evacuation of intracranial hematomas. The medical team must be aware of the presence of coagulopathy and a pro-thrombotic state in these hospitalised COVID -19 patients, which may be related to the higher incidence of some of these complications and directly interfere with the treatment.

REPRESENTATIVE CASES

INTRA-CRANIAL VASCULAR COMPLICATIONS IN COVID-19 PATIENTS

CASE 1



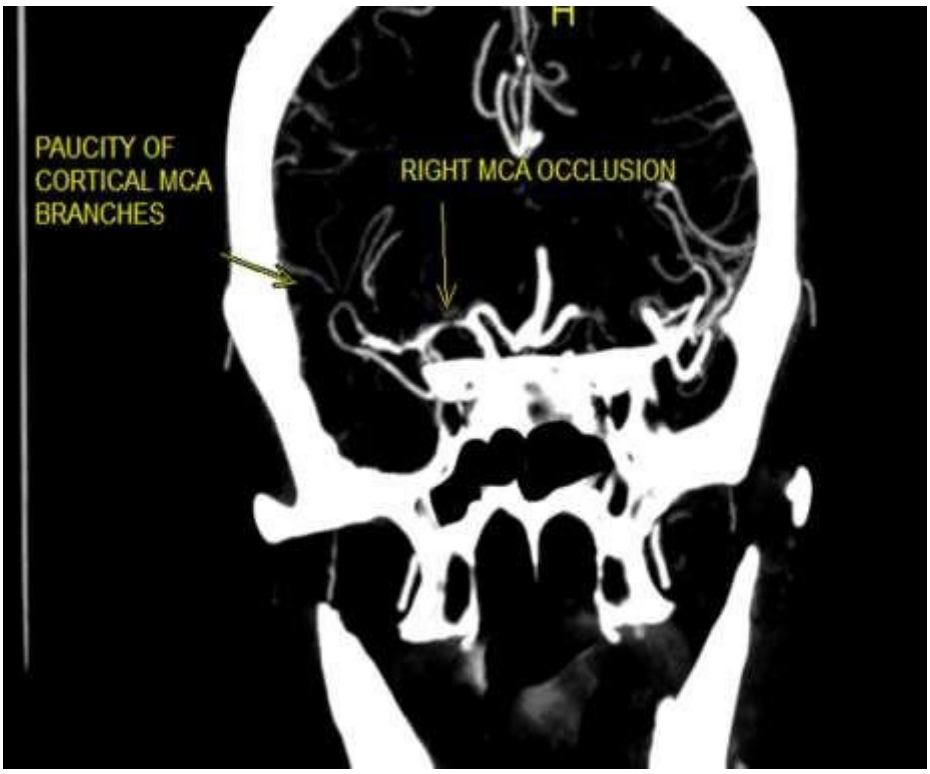
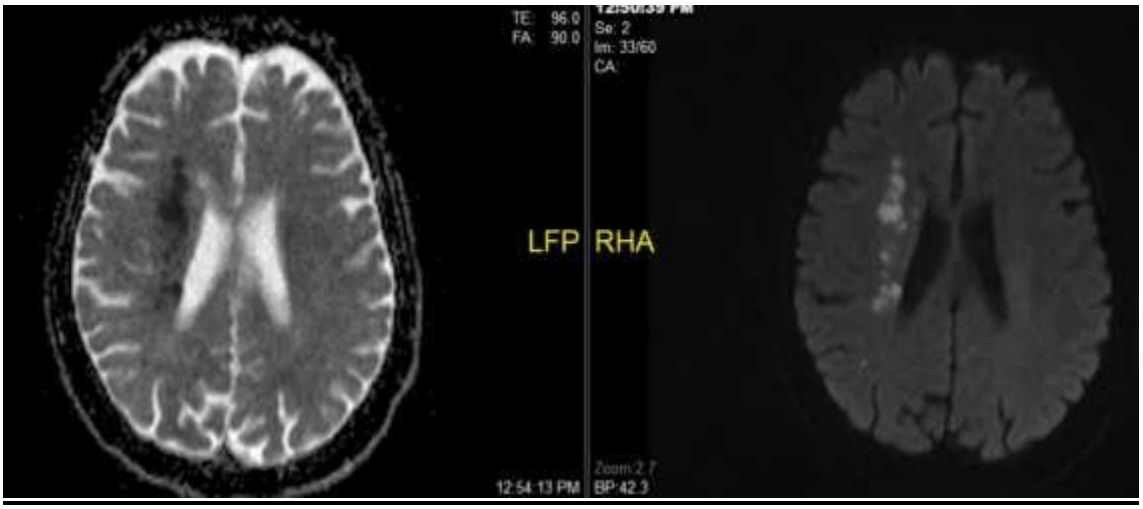


FIGURE 18: CT NECK AND BRAIN ANGIOGRAM IN OUR HOSPITALISED COVID-19 PATIENT SHOWS A) ACUTE INFARCT IN RIGHT CORONA RADIATA AND B) RIGHT MCA OCCLUSION

CASE 2



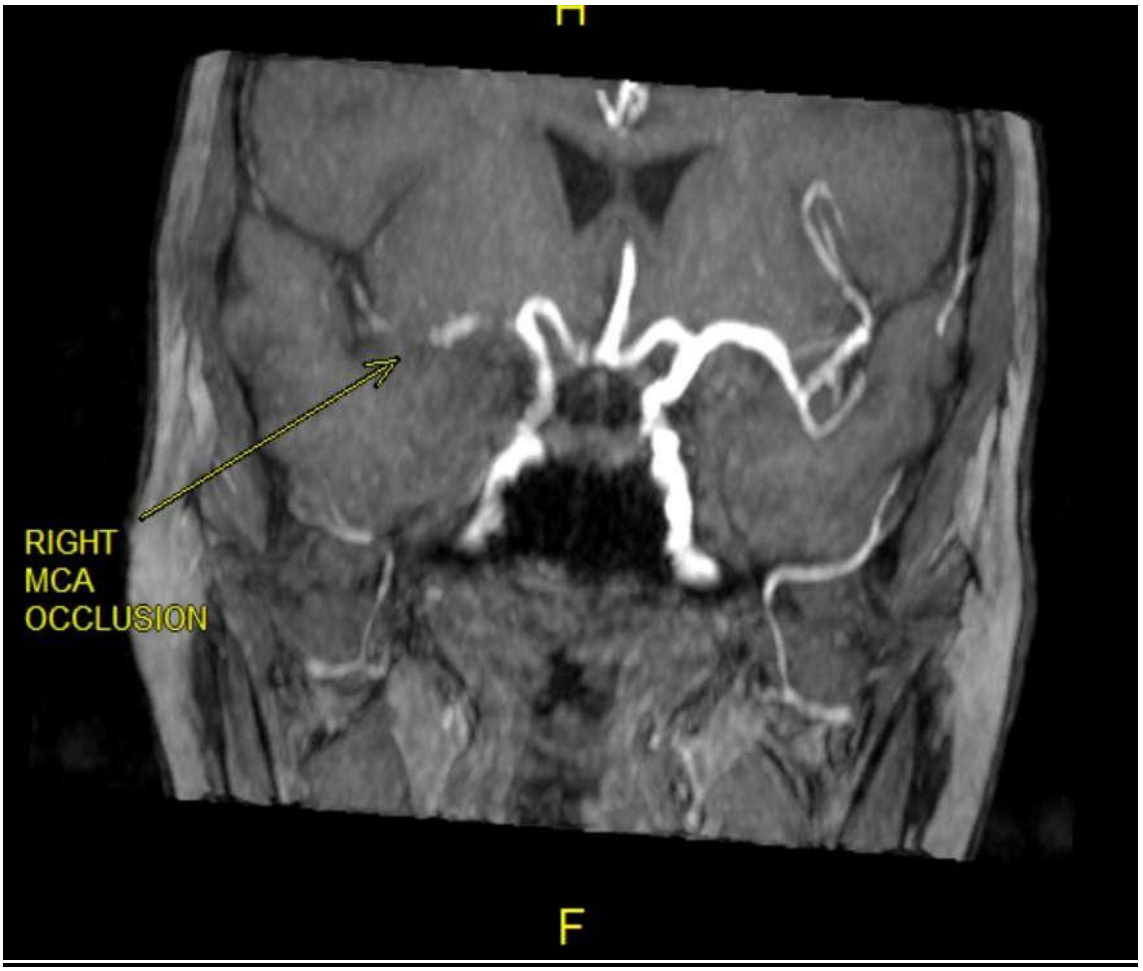


FIGURE 19: MRI BRAIN OF COVID-19 PATIENT A) (DWI AND ADC) SHOWING DIFFUSION RESTRICTION IN THE RIGHT CEREBRAL HEMISPHERE - S/O ACUTE INFARCT B) MRA-TOF IMAGING SHOWS OCCLUSION OF RIGHT MIDDLE CEREBRAL ARTERY AND INTRACRANIAL RIGHT INTERNAL CAROTID ARTERY.

CASE 3

ABDOMINAL VASCULAR COMPLICATIONS IN COVID-19 PATIENTS

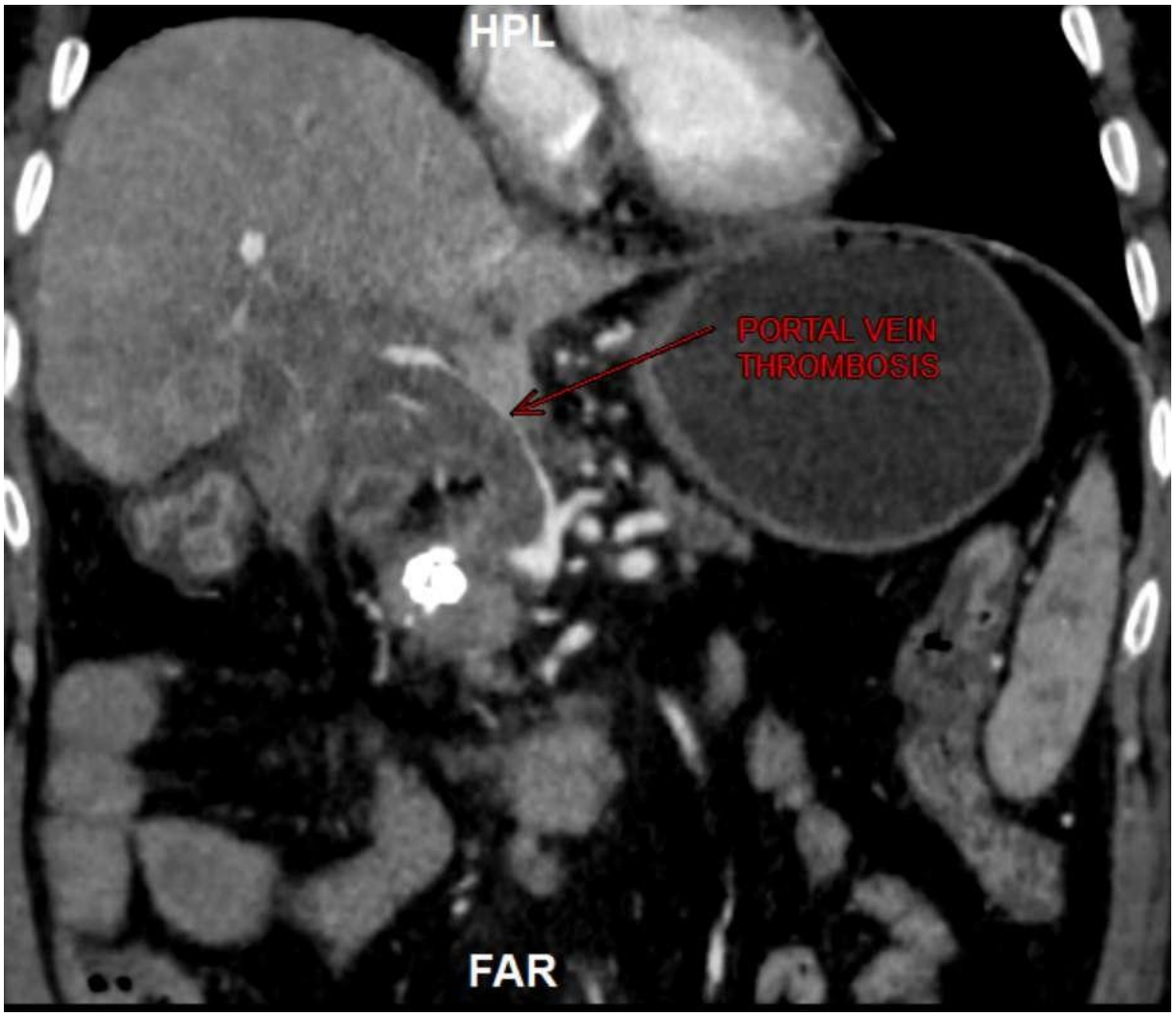


FIGURE 20: A CASE OF COVID-19 PATIENT WHO UNDERWENT CECT/CT ABDOMINAL ANGIOGRAM AND FILLING DEFECT IN PORTAL VEIN - S/O PORTAL VEIN THROMBOSIS

CASE 4

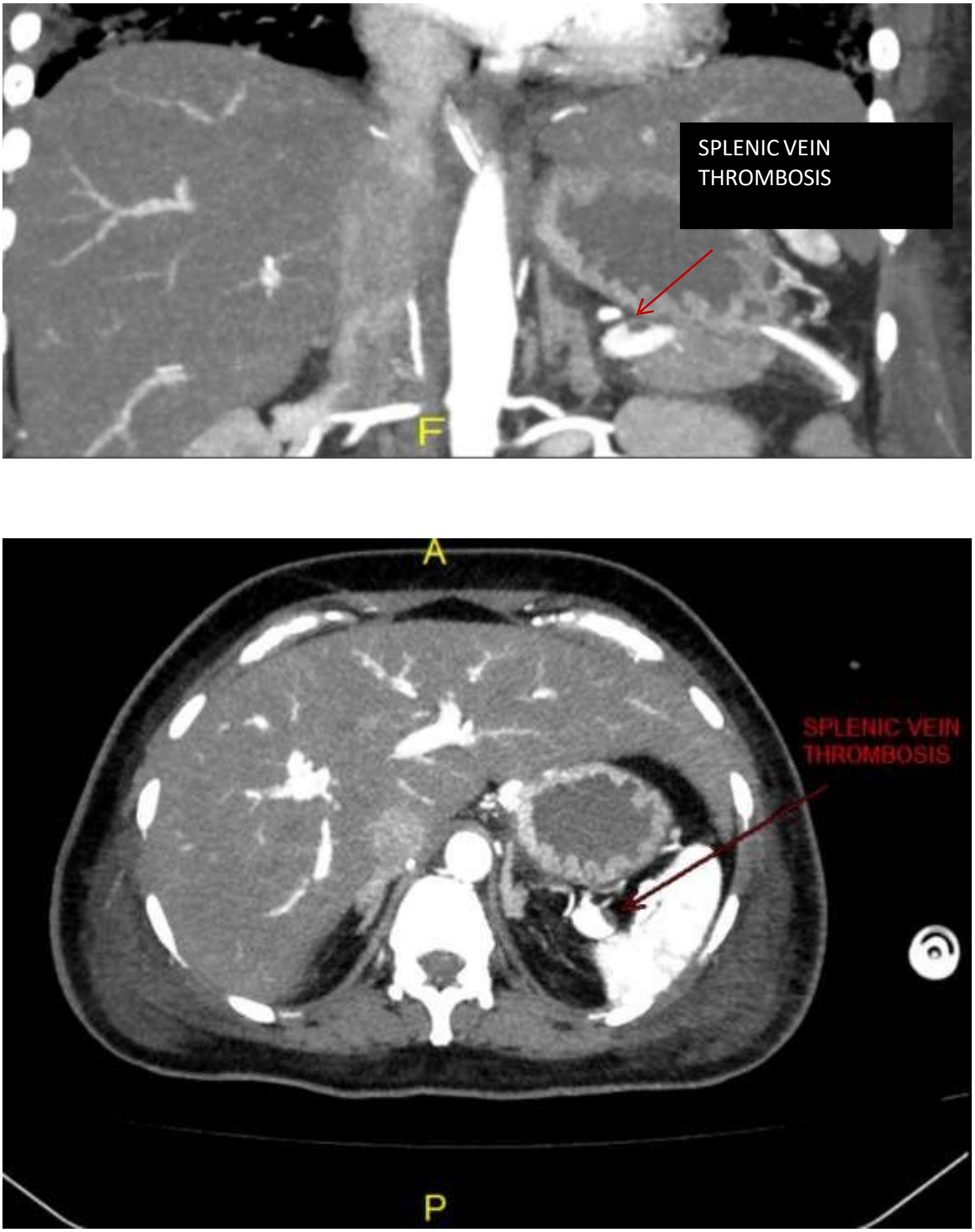


FIGURE 21: CT ABDOMINAL ANGIOGRAM (AXIAL AND CORONAL MIP) OF COVID-19 PATIENT SHOWING SPLENIC VEIN THROMBOSIS.

CASE 5

PULMONARY VASCULAR COMPLICATIONS IN COVID-19 PATIENTS

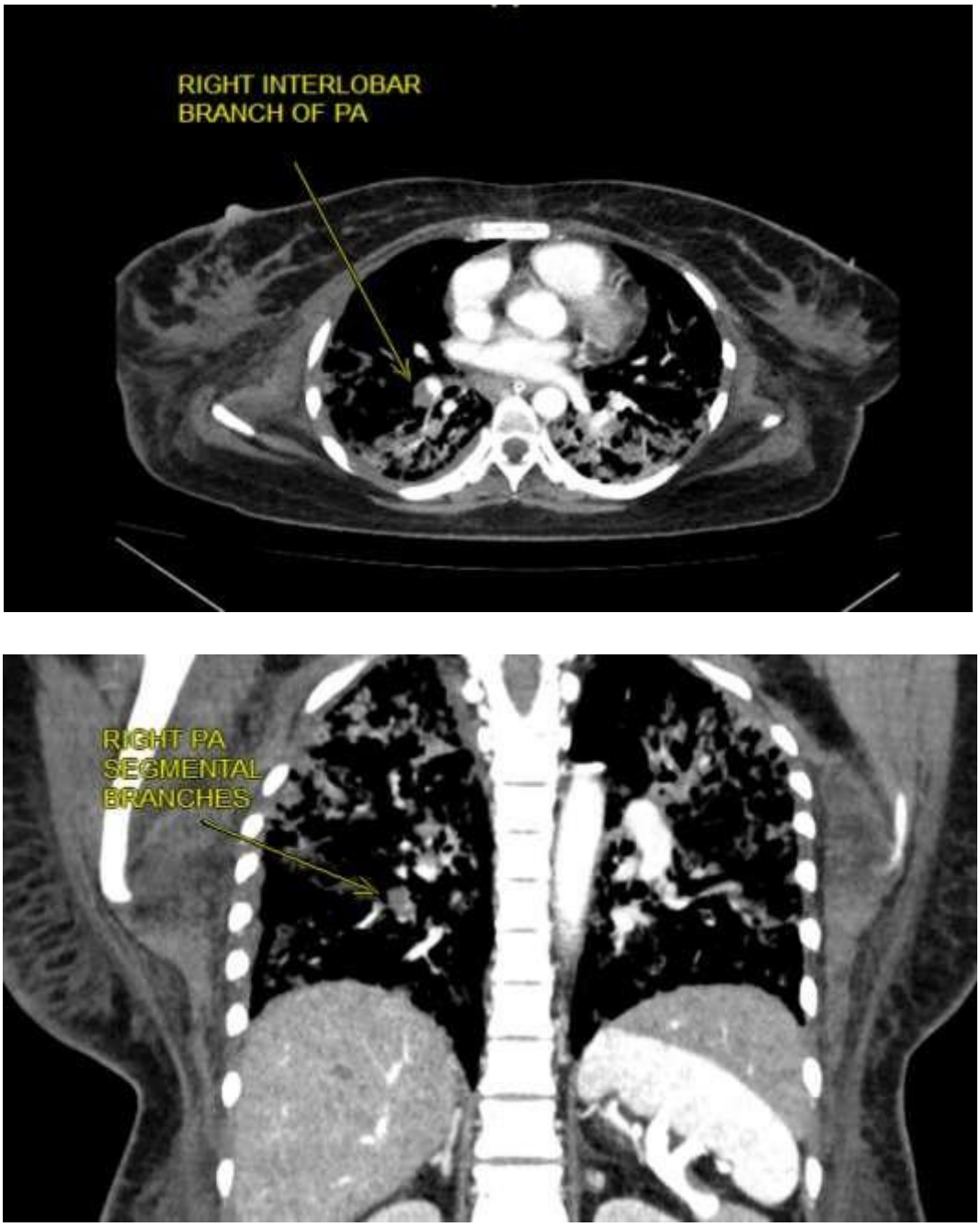


FIGURE 22: CT PULMONARY ANGIOGRAM (CORONAL AND AXIAL) OF COVID-19 PATIENT DEMONSTRATING ACUTE PULMONARY THROMBOEMBOLISM INVOLVING INTERLOBAR AND SEGMENTAL BRANCHES OF RIGHT PULMONARY ARTERY.

CASE 6

PERIPHERAL VASCULAR COMPLICATIONS IN COVID-19 PATIENTS

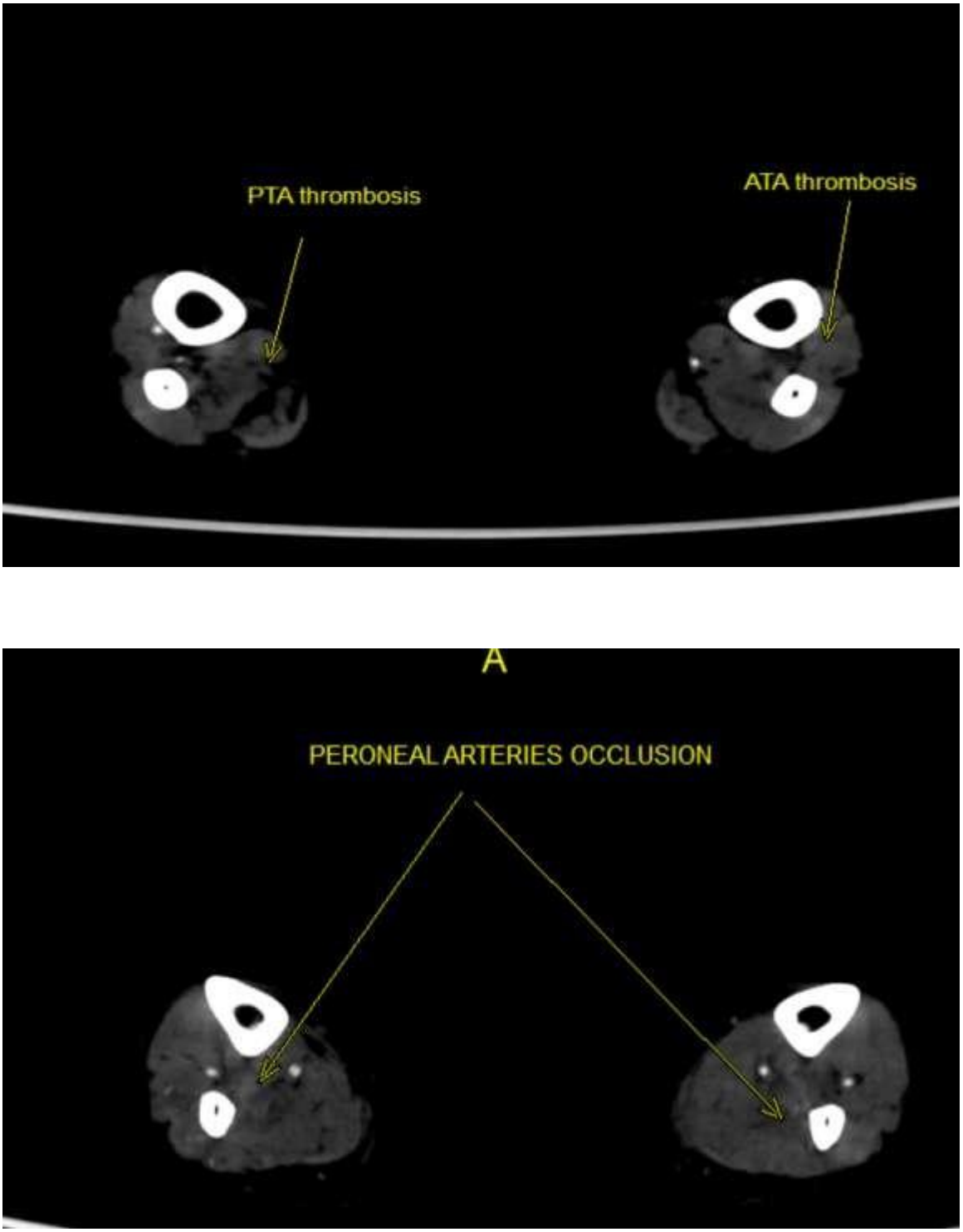


FIGURE 23: CT LOWER LIMB ANGIOGRAM (AXIAL) OF A COVID-19 PATIENT SHOWING THROMBOSIS OF THE LOWER LIMB TIBIO-PERONEAL ARTERIES.

CASE 7

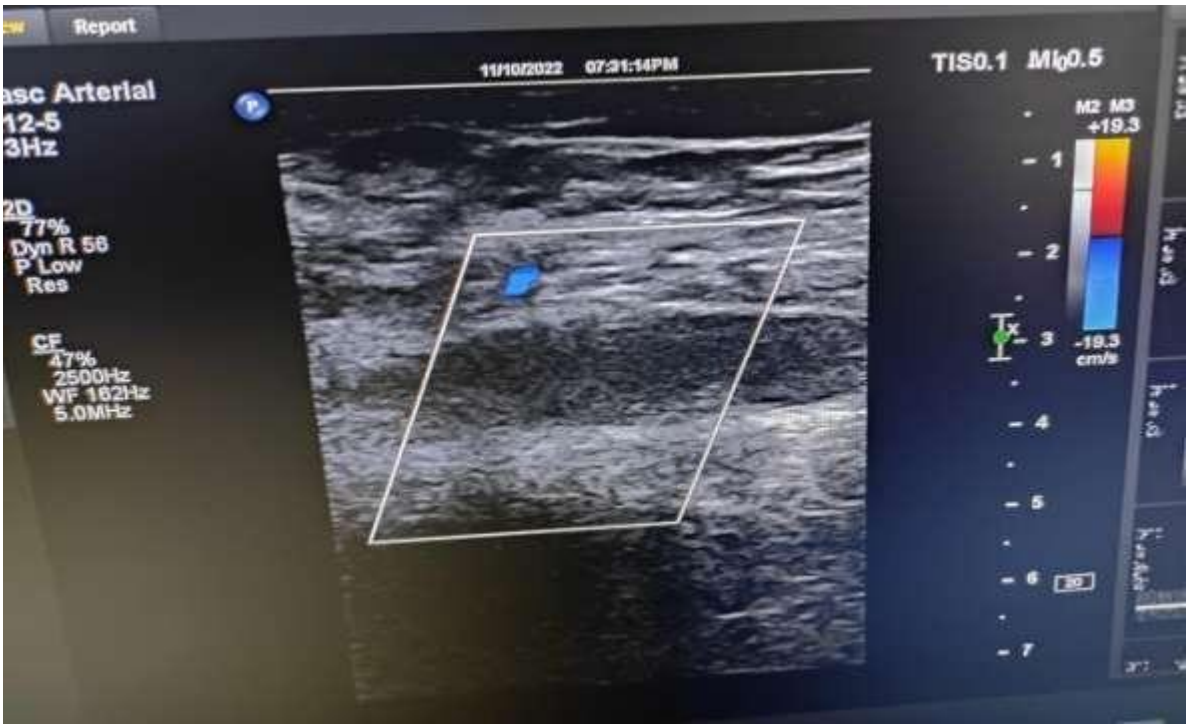


FIGURE 24: VENOUS DOPPLER OF LOWER LIMB IN COVID-19 PATIENT DEMONSTRASTES NON-COMPRESSIBLE, ECHOGENIC LEFT COMMON FEMORAL VEIN WITH NO COLOR FLOW ON DOPPLER - S/O ACUTE DEEP VENOUS THROMBOSIS

Summary

The purpose of this retrospective study was to determine the incidence of vascular systemic complications in COVID-19 positive patients hospitalised in care hospitals, Banjara Hills, Hyderabad. During the study period (May 1, 2020 to May 1, 2021), 349 COVID-19 patients were admitted to our hospital, and 33 of them underwent various modalities of vascular imaging in our radiology department. CT-Pulmonary Angiogram (34.3%) and cerebral imaging including MRI Brain with time of flight imaging /CT neck and Brain Angiogram (34.3%) was the most common imaging modality in our study group. Out of 33 hospitalised COVID-19 patients, 16 (48.5%) patients had vascular systemic complications and 17 (51.5%) patients had no vascular pathologies in imaging. The incidence rate of thrombo-embolic complications among the hospitalised COVID-19 patients in our study group was found to be 4.58%. Maximum number of systemic thrombo-embolic complications were found in 40-50 years (25%), followed by 50-60 years (18.7%), and the 80-90 years age group (18.8%) . The mean age of COVID-19 patients with vascular complications was 59.75±15.56 years. In the present study, among the 16 COVID-19 patients with vascular complications, 62.5% were female and 37.5% were male patients.

In these patients, Cerebrovascular complications was found to be more than other vascular systemic thrombo-embolic complications. Acute ischemic brain infarcts predominated in our cases more than the hemorrhagic brain infarcts. The majority of the ischemic infarcts were due to internal carotid and middle cerebral arterial thrombosis. Pulmonary & abdominal vasculopathies were 2nd most common (23.5%). Patients with acute pulmonary thrombo-embolism had involvement of the inter-lobar and segmental branches of right pulmonary artery. In the abdominal imaging studies, cases with splenic infarct, splenic vessel thrombosis, portal vein thrombosis and superior mesenteric artery thrombosis were found. However, there were no cases of acute bowel pathologies such as mesenteric ischemia with bowel infarcts. We did not encounter cases of renal infarcts due to renal arterial occlusion. The peripheral vascular system was found to be the least involved (17.6%). There was arterial thrombosis involving the tibio-peroneal arteries in the lower limb and the radial artery in the upper limb, as well as deep venous thrombosis involving the common femoral vein.

Limitations of Our Study

- Due to several restrictions and precautions that were out in the COVID-19 era, not all COVID-19 patients have undergone imaging studies.
- Even critically ill COVID-19 patients did not undergo imaging other than HRCT unless there was a clear clinical indication.
- Since many patients were put on anticoagulants regardless of the presence of thrombosis, bedside ultrasound Doppler for the extremities was only performed on a small number of patients during the COVID-19 era.
- Patients who did not have imaging may have had vascular complications that were missed by our study.

- Since this is a single-center study, our findings must be substantiated in a multi- center study.

Conclusion

Vascular complications, such as thrombo-embolism due to hypercoagulable state and bleeding due to anti-coagulation, are clinically significant issues for critically ill COVID-19 patients. Hemorrhagic events were much less common than venous and arterial thrombo-embolism. Thrombo-embolic events are also said to be more common in ICU patients. The pulmonary artery, gastrointestinal tract, kidney, hepato-biliary organs, extremity vessels, and aorta are commonly affected. Anticoagulants play a major role in the COVID-19 patients at risk of thrombosis. As a result, when starting anti-coagulation, the risk of bleeding must be considered, and patients should be closely monitored for potential hemorrhage.

All radiologists and clinicians must be aware of the vascular (thrombo-embolic and hemorrhagic) complications in COVID-19 patients, as well as the importance of vascular imaging modalities other than HRCT chest in COVID-19 patients, in order to make timely diagnoses and recommend the best course of treatment for their vascular complications.

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APPENDICES APPENDIX – 1

STUDY PROFORMA

NAME:
AGE:
SEX:
COVID-19 STATUS/DIAGNOSED AT:
INPATIENT ADMISSION (ICU/WARDS):
VASCULAR IMAGING DONE: YES/NO
SPECIFICATION OF MODALITY OF IMAGING DONE:
VASCULAR COMPLICATION: PRESENT/NO

SYSTEMWISE SPECIFICATION OF VASCULAR PATHOLOGY	YES/NO
CEREBROVASCULAR INVOLVEMENT	
PULMONARY VASCULAR INVOLVEMENT	
ABDOMINAL VASCULAR INVOLVEMENT	
PERIPHERAL VASCULAR INVOLVEMENT	

OCCLUDED/THROMBOSED VESSEL AND ITS RELATED COMPLICATIONS:

MASTER CHART								
S.NO	**AGE**	**AGE GROUP**	**SEX**	**COVID SAMPLE TESTING CENTRE OF THE POSITIVE CASE**	**RADIOLOGICAL IMAGING DONE**	**GROSS RESULT**	**VASCULAR COMPLI-CATION**	**SPECIFICATION OF PATHOLOGY**
1	67	60-70	M	TENET DIAGNOSTICS	CT LOWER LIMB ANGIOGRAM	Non-opacification of left tibial and peroneal, distal right posterior tibial arteries.	YES	Complete thrombosis of left tibial, peroneal and distal right posterior tibial arteries.
2	71	70-80	F	TENET DIAGNOSTICS	CT NECK AND BRAIN ANGIOGRAM	Acute infarct in left gangliocapsular region, left insular cortex and left corona radiata.	YES	Near total occlusion of left intra-cranial internal carotid artery, M1 and M2 segment of left middle cerebral artery.
3	37	30-40	F	CARE HOSPITALS	MRI BRAIN + CT BRAIN ANGIO	Deep watershed infarcts in right cerebral hemisphere.	YES	Severe occlusion of terminal portion of right Internal carotid and Middle cerebral arteries.
4	57	50-60	M	CARE HOSPITALS	CT PULMONARY ANGIO	MR - Infarct with hemorrhagic	YES	CT-PA - acute thrombus in right inter-lobar pulmonary artery.
					&MR BRAIN			MRA - severe stenosis in ophthalmic segment of both internal carotid arteries.
5	57	50-60	F	RIVAARA LABS	VENOUS DOPPLER OF BOTH LOWER LIMBS	Negative for DVT.	NO	No evidence of acute deep venous thrombosis.
6	49	40-50	F	K/C/O COVID-19 PNEUMONIA WITH SEVERE ARDS ON ECMO, CARE HOSPITALS	CT NECK AND BRAIN ANGIOGRAM	Normal cerebral angiogram.	NO	No evidence of occlusive changes of the intra-cranial vessels.
7	83	80-90	M	CARE HOSPITALS	CT PULMONARY ANGIO	F/S/O Acute PTE	YES	Thrombo-embolism in segmental pulmonary arteries of right middle and right lower lobe.
8	44	40-50	F	CARE HOSPITALS	CT NECK AND BRAIN ANGIOGRAM	No acute infarcts/vasculopathic changes	NO	No acute infarcts/occlusive changes of the intra-cranial vessels.
9	39	30-40	F	CARE HOSPITALS	CT PULMONARY ANGIOGRAM	No evidence of acute PTE	NO	No evidence of acute vasculopathic changes.
10	52	50-60	F	CARE HOSPITALS	CT PULMONARY ANGIOGRAM	No evidence of acute PTE.	NO	No evidence of acute vasculopathic changes.

11	38	30-40	F	CARE HOSPITALS	CT ABDOMINAL ANGIOGRAM	F/S/O portal vein thrombosis	YES	Thrombosis of the portal vein and its anterior branch of right division.
12	57	50-60	F	RIVAARA LABS	MRI DIFFUSION + MRV	Acute hemorrhagic infarct involving the left temporo-parietal lobe.	YES	MRV - Thrombosis in the left transverse and sigmoid sinus.
13	73	70-80	F	TENET DIAGNOSTICS	CT LOWER LIMB ANGIOGRAM	Atherosclerotic wall calcifications of lower limb arteries.	NO	No acute thrombus of lower limb arteries.
14	59	50-60	F	RIVAARA LABS	VENOUS DOPPLER OF BOTH LOWER LIMBS and CT PULMONARY ANGIO	Negative for DVT/NO acute PTE	NO	No evidence of acute vasculopathic changes.
15	46	40-50	F	K/C/O COVID-19 PNEUMONIA,CARE	CT SCAN OF BRAIN (PLAIN)	Extra-axial hemorrhage	YES	Sub-arachnoid hemorrhage in right parietal and left fronto-parietal region.
								Focal sub-dural hemorrhage in left frontal region
16	37	30-40	M	CARE HOSPITALS	CT PULMONARY ANGIOGRAM	No evidence of acute PTE	NO	No evidence of acute vasculopathic changes.
17	47	40-50	F	TENET DIAGNOSTICS	CECT OF ABDOMEN	Multiple areas of infarctions throughout the spleen.	YES	Thrombus in the distal region of the splenic artery.
18	83	80-90	M	CARE HOSPITALS	CT PULMONARY ANGIOGRAM	No evidence of acute PTE	NO	No evidence of acute vasculopathic changes.
19	44	40-50	F	K/C/O COVID-19 PNEUMONIA,CARE HOSPITALS	CECT SCAN OF ABDOMEN	Partial filling defect 1.3 cm in length in superior mesentric artery.	YES	Partially occlusive thrombus in Superior mesentric artery with no imaging evidence of mesenteric ischemia/bowel infarcts.
20	64	60-70	F	CARE HOSPITALS	CT PULMONARY ANGIOGRAM	F/S/O Acute PTE.	YES	Thrombus in right inter-lobar pulmonary artery and in posterior segmental branch of right lower lobe
21	47	40-50	F	CARE HOSPITALS	CT PULMONARY ANGIOGRAM	No evidence of acute PTE	NO	No evidence of acute vasculopathic changes.
22	56	50-60	M	CARE HOSPITALS	CT PULMONARY ANGIOGRAM	No acute infarcts/vasculopathy	NO	No evidence of acute vasculopathic changes.
					&MRI BRAIN			

23	57	50-60	F	RIVAARA LABS	CT LOWER LIMB ANGIOGRAM and CT PULMONARY ANGIOGRAM	Normal lower limb arterial system/No acute PTE	NO	No evidence of acute vasculopathic changes.
24	84	80-90	F	TENET DIAGNOSTICS	MR DIFFUSION +MRA (TOF IMAGING)	Acute infarcts in the the left corona radiata and external capsule.	YES	MRA TOF - occlusion of the horizontal and insular segments of left Middle cerebral arteries.
25	56	50-60	F	CARE HOSPITALS	MRI BRAIN + CT BRAIN ANGIOGRAM	No acute infarcts/vasculopathicch anges.	NO	No acute infarcts/occlusive changes of the intra-cranial vessels.
26	73	70-80	F	TENET DIAGNOSTICS	VENOUS DOPPLER OF LEFT LOWER LIMB	F/S/O acute DVT	YES	Evidence of distended non-compressible veins with low echogenicity thrombus within involving the distal left common
27	80	80-90	M	CARE HOSPITALS	CT PULMONARY ANGIOGRAM	F/S/O Acute PTE	YES	Thrombus in right lower lobe pulmonary artery and its segmental branches.
28	74	70-80	F	CARE HOSPITALS	MRI BRAIN + CT BRAIN ANGIOGRAM	Chronic lacunar infarcts in both thalamus.	NO	Mild atherosclerotic changes of both intra-cranial internal carotid arteries. No acute occlusive vasculopathic changes.
29	82	80-90	F	TENET DIAGNOSTICS	CT BRAIN ANGIOGRAM	Gliotic changes in the right temporal lobe. Fazekas grade II chronic small vessel ischemic changes.	NO	No acute occlusive changes of the intra- cranial vessels.
30	49	40-50	M	K/C/O COVID ON VENTILAT	LEFT UPPER LIMB ART	Echogenic lumen of left radial artery without any flow on colour doppler. No evidence of venous thrombosis.	YES	Thrombosis involving the left radial artery.
31	59	50-60	M	CARE HOSPITALS	CECT OF ABDOMEN	Filling defect in splenic vein	YES	Partial thrombosis of splenic Vein.
32	57	50-60	F	RIVAARA LABS	VENOUS DOPPLER OF BOTH LOWER LIMBS	Negative for DVT	NO	No evidence of acute deep venous thrombosis.
33	46	40-50	M	TENET DIAGNOSTICS	CT BRAIN ANGIOGRAM	Normal cerebral angiogram.	NO	No acute infarcts/occlusive changes of the intra-cranial vessels.