

# Peripheral Vascular System Thrombosis and COVID-19: A Chilling Revelation

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## Abstract

**Introduction:** As the COVID-19 pandemic reaches, its zenith a worrying trend has been noticed of late, that is arterial and venous thrombosis in patients presenting with COVID-19. Arterial and venous thrombosis was found in patients with asymptomatic state to severe affliction and most of them had a delayed presentation. **Materials and Methods:** An observational study was carried out by the Department of Vascular Surgery, Madurai Medical College. There were around 15200 total admissions between March 15, 2020, to September 30, 2020, in corona specialty hospital and trauma care center affiliated to Madurai medical college, out of which: (1) Acute deep venous thrombosis (DVT) was seen in 349 patients. (2) Acute limb ischemia (ALI) was found in 75 patients, out of which 70 patients had lower limb involvement and 5 patients had upper limb involvement. (a) Class 3–50 patients, (b) Class 2b–15 patients, (c) Class 1–10 patients. (3) Acute mesenteric ischemia was seen in 8 patients. **Conclusion:** COVID-19 is associated with an increased incidence of arterial and venous thrombosis of peripheral vascular system wherein arterial thrombosis, presenting, as ALI is profound and has a multi fold increased incidence than in non-COVID-19 patients and venous thrombosis is much higher than the non COVID-19 state.

**Keywords:** Acute limb ischemia, COVID-19, deep venous thrombosis

## INTRODUCTION

As the coronavirus pandemic reaches its zenith a worrying trend has been noticed of late, that is an exponential rise in arterial and venous thrombosis in patients presenting with COVID-19. Several thrombotic complications have been documented until date.<sup>[1,2]</sup> Our hospital witnessed a sudden and significant increase of COVID-19-infected patients presenting with arterial and venous thrombosis presenting as acute limb ischemia (ALI) and deep venous thrombosis (DVT). Coronavirus principally enters cells by attaching to ace inhibitors found on alveolar epithelium and endothelium of blood vessels.<sup>[3]</sup> This leads to endotheliitis and subsequent thrombosis in the arterial system and the venous system.<sup>[4]</sup> This phenomena is attributed to the immune response against the coronavirus which generates clotting substances as fibrinogen and d-dimer, which can increase up to 3 folds, resulting in overt thrombosis.<sup>[5]</sup>

## MATERIALS AND METHODS

From March 24, 2020, to September 30, 2020, in our institution

(Madurai Medical College) we have had 15200 admissions in the COVID-19 specialty hospital and its subsidiary hospital Trauma Care Centre. The data from all the patients who had presented with and been treated for ALI, DVT, and mesenteric ischemia were identified and analyzed. All patients underwent computed tomography (CT)-chest and swab for reverse transcriptase-polymerase chain reaction (RT-PCR) at the time of admission. All patients had ground glass opacities ranging from 10% to 80%. Patients with ALI and DVT were subjected to echocardiography examination to rule out any cardiac emboli. At time of admission, all patients who had COVID-19 or suspected COVID-19 with d-dimer (>500 ng/ml) were put on low molecular weight heparin (1 mg/kg/bd) as our hospital treatment protocol. All positive patients had elevated levels of C-reactive protein, d-dimer, and interleukin.

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### Inclusion criteria

- RT-PCR positive
- CT Chest – corads 4, 5
- RT-PCR swab negative but CT positive.

### Exclusion criteria

- Corads 1, 2, 3
- Patients with trauma
- Patients with cerebrovascular accident.

### Observations

Among the 15200 cases, patients presenting as acute DVT were seen in 349 patients. One hundred and thirty-two had presented with DVT and found to have concomitant COVID-19 and 217 were in patients who later developed DVT. Out of the 349 patients lower limb involvement was seen in 342 patients and upper limb involvement was seen in 7 patients. Left-sided was more common than the right side. Thirty-four patients had a history of smoking<sup>[6]</sup> had a history of hyperhomocysteinemia, 3 patients had a previous history of DVT. Male patients were 209 and female were 140 [Figure 1].

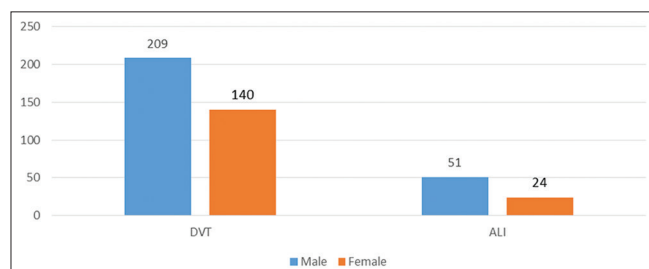
DVT involvement was seen as [Figure 2]

- Infrarenal inferior vena cava to bilateral external iliac vein 4 patients
- Common iliac vein to common femoral vein 245 patients
- Common femoral vein extending to popliteal vein 74 patients
- Popliteal vein to tibial veins 26 patients.

Mean age of presentation was 49 years. Catheter-directed thrombolysis (CDT) was performed in 6 patients with impending venous gangrene, using the popliteal vein as an access site. The rest were managed with enteral and parenteral anticoagulation. INR was maintained between 2 and 3 and anticoagulant dosage was titrated accordingly. At the time of discharge, the patient was put on enteral acenocoumarol, biweekly PT-INR values were monitored, and dosage adjusted accordingly.

Post COVID-19 DVT was seen 21 patients and all had common femoral vein to distal-tree involvement. The duration was between 22 and 63 days, with a mean of 36 days. None of the patients developed venous gangrene.

The pattern of venous and arterial thrombosis was as follows [Figure 3]



**Figure 1:** Male vs. Female occurrence of DVT & ALI

ALI was diagnosed in 75 patients 51 were male and 24 were female, 50 patients presented with a profound class 3 ischemia. The mean duration was 11 days at the time of admission. Class 2b ischemia was noted in 15 patients, 12 were inpatients with a mean hospital stay of 3 days and 3 had got admitted with ALI and concomitant COVID-19. Class 1 ischemia was present in 10 patients, 4 were admitted with primary class 1 ischemia and 6 were inpatients being treated for COVID-19.

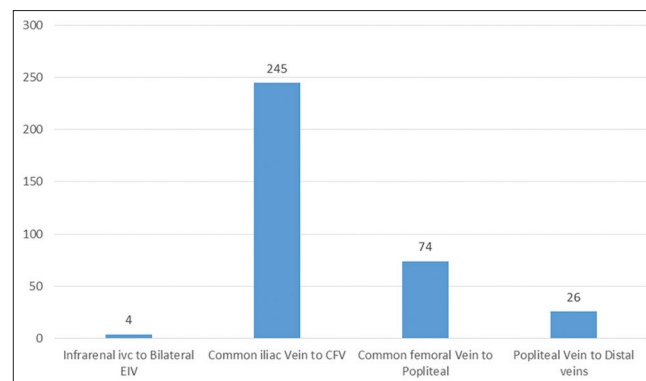
Post COVID-19 ALI was seen in 3 patients after a mean duration of 22 days and all had class 1 ischemia of infrapopliteal segment. Out of the 75 patients with ALI only 12 had prior history of smoking and one had hyperhomocysteinemia on irregular treatment.

- Saddle embolism was noted in 2 patients of class 3 ischemia and 1 patient of class 2b ischemia [Figure 4]
- Iliac occlusion was present in 24 patients of class 3 and 9 patients of class 2b and 5 cases of class 1
- Fem pop occlusion was present in 14 cases of class 3 ischemia, 2 cases of class 2b ischemia, and 2 cases of class 1 ischemia.
- Infrapopliteal occlusion was seen in 8 patients of class 3 ischemia, 1 patient of class 2b, and 2 patients of class 1 ischemia
- Axillary occlusion in 2 patients with class 3 ischemia and 2 patients with class 2b ischemia [Figures 5 and 6]
- Brachial occlusion was noted in 1 patient with class 1 ischemia.

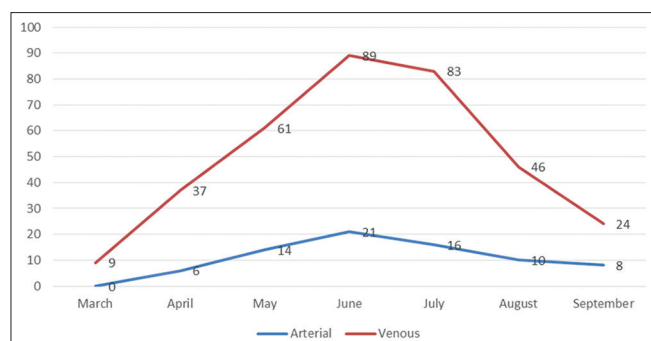
One patient had concomitant left axillary and left iliac artery occlusion, and one had left iliac and right infra popliteal occlusion.

The mean age was 53 years.

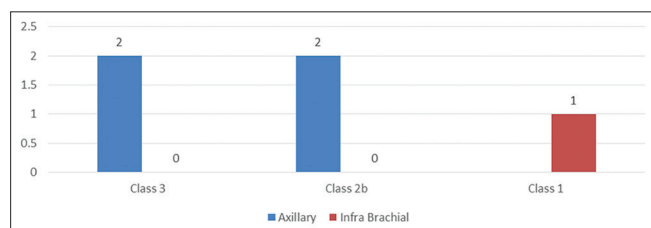
- Among the 50 patients with class 3 ischemia, 47 went for primary amputation, 37 above knee amputation 8 below knee amputation 2 above elbow amputations. 3 had died before any intervention could be performed
- Transfemoral embolectomy was performed in 19 patients
- Transpopliteal embolectomy was performed in 2 patients
- Transbrachial embolectomy was performed in 2 patients
- Conservative management was done for 2 patients with class 1 ischemia.



**Figure 2:** DVT segment involvement



**Figure 3:** Month wise occurrence of DVT and ALI



**Figure 5:** Acute limb ischemia-upper limb

Out of the 23 patient who underwent embolectomy 19 had salvaged limbs. Palpable distal pulse was present in 14 patients and 5 patients had a post op ABI ranging from 0.7 to 0.8. Post embolectomy re-thrombosis was seen in 4 patients, 1 fem pop, 1 axillary, and 2 had iliac segment involvement which went for recurrent thrombosis resulting in amputation in all the 4. Surgical intervention was performed under local/locoregional anesthesia with intravenous sedation with intravenous heparin at time of arterial clamping. Fasciotomy was performed in all cases. Post embolectomy angiogram could not be taken due to logistic issues.

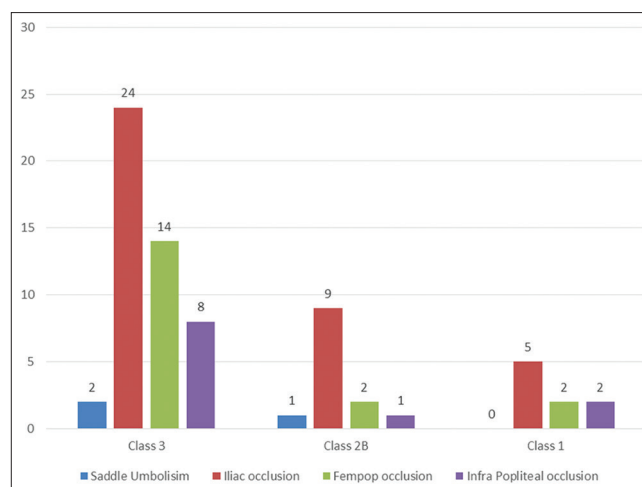
Acute mesenteric ischemia was seen in 8 patients, with involvement of superior mesenteric artery in all the 8 patients. Six patients underwent resection of the small bowel for frank gangrene and 2 patients were managed conservatively with systemic anticoagulation.

In the patients who underwent amputations, segment of the artery and vein was sent for histopathological examination from the amputated site, which revealed thrombosis with endothelialitis and periadventitial inflammation.

At the time of discharge, the patient was put on dual antiplatelets (aspirin 75 mg + clopidogrel 75 mg) statins (atorvastatin 40 mg) along with enteral anticoagulant acenocoumarol and reviewed weekly for 3 months, while maintaining INR between 2-3. 50% of the patients turned up for follow-up.

## DISCUSSION

We performed a comprehensive observational analysis. Patients presented very late to our hospital, due to various issues encountered as logistics, social stigma associated with COVID-19 in the initial period, and fear of contracting



**Figure 4:** Acute limb ischemia-lower limb

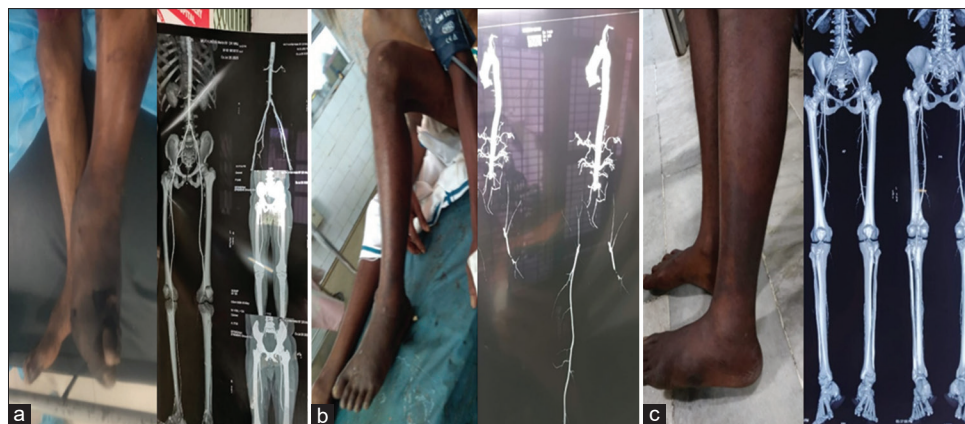


**Figure 6:** (a) Right brachiocephalic trunk occlusion (b) Left axillary occlusion

COVID-19 in a COVID-19 facility. As ours is a tertiary care center and a referral center for the southern, western, and few eastern districts of the state of Tamil Nadu and a few districts of the state of Kerala, we had a huge number of patients. It was seen that, despite the use of anticoagulant prophylaxis, the venous and arterial thrombosis in hospitalized COVID-19 patients was strikingly high. We observed that the majority of thrombotic complications were venous and primarily represented as DVT, DVT can be managed conservatively with parenteral heparin and enteral acenocoumarol unless there is risk and signs of progression to venous ischemia and gangrene<sup>[7,8]</sup> CDT is a good option in patients who are not amenable to conservative management. In patients with DVT the male to female ratio was 1.4:1 and in ALI, it was found to be 2:1, indicating that male sex is prone to thrombotic complications of COVID-19.

Emergency embolectomy is the dictum in all cases of class 2b ischemia.<sup>[9]</sup> In class 1 ischemia, we resorted to embolectomy in majority of the cases and it yielded excellent results.





**Figure 7:** (a) Left tibial occlusion (b) Saddle embolism (c) Left fem pop occlusion



**Figure 8:** Profound Class 3 Ischemia: Neglected limb



**Figure 9:** Extracted thromboembolus

Distal occlusion below the popliteal artery presented as a pattern similar to endarteritis with patchy involvement of

the toes and fingers. Arterial thrombosis presented as ALI, predominantly class 3 [Figures 7-9]. The histopathological analysis was suggestive of periadventitial inflammation and endotheliitis with thrombosis of the arterial wall, indicating that COVID-19 has inflammatory properties.<sup>[10]</sup> We observed that at least half of thrombotic events were diagnosed within the first 72 h of admission and, therefore, not preventable by in-hospital routine (1 mg/ kg/ bd) dosage of lmwh. It was observed that the use of higher dosages (1.5 mg/kg/bd) might improve the outcome, along with corticosteroid treatment.<sup>[11,12]</sup> Patients presenting with DVT can be managed with parenteral and enteral anticoagulants unless there is impending venous gangrene. The maximum cases of ALI and DVT coincided with the peak of COVID-19, which is suggestive of a directly proportional pattern. Interventional and management trials should be considered to improve the diagnosis and treatment of thrombotic complications in patients presenting with COVID-19 and its complications.

## CONCLUSION

In our observation over a large subset of patients, we have seen that COVID-19 is a vascular catastrophe, afflicting the peripheral vascular system like no other condition. The arterial thrombosis presenting as ALI is almost 30 folds when compared to the non COVID-19 population.<sup>[13]</sup> The incidence of venous thrombosis presenting as DVT was much more when compared with the non COVID-19 population.<sup>[14]</sup>

The majority of the patients who were admitted at our institute had presented with advanced ischemia. The rate of major amputation was high. ALI and DVT was also seen in patients who had recovered from COVID-19 clinically and were swab negative. The average duration was 36 days for DVT, and 22 days for ALI. From our experience and observation, we have seen that patients who have had COVID-19 infection, the rate of progression to class 3 was quite rapid. COVID-19 presents as a pan vascular system inflammatory response with endotheliitis and periadventitial inflammatory cells. The bottom line is that all patients of COVID-19 are at a crossroad of a vascular catastrophe and need early diagnosis, timely

intervention, meticulous management, and a routine follow-up for a minimum of 3 months.

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### Conflicts of interest

There are no conflicts of interest.

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