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RESEARCH ARTICLE

MANAGEMENT OF ACUTE LIMB ISCHEMIA IN POST-COVID RECOVERY PATIENTS

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ABSTRACT

Background: The transmission of the coronavirus disease (COVID-19) pandemic resulted in new challenges across all medical specialities. A hypercoagulable state is being observed in many patients with SARS-CoV-2 and is a predictor of a worse prognosis. Acute limb ischemia (ALI) is a limb and life-threatening condition with high morbidity and mortality. It is a relatively rare manifestation of the spectrum of COVID-19 related coagulopathy. **Methods:** A single centre, prospective, interventional study was performed from JUNE 2020 to JUNE 2021 in post-COVID recovery patients who developed ALI using endovascular therapy for revascularisation. Data collected included demographics, anatomical location of the arterial occlusion, treatments, and outcomes. **Results:** Over the 13 months, a total of 38 patients participated in the study. The mean age is 64.45 years, ranging from 16-75 years. 25 (65.78%) are men. 30 (78.94%) participants had lower limb involvement, and 8 (21.06%) had upper limb involvement. Pain and pulselessness were present in all the patients. However, only four patients (10.52%) presented with paresis. Tibial arteries (most commonly) were affected in 24 (63.15%) patients. Radial arteries were involved in only 5.26%. 55.26% of presentations were Rutherford stage IIb. We used a combination of transluminal balloon angioplasty, thromboaspiration, Catheter-directed thrombolysis and stenting. Revascularisation was achieved in 35 (92.1%). Two (5.26%) patients were amputated. One (2.36%) patient died. **Conclusion:** A thorough understanding of endovascular techniques, associated pharmacology, and perioperative care is paramount to endovascular management success in patients presenting with AIL.

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INTRODUCTION

Coronavirus is a positive-sense, single-stranded, enveloped RNA virus with a helical capsid. The 2019 novel coronavirus pandemic or coronavirus disease (COVID-19), initially identified in Wuhan, Hubei, China, in December 2019, has spread exponentially to 200 countries, causing a global pandemic (Zhou *et al*.,2020). On January 3, 2020, WHO declared COVID-19 a public health emergency of international concern (COVID-19, 2020). India is one of the most affected nations by the pandemic. Most infections are not severe. 81% of patients have a mild-to-moderate disease (asymptomatic or mild pneumonia), 14% have severe disease (dyspnea, hypoxia, or >50% lung involvement on imaging within 24–48 h), and only 5% have an acute illness with multiple organ failure (respiratory failure, shock, or Multiorgan dysfunction) (Wu, 2020). COVID-19 may predispose to both arterial and venous thromboembolic complications. The cumulative incidence of thrombotic complications in critically ill patients with COVID-19 was 31% despite systemic thromboprophylaxis, including 27% venous thromboembolism and 4% arterial thrombotic events (Klok, 2020). Investigations have shown that the coronavirus infection initiates severe inflammatory responses that lead to blood stasis, endothelial injury, and increased risk of thrombosis and embolism. Arterial thromboembolic complications may have devastating consequences, including limb loss, early intubation, multiorgan dysfunction, stroke, and death. Although ALI is a rare complication of COVID-19, there are increasing reports of peripheral arterial thrombosis in COVID-19 patients (Hasan, 2020; Veerasuri, 2020).

Acute limb ischemia is defined as an abrupt decrease in limb perfusion that threatens limb viability and is less than 14 days in duration (Creager, 2012; Gilliland, 2017; Patel, 2013). More commonly, ALI involves the lower extremities more than the upper limbs. Morbidity is high, with amputation rates approaching 15% during acute hospitalisation, many above the knee, and mortality rates between 15 and 40%.[7,8] The acuity and severity of the inciting event are due to the lack of opportunity to develop collateral vessels, unlike chronic ischemia. In a non-COVID-19 scenario, the predominant causes of acute arterial occlusion include embolism, thrombus in situ, arterial dissection, and trauma. A wider variety of diseases affect the upper extremity arteries. While atherosclerotic disease predominates as a cause of ischemia in the lower extremities, other etiologies are more common in the upper extremities (Stonebridge, 1989; Rapp, 1986; Deguara, 2005) Less common causes include thoracic outlet compression syndrome, Aortitis/arteritis and hypercoagulable disorders (Kasper *et al.*, 2018). Acute arterial occlusion symptoms depend on the location, duration, and severity of the obstruction. Pain, numbness, paresthesia, and coldness develop in the involved extremity within one hour. Paralysis occurs with persistent and severe ischemia. Physical findings include loss of distal pulses, cyanosis or pallor, mottling, decreased skin temperature, muscle stiffening, loss of sensations, weakness, and absent deep tendon reflexes. Resistance to ischemia differs with the tissues. In complete arterial occlusion, irreversible changes occur to the nerves within 4 to 6 hours, the muscles in 6 to 8 hours, and the skin in 8 to 12 hours (Obara, 2018).

If an acute arterial occlusion occurs with adequate collateral circulation, the symptoms and findings will be less severe. The clinical evaluation includes a Doppler assessment of peripheral blood flow. Magnetic Resonance Angiogram (MRA) or Computed Tomography Angiogram (CTA) is used to confirm the diagnosis and demonstrate the location and extent of arterial occlusion (Kasper, 2018). Typically, the patient is anticoagulated with intravenous heparin to prevent the propagation of the clot and recurrent embolism. If limb viability is jeopardized, immediate reperfusion is indicated. Endovascular therapy (ET) is most effective when acute arterial occlusion is recent (<2 weeks). It is also indicated when the patient's overall condition contraindicates surgical intervention or when smaller distal vessels are occluded, thus preventing surgical access. Surgical revascularization is preferred when restoration of blood flow must occur within 24 h to avoid limb loss or when occlusion symptoms have been present for >2 weeks. Amputation is necessary when the limb is not viable, as characterised by paralysis, loss of sensations, and the lack of Doppler-detected blood flow (Table 1) (Kasper, 2018).

MATERIALS AND METHODS

We prospectively studied ET's procedural safety and clinical efficacy in ALI among post-COVID-19 recovery patients in this study. Consecutive patients with documented SARS-CoV-2 infection and ALI clinical and radiological characteristics were recruited from Medicover Hospitals Visakhapatnam. In this interventional study from JUNE 2020 to JUNE 2021, 63 patients presented with ALI. The patients were thoroughly examined, and based on their presentations, managed either conservatively, surgically or with ET.

The staging of ALI was based on the Rutherford classification (Table 1).

Inclusion Criteria

- Signs and symptoms of ALI < 14 days
- Features of tissue loss
- Non-healing ulcer
- Severe claudication
- Rest pain
- History of documented COVID-19
- Recovery from COVID-19 and presentation between two to four weeks of a negative Reverse transcription-polymerase chain reaction test for COVID-19

Exclusion Criteria

- Patients who denied consent
- History of Peripheral artery disease
- Other known risks for ALI
- Patients with active COVID-19 infection
- Rutherford ALI stage III

Out of the 63 patients, only 38 patients were included in the study based on the above criteria. The rest were managed with anticoagulation, surgical revascularization or amputation. For the 38 participants, medical records, radiographic imaging, and procedural data analysis were done, and we recorded demographic features like age, sex, location of arterial occlusion, and treatment approach. Clinical examination findings before and after the treatment were noted. Doppler study and Computed tomography angiogram were applied to determine the location and extent of the arterial occlusion. Furthermore, blood investigations like complete blood counts**,** routine biochemical panel and thrombophilia screening were also recorded**.** Other tests to establish the etiology or identify the known risk factors of ALI were also conducted. We reviewed the angiographic results, procedure associated complications and clinical outcomes to assess the efficacy and safety of endovascular therapy. All patients were managed according to a standardized treatment protocol: anticoagulation with enoxaparin[15] and newer oral anticoagulants like dabigatran 150mg twice daily or rivaroxaban 20mg once daily except for recipients of thrombolysis. An angiogram was performed berore the initiation of ET (Figure 1). ET modalities implemented are Catheter-directed thrombolysis (CDT), Transluminal balloon angioplasty (TBA), thromboaspiration (TA) and stenting of the involved artery.

Catheter-directed thrombolysis: An angiogram is done to determine the location and extent of the thrombus. The vessels of the affected limb are directly accessed through the transfemoral arterial route or the pedal approach (either the anterior tibial artery or posterior tibial artery). A catheter is placed into the thrombus, and thrombolysis is initiated with an infusion catheter [MULTI-SIDEPORT catheter infusion set from COOK]. Alteplase [ACTILYSE] dose was 0.9mg/kg body weight (up to 50mg maximum). 20% of the dose was given as a bolus over 1 to 2 minutes. The remaining amount was given over the next 24 hours as CDT at the thrombus. After 24 hours, a check angiogram was done to assess the efficacy of thrombolysis and the degree of the revascularization.

A decision was taken to either stop the procedure or do a thromboaspiration according to the check angiogram.

Transluminal balloon angioplasty: The artery is effectively mapped with an angiogram. An appropriate size of the balloon is selected based on the diameter of the involved artery. A transfemoral arterial approach is taken, and a 6F short sheath was placed. The thrombus was navigated and crossed with a 5F Head Hunter with Terumo 0.035 hydrophilic wire combination. The Head Hunter catheter was removed and guided the balloon over the wire, and balloon angioplasty was done. We used a 2.5 x 100/150 mm balloon for below-knee angioplasty in the anterior tibial artery, posterior tibial artery, or peroneal artery. After crossing the lesion with an 0.014 wire, the balloon was placed across the diseased segment, and angioplasty is performed (Figure 2). A check angiogram was done to assess the results of the angioplasty. For the pedal arch angioplasty, a 2 x 100 mm balloon and 0.014 wire combination are used, and the arch is crossed from the anterior to the posterior tibial artery or vice versa to the other side. Balloon inflation was maintained for 2 minutes approximately. A final check angiogram is done to see the flow across the involved site, patency and calibre.

Thromboaspiration: During the angiogram and when navigating the clot, if we realise that the thrombus is fresh, a thromboaspiration was initially attempted with a 6.4F distal access catheter [Stryker]. The TA catheter was navigated through the thrombus and aspirated manually with a backward pull of the distal access catheter (Figure 3). If the catheter is blocked, it is cleaned, and the procedure is repeated till clot removal is satisfactory, and the lumen is restored (Figure 4).

Stenting: After the procedures for recanalizing the occluded vessel, including balloon angioplasty, thromboaspiration and thrombolysis, a check angiogram was done (Figure 5,6). In case of a flow-limiting dissection, etc., stenting was planned. Patient was given aspirin 150 mg with ticagrelor 180 mg if thrombolytic therapy is not done. After one hour of oral antiplatelet drugs, an appropriately sized stent was deployed across the dissection or the non-responsive occlusion. After the ET, the patients who did not undergo any CDT were given anticouagulation with enoxaparin (Tang, 2020) and newer oral anticoagulants like dabigatran 150mg twice daily or rivaroxaban 20mg once daily. CDT patients were observed very closely in the intensive care unit for neurological or vascular changes, new-onset flank pain, tachycardia, hypotension, or significant reductions in haemoglobin concentration (>1 g/dL). Anticoagulation was started after 12 hours of CDT cessation. All patients received advice to be in follow up for the next twelve months (Figure 7).

The criteria for favourable outcomes are

- Revascularization and absence of early (<30 days) re-occlusion
- Limb loss prevention
- Improvement in clinical features

RESULTS

Of the 38 patients included in the present study

- The ages ranged from 16 to 75 years, with a mean age of 64.45 years. The most affected age group is 55 to 75 years.
- The male to female ratio in our study is 1.92.
- Lower limb involvement is 3.75 times more likely than upper limb involvement.
- Pain and pulselessness are the most common initial findings present in all the patients. However, paralysis is a relatively rarer finding affecting 10.52% of the study participants.
- The lower limb arteries, especially below-knee arteries, are more commonly affected than the upper limb arteries.
- Most presentations were of Rutherford stage IIb (55.26%)
- Most patients require a combination of endovascular procedures. The frequency of used techniques is transluminal balloon angioplasty in 100% of patients (n=38), thromboaspiration in 57.89% (n=22), Catheter-directed thrombolysis in 36.84% (n=14) and stenting in 5.26% (n=2).
- We observed favourable outcomes in 35 (92.1%). Two (5.26%) of the patients needed amputations. One (2.36%) patient died.

DISCUSSION

ALI is one of the common vascular surgical emergencies with significant mortality and limb loss rates, reported as great as 20–40% and 12–50%, respectively.[16] Any segment of the arteries can be involved in this condition. The upper extremity accounted for an average of 17% (range 7 to 32%) of cases of acute limb ischemia in one systematic review.[17] Many retrospective analyses have demonstrated an incidence of thrombosis ranging from 12% to 31%, with a minority of these events are arterial (Veerasuri *et al*., 2016; Mecl, 2020). Some studies showed that arterial thrombosis accounts for about 4% of thromboembolic complications due to COVID-19 infection (Bozzani, 2020). Covid-19 is an endothelial thromboinflammatory syndrome involving the microcirculation of organs, leading to multiple organ failure and death (Ciceri). The pathophysiology behind the hypercoagulable state is multifactorial.

- COVID-19 directly attacks the endothelial cells, causing damage and activating the coagulation cascade, leading to vessel thrombosis in peripheral arteries and the aorta and causes major vascular events such as acute arterial ischemia.21
- The association of COVID-19 with increased pro-inflammatory cytokines (TNF, G-CSF, IL-2, IL-6, IL-7, IP-10, MCP1, MIP1-α, etc.) in patients with a severe disease, which leads to cytokine release syndrome (CRS).5
- Immobility and hypoxia of critically ill patients.

The mean age in our study is 64.45 years which is comparable to Etkin et al., (2021) Sánchez et al. (2021) andBozzani et al.[19]However, in the survey by Bellosta et al., (2020) the mean age was 75 ±9 years. The ages in our study ranged from 16 to 75 years. However, in the studies done by Etkin et al., (2021) Bozzani et al., (2020) Sánchez et al. (2020) and Bellosta et al., (2020) the ages ranged from 58-75 years, 30-94 years, 60 ±15 years and 62-95 years respectively. We are a tertiary care centre that specialises in vascular interventions.

Table 1. Rutherford staging of Acute Limb Ischemia

Stage	Prognosis	Sensory loss	Muscle weakness	Arterial Doppler signal	Venous Doppler signal
I	Limb viable, not immediately threatened	None	None	Audible	Audible
IIa	Limb marginally threatened, salvageable if promptly treated	Minimal (Toes)	None	Often Inaudible	Audible
IIb	Limb immediately threatened, salvageable with prompt recanalisation	More than toes, pain at rest	Mild or moderate	Inaudible	Audible
III	Limb irreversibly damaged, major tissue loss or permanent nerve damage inevitable	Profound, anaesthetic	Paralysis (rigor)	Inaudible	Inaudible

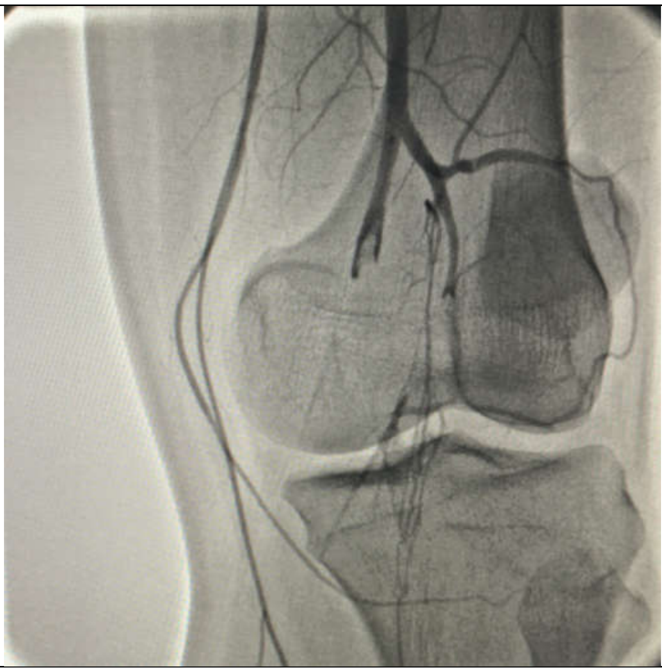

Figure 1. Angiogram demonstrating thrombotic occlusion of the popliteal artery in its proximal course with no flow beyond the site of occlusion

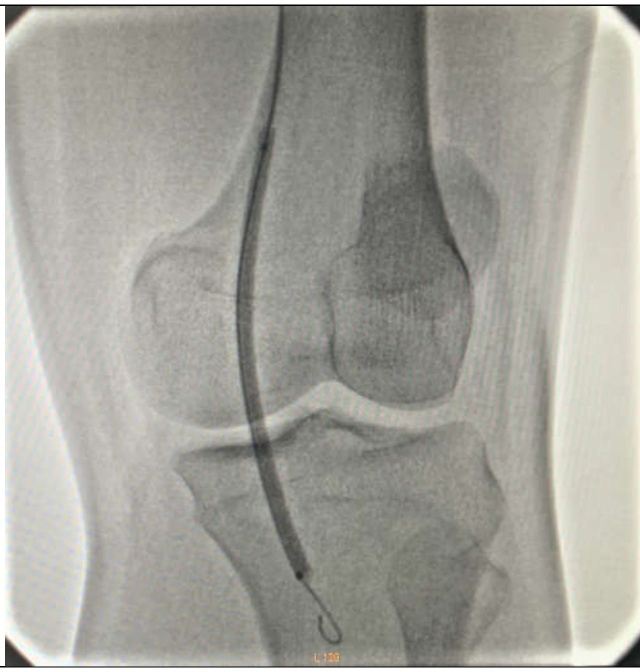

Figure 2. Balloon angioplasty of the popliteal artery to macerate the clot and create a channel

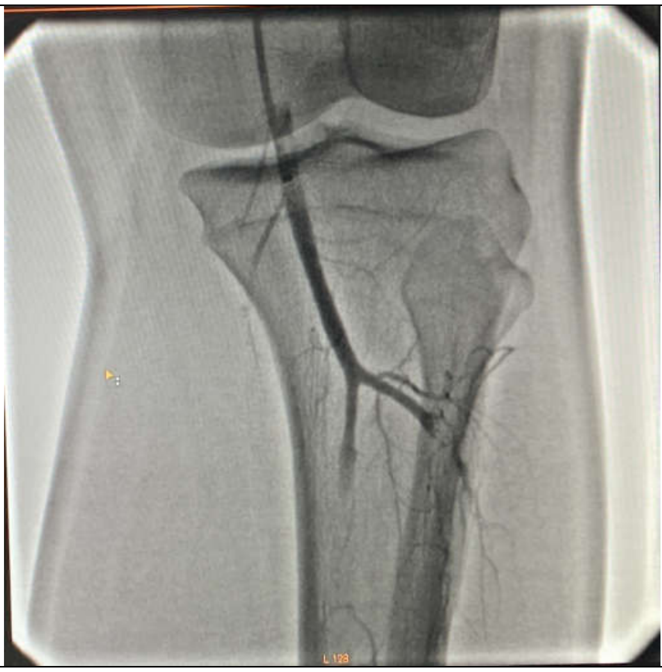

Figure 3. Recanalization of thepopliteal artery and the tibioperoneal trunk after thromboaspiration.

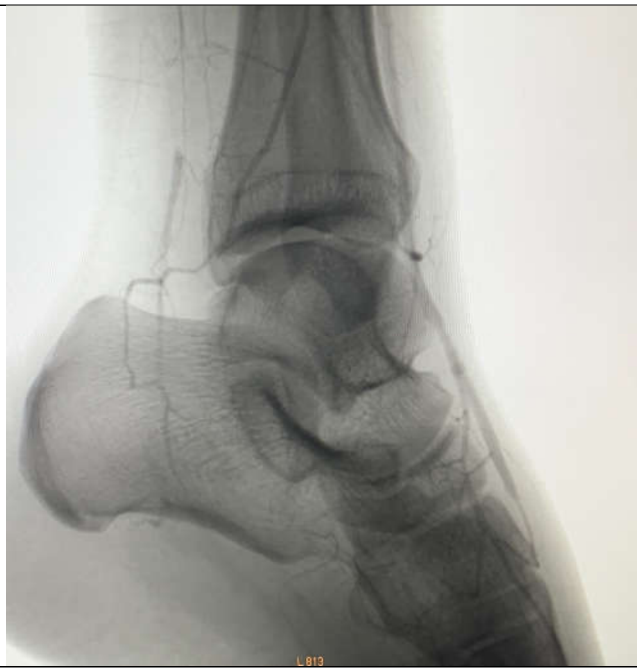

Figure 4. Thromboaspiration from the tibial vessels and dorsalis pedis artery. Arrow indicates the tip of the aspiration catheter

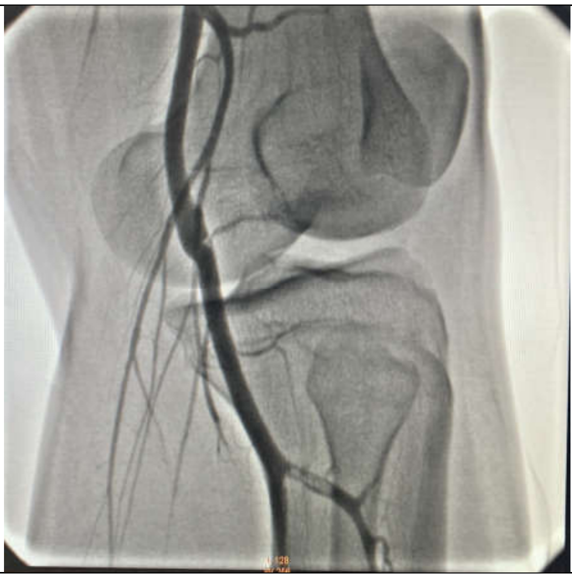

Figure 5: Final angiogram demonstrating good recanalization of thepopliteal artery and tibial vessels.

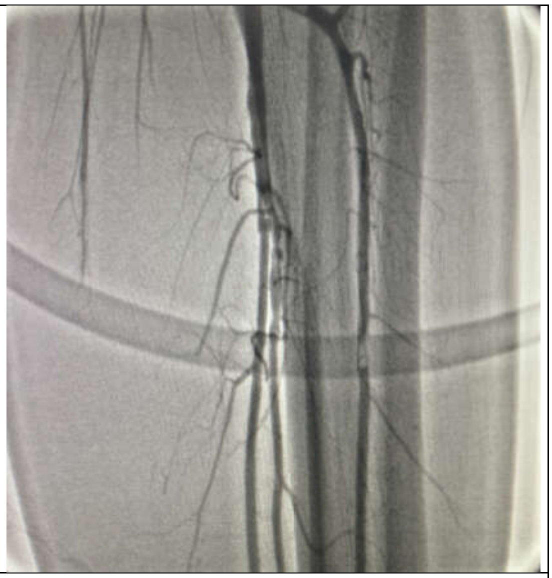

Figure 6: Final angiogram showing good flow in the anterior tibial artery, posterior tibial artery and the peroneal artery

Table 2. Clinicodemographic and radiological profile of the participants

Variable	Number (Frequency)
Demographic variables	
Age (years)	
<35	8 (21.05%)
35-55	12 (31.57%)
55-75	18 (47.38%)
Sex	
Male	25 (65.78%)
Female	13 (34.22%)
Limb involvement	
Upper Limbs	8 (21.05%)
Lower Limbs	30 (78.95%)
Clinical variables	
Pain	38 (100%)
Pallor	30 (78.95%)
Pulselessness	38 (100%)
Paresthesia	24 (63.15%)
Paralysis	4 (10.52%)
Reduced skin temperature	30 (78.95%)
Rutherford staging of Limb ischemia	
I	4 (10.52%)
IIa	13 (34.22%)
IIb	21 (55.26%)
III	-
Radiological variables	
Aorto-iliac arteries	5 (13.15%)
Femoral arteries	18 (47.38%)
Popliteal arteries	17 (44.73%)
Tibial arteries	24 (63.15%)
Subclavian arteries	2 (5.26%)
Axillary-Brachial arteries	3 (7.89%)
Radial arteries	2 (5.26%)
Ulnar arteries	3 (7.89%)

We receive referrals from most states in India, explaining the subtle discrepancies from other observations mentioned above. 65.78% of the participants in our study were men. The percentage of males in studies by Etkin et al., (2021) Bozzani et al., (2020) Sánchez et al.[23]and Bellosta et al., (2020) are 76%, 73.68%, 76.6% and 90%, respectively. 78.94% of the participants had lower limb involvement, similar toEtkin et al., (2021) (71%) andSánchez et al. (2021) (73.3%). The reason for higher lower limb involvement is unclear. Altered shear stress, intimal injury due to endothelial thromboinflammatory syndrome or increased turbulence are probable mechanisms.

Patients with class I acute limb ischemia need urgent revascularization (i.e., within 12 hours of presentation), and patients with class II acute limb ischemia need emergent revascularization (i.e., within 2–6 hours of presentation). Patients with irreversible limb ischemia (Rutherford class III) may require amputation without attempted revascularization as reperfusion abruptly releases toxic by-products of ischemic tissue (potassium, myoglobin, and reactive oxygen species) into the systemic circulation.

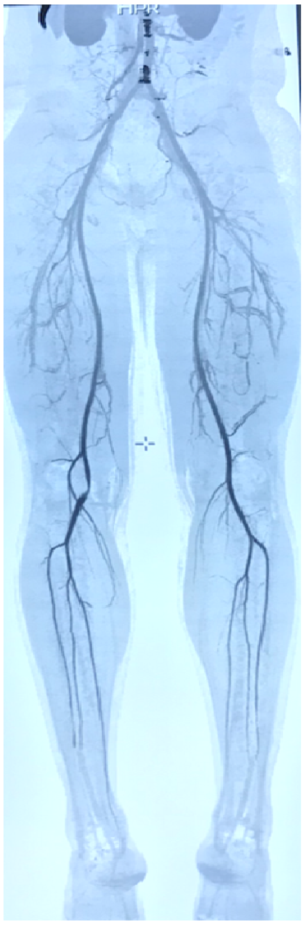

Figure 7: A CT angiogram at 6 month follow up showing good and sustained recanalization.

Patients with Rutherford class I and IIa limb ischemia are often amenable to endovascular treatment, and it is recommended over surgical approach.[25] Patients with class IIb limb ischemia require immediate revascularization and have traditionally been treated with open surgical techniques (e.g., open thromboembolectomy, endarterectomy, bypass surgery, patch angioplasty, or intraoperative thrombolysis). However, more recent case series have demonstrated similar revascularization rates with endovascular revascularization with decreased 30-day morbidity and mortality compared with open surgery (Hage, 2018). In the absence of contraindications, CDT should be considered when there is time, such as in severity classifications I and IIa. Reperfusion after CDT is slower than with surgical thromboembolectomy and can reduce the risk of ischemia-reperfusion injury. TBA gives us a chance to reopen the vessel instantly. However, TBA is not as effective as a tool of revascularization in acute thrombotic settings vs a chronic atherosclerotic lesion. However, TBA helps subsequent thromboaspiration and CDT. Thromboaspration is an excellent modality of treatment for acute arterial thrombotic occlusion. The recanalization is instantaneous primarily, and a good amount of thrombus can be removed through a dedicated thromboaspiration catheter, e.g. Indigo, CAT6, Penumbra, DAC. Stenting is not the first-choice treatment for acute thrombosis of limb arteries. It helps restore the lumen in flow-limiting dissections else on an acute on chronic occlusion.

Open surgery is invasive, and exposure is a risk to COVID. General anaesthesia was reported to increase postoperative mortality in patients COVID-19.[27] An endovascular approach, as the first-line option, was recommended by the Vascular Society of Great Britain and Ireland guidelines during the COVID-19 pandemic (https://fssa.org.uk/_userfiles/pages/files/covid19/prioritisation_master_240720.pdf). Currently, the evidence for endovascular treatment for COVID-19–induced arterial thrombosis is lacking. However, our opinion is that ET would minimise the intimal trauma (compared to the surgical approach) and the risk of recurrent thrombosis. In acute arterial occlusion, prompt recanalization of ALI is critical for improved clinical outcomes, which could be the reason for the observed favourable results (92.1%) in our study. Unfavourable sequelae were seen in three patients. There was a dissection of the distal anterior tibial artery and posterior tibial artery in two patients, which caused occlusion and could not be reopened. Therefore, subsequent amputation of the foot was done in both of those patients. One patient presenting with grade IIb limb ischemia was treated with a combination of TBA and CDT. The procedures were successful; however, signs of reperfusion-injury developed within one hour after the therapy. The patient was closely monitored in the intensive care unit, and a timely decision was taken to initiate dialysis on the count of worsening renal parameters (notably hyperkalemia). The patient had a sudden cardiac arrest on dialysis and could not be resuscitated. Early and effective recanalization is vital against the risk of amputation. Amputation is a significant health burden on the patients, their families, society, and medical services. It results in poor quality of life (Sahu, 2016). There are some limitations to our study. First, this study is a smaller population and non-randomized review. The relationship between the amputation rate and Rutherford classification, or patency rate post recanalization, and preference of the treatment strategy in each Rutherford classification is essential (De Athayde Soares, 2020). However, we did not analyze this issue because of fewer patients and treated limbs.

CONCLUSION

Advances in endovascular therapies in the past decade have broadened the options for treating ALI percutaneously in the COVID-19 positive scenario. Endovascular treatment offers a lower-risk alternative to open surgery in many. Noninvasive physiological tests and arterial imaging precede an ndovascular intervention, help localise the lesion, and plan the procedure.

CONFLICT OF INTEREST

In compliance with the ICMJE uniform disclosure form, all authors declare the following:

- Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work.
- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.
- Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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KEY-POINTS

- COVID-19 is being increasingly recognised as a pro-thrombotic state.
- Although ALI is a rare complication of COVID-19, there are increasing reports of peripheral arterial thrombosis in COVID-19 patients.
- Acute arterial occlusion leads to devasting consequences such as early limb loss, psychological trauma and mortality.
- Endovascular therapy is most effective when the arterial occlusion is recent (<2 weeks). Treatment modalities include Catheter-directed thrombolysis, Transluminal balloon angioplasty, thromboaspirationand stenting of the involved artery.

Endovascular treatment offers a lower-risk alternative to open surgery for many patients.

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