ACUTE LIMB ISCHEMIA IN COVID-19 PATIENTS WITH DELTA VARIANT IN INDIA: COHORT STUDY

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Abstract- The aim of our study was to determine the incidence, characteristics, and clinical outcomes of patients with the novel coronavirus (COVID-19) infection who had presented with and been treated for acute limb ischemia (ALI) during the 2021 coronavirus pandemic.

Methods: A single-center observational cohort research was conducted. A prospectively maintained database was used to gather data from all patients who tested positive for COVID-19 and presented with ALI necessitating urgent surgical therapy. All patients were classified according to Rutherford classification for acute limb ischemia. The Data is subjected to statistical analysis to find the association and P<0.05 was considered significant.

Results: Evaluation of 15 patients who tested positive for Covid-19 with ALI was included in the study. The study results demonstrated that the Mean age of the patients was 51.2±10.7. The hypercoagulability condition was seen in both younger and older patients in our collection, with a male predominance (79.90%). In 12 individuals, surgical therapy was conducted (80%). The patients who had died were significantly younger (40 ± 10). It was noted that there is significant influence of Covid-19 illness on the ALI. Revascularization was successful in 12 of the 15 (80.1%).

Conclusion: According to our preliminary results, the prevalence of ALI has grown dramatically in India during delta variant of COVID-19 pandemic. Revascularization success was lower than predicted, which we attributed to a virus-induced hypercoagulable condition.

Index Terms- SARS-CoV-2 infection; acute limb ischemia; amputation ;

I. INTRODUCTION

The COVID-19 pandemic has swept the globe after the first case cluster was discovered in Wuhan, China, in December 2019. Despite the fact that ALLI is an uncommon consequence of COVID-19, reports of peripheral arterial thrombosis in COVID-19 patients are on the rise.

Acute lower limb ischemia (ALLI) is a rapid decrease in lower limb blood flow due to acute occlusion of peripheral artery and in ALI not only limbs but also life prognosis will be poor unless quick and appropriate treatment is given. The symptoms of ALI are abrupt with pain, numbness, and coldness of lower limb, and paresthesia, contracture, and irreversible purpura will appear with the exacerbation of ischemia.[1] There are different causes which can lead to ALI, like arterial embolism (30%), arterial thrombosis due to plaque progression and complication (40%), thrombosis of a popliteal aneurysm (5%), trauma (5%) or graft thrombosis (20%).[2] The rate of ALI in the general population is approximately 10 to 15 per 100,000 per year (about 30,000 to 50,000 cases). Coagulation defects have been described with respiratory viruses including severe acute respiratory syndrome coronavirus 1 (SARS CoV-1), Middle East respiratory syndrome coronavirus [MERS-CoV], and severe acute respiratory virus syndrome coronavirus 2 [SARS-CoV-2]. Findings suggest that endothelial dysfunction, inflammation, cytokine release, hypercoagulability, and hypoxia contribute to thrombosis. Thrombotic complications in patients with coronavirus disease 2019 (COVID-19) present in a variety of ways, most commonly with venous thromboembolism, but also with ischemic complications related to thrombosis of extremity, cerebral, coronary, and visceral arteries. [3]

COVID-19 associated ALI has occurred in patients receiving thromboprophylaxis. The prevalence of ALLI in patients infected with COVID-19 was 0.54% [4] In a review of 209 patients with severe COVID-19 infection, 20 patients (9.6 percent) developed 24 arterial thromboembolic events . At the time of the event, 50 percent of patients were receiving thromboprophylaxis. Among the thrombotic events, 8 were ALI. The incidence of ALI associated with patients with COVID-19 who require hospitalization ranges from 3 to 15 percent. Early in the experience of COVID-19, this corresponded to between 600 and 3000 ALI cases in the United States (based on an estimated 20,000 patients requiring intensive care at that time), and an ALI prevalence of 4 to 21 per 100,000 hospitalized patients with COVID-19.[5] A sudden and significant increase of COVID-19–infected patients who were presenting with ALI has been noted at our institutions with the viral spread. The aim of the present study was to determine the incidence, characteristics, and clinical outcomes of patients presenting with and treated for ALI during the COVID-19 pandemic at an Indian tertiary care hospital.

II. MATERIALS AND METHODS:

A single-center observational cohort research was conducted. The current prospective study was reviewed and authorized by the local institutional review board due to the clinical emergency environment created by the current pandemic, and all included patients provided written informed consent. A prospectively

managed database was used to gather data from all patients who tested positive for COVID-19 and presented with ALI necessitating urgent surgical intervention. Physicians participating in direct patient care were in charge of data input.

The study is carried out between March 2021 to June 2021, during the second wave of COVID-19. All of the individuals who had been diagnosed with ALI and treated for it were identified and examined for this study. We also compared the data to data collected over the same time period in 2020. During hospitalisation and the immediate postoperative period, the following factors were recorded: demographics, comorbidities, laboratory blood test results, including coagulation panels, medical and surgical history, operating details, and postoperative occurrences.

Preoperative evaluation

According to our standardized approach, all patients with a clinical suspicion of aortoiliac and/or infrainguinal ALI and/or upper limb ischemia received preoperative screening blood tests, including creatine phosphokinase and D-dimer, as well as chest radiography and electrocardiography. Preoperative computed tomography revealed COVID-19-related pneumonia (Fig 1). These tests were carried out in the emergency department to avoid cross-contamination and the spread of viruses. Patients with aortoiliac occlusion had computed CT angiography to establish the severity of their sickness and the size of their arteries (Fig 2). The arterial and venous systems of patients with infrainguinal and/or upper limb occlusive disease were assessed using an echocardiographic colour Doppler approach. All patients were additionally evaluated with transthoracic echocardiography for the identification of probable cardiac emboli sources throughout their stay in the hospital. A multidisciplinary review, which included a physical examination and laboratory blood test findings, was used to define the surgical risk profile.

Post-Operative Evaluation:

Open surgery was conducted in the operating room under locoregional or local anaesthesia and intravenous sedation, with 100 U/kg intravenous heparin upon arterial clamping and regular antibacterial prophylaxis. All of the patients were given oxygen. No patient has required preemptive intubation due to COVID-19-related pneumonia at the time of the current analysis. A conventional groin incision was utilized to reveal the femoral bifurcation in individuals with aortoiliac or femoropopliteal blockage. Direct open brachial artery exposure was used to treat upper limb ischemia. Standard embolectomy catheters were used for thromboembolectomy, which were sized according to the site of the blockage. Completion Doppler was done in all instances via the surgical approach. Physical examinations were conducted every hour, and full blood panel tests were performed every 8 hours, as part of the postoperative monitoring. Only if the hemoglobin level had dropped below 8 g/dL were packed red blood cell transfusions administered. Throughout the hospitalization, an infectious disease expert assessed each patient on a regular basis to determine the best kind, dose, and duration of antibiotic and antiretroviral medication. At the time of release, all patients were given therapeutic doses of enoxaparin sodium injections to take home and advised to follow-up and take part in surveillance imaging. Duplex ultrasonography and computed tomography angiography will be used to confirm any changes in the examination results.

III. STATISTICAL ANALYSIS

Clinical data was collected and tabulated prospectively in a Microsoft Excel database. SPSS 25.0 was used to conduct the statistical analysis. The Shapiro-Wilk test was used to determine if continuous variables were normal. The mean, standard deviation, and range of normally distributed variables are displayed. Frequencies and percentages are used to represent categorical variables. The chi-square test was used to examine categorical variables. For continuous variables, an independent samples Student t test was utilized. The difference in blood test results before and after revascularization was evaluated using a Wilcoxon signed-rank test, with $P<0.05$ being statistically significant.

IV. RESULTS:

Study cohort. We examined at the data of 15 ALI patients who had COVID-19-related pneumonia. During the same time frame, three patients with ALI who had tested negative for COVID-19 were treated. The participants in this study were 10 patients who presented to our emergency department and five patients who were transferred from other hospitals. Twelve of the 15 patients were male (80%) and three were female (20%). The Mean age of the patients was 51.2±10.7. Table 1 demonstrates the demographics, comorbidities, and risk factors.

In summary, all 11 patients developed COVID-19-related pneumonia, as shown by preoperative RTPCR and computed tomography scans and one patient was tested positive for antibody test.

The mean arterial oxygen pressure was 75±28 mm Hg (range, 31-115 mm Hg). At the time of admission, 2 patients (13.3%) had Rutherford stage IIa, 3 patients (20%) had Rutherford stage IIb, and 6 patients had Rutherford stage III (40 percent). The average WLFI score before surgery was 5± 4 . (range, 1-15).

Treatment details.

Three patients (15%) did not undergo revascularization. These patients had severe COVID-19-related pneumonia, and intervention was not performed owing to their moribund condition (mean oxygen pressure, 42 mm Hg; mean SVS score, 8.6; and Rutherford stage III [2 patients]). Operative treatment was performed in 12 patients (80%).

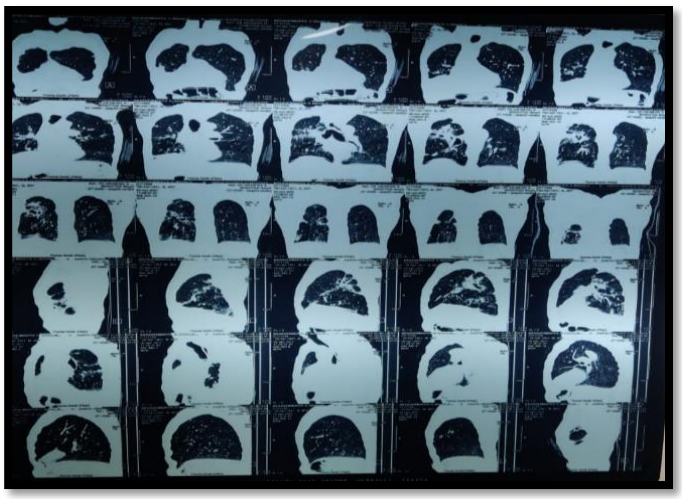

Figure 1 : Preoperative computed tomography scan of a 56-year-old man with COVID-19-related pneumonia and acute limb ischemia.

Figure 2 : Preoperative computed tomography angiography

Local anesthesia with sedation was used for 11 patients (91.6%) and loco regional anesthesia for one patients (8.3%). Infrainguinal occlusion was treated by thromboembolectomy in 09 patients (60.1%) and upper limb occlusion in 05 patient (33.3%). No major chronic atherosclerotic obstructive lesion was seen on completion Doppler, and no anastomotic abnormalities were found in the surgical or endovascular grafts that had previously been implanted. All patients were given systemic anticoagulation after surgery, either with a weight-adjusted therapeutic regimen of low-molecular-weight heparin (n= 8) or intravenous heparin infusion (n=4).

There were no bleed-related issues found. All of the patients exhibited black and gray-striped thrombus on macroscopic examination (Fig 3). The histopathological study of every thrombi was performed.

Mortality.

Of the 15 patients, 4 patients (40%) had died in hospital; the cause of death and clinical findings are reported in Table 2. The patients who had died were significantly younger, with the mortality rate for those aged 60 years or older significantly greater than that for those younger than 60 years old. On univariate analysis, no comorbidity or risk factors was associated with mortality. The preoperative SVS score (7.8 ±5.1 Vs 4.8 ±3.3 ; P =0.071) and preoperative creatinine phosphokinase value (12,082 vs 3618; P= 0.087) showed a tendency to be associated with mortality; however, the differences were not statistically significant. In contrast, on univariate analysis, the use of intravenous heparin was significantly associated with survival (0% vs 60.8% ; P = 0.03). For historical context, during 2020, only 38 of 410 arterial interventions (9.2%) were performed for ALI. Also, during the calendar period of March to June, the incidence rate of patients presenting with ALI in 2021 was significantly higher (84 of 350). The statistical analysis demonstrated that there is significant differences in the case reported in 2020 and 2021 (Fig.4).

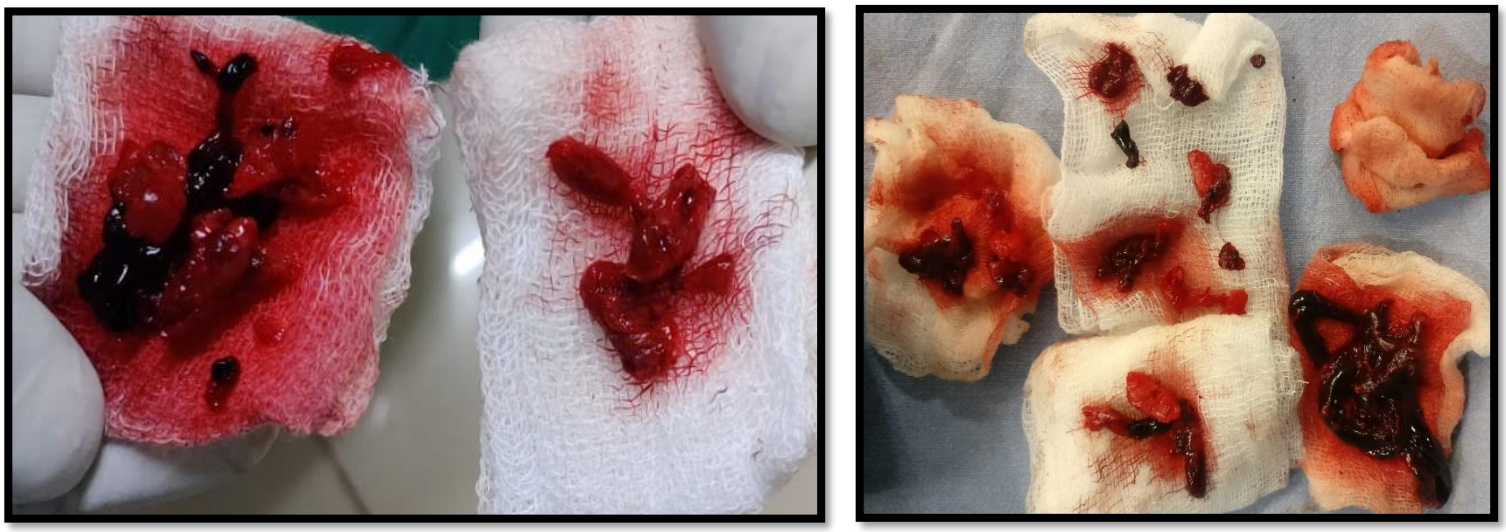

Figure 3 : Thrombus (A and B) specimen after Embolectomy

Demographic Variable	Value
Gender	
Male	12(80.0%)
Female	03(20%)
Age, year	
Age, group, years	
35-44	5(33.3%)
45-54	5(33.3%)
55-64	3(20%)
65-74	1(6.66%)
75-85	1(6.66%)
Comorbidities	
Hypertension	08(53.3)
Dyslipidemia	5(33.3)
CKD (eGFR<30ml/min)	04(26.6)
obesity	6(40%)
Diabetes	8(20%)
COPD	2(13.3%)
Risk factors	
WLFI Score	5± 4
Rutherford classification	
IIA,	2(13.33%)
IIB,	3(20%)
III	6(40%)
Preoperative blood parameters	
Hemoglobin, g/dL	12.9 ±8.6
Leukocytes	15 ± 4
D-dimer, ng/mL	
Median	2450
IQR	162 - 403
Platelets,	256 ± 79
CPK, U/L	6843 ± 2531

Table 1: Demographic data, comorbidities, and risk factors for entire cohort (N=15)

Revascularization.

Revascularization was successful in 12 of the 17 patients (70.6%) treated. During hospitalization, 2 of 15 patients (13%) had undergone reintervention because of a recurrent thrombotic occlusion of the treated arterial segment on postoperative days 1 and 3. No ipsilateral deep venous thrombosis was detected in patients with desert foot or in those who had developed recurrent thrombotic occlusion. Overall, limb salvage was obtained for 14 of 15 patients (93.3%). A major amputation was needed in 8 patients. Univariate analysis showed no significant differences in comorbidities or the SVS risk profile between those with and without successful revascularization (P = 0.081). The presence of COVID-19-related pneumonia was not significantly associated with successful revascularization (48.6% vs 69.2%; P= 0.710). In contrast, the preoperative oxygen pressure was significantly lower in those without successful revascularization (50±9 mm Hg Vs 82±21% mm Hg; P= 0.038).

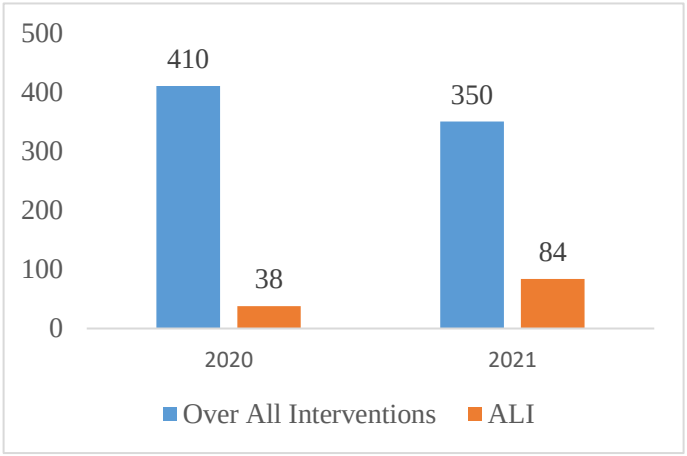

Figure 4 : Estimated projection of patients with acute limb ischemia (ALI) in 2021 compared with those treated in 2020 at the same center.

V. Discussion;

According to extant research, Covid-19 infections are linked to coagulopathy, which might show as acute limb ischemia. This research could help researchers better understand the hypercoagulation condition in Covid-19 patients, as well as the possibility of acute limb ischemia as a symptom. Covid-19 individuals with an increased risk of acute limb ischemia have been identified in several earlier papers with little clinical and therapeutic evidence. [6,7]

The main findings from this preliminary phase of COVID-19 health emergency are twofold. First, the number of patients in our population presenting with ALI has significantly increased compared with the same period in 2020. Second, the high rate of clinical and technical failure was consistent with the presence of a hypercoagulable state triggered by COVID-19.

The patients after the examination, the severity of the disease is classified based on the Rutherford lower limb ischemia and interventions will be made accordingly in the patients.
Preliminary findings on the link between COVID-19 infection and hypercoagulability have recently been presented. Tang et al., [7] discovered that aberrant coagulation outcomes, such as a significantly raised D-dimer level and fibrin breakdown products, are prevalent in COVID19-related pneumonia patients. Elevated D-dimer values in Covid-19 patients have also been linked to the severity of the hypercoagulable condition. Based on the clinical characteristics, it's reasonable to assume that the patient's hypercoagulation and clinical ischemia indicated serious sickness, necessitating close monitoring and prompt action. To avoid irreversible damage or amputation, close monitoring of the extremities for thromboembolism is required. [8] Observations of hypercoagulable condition in COVID-19 patients following surgery have not been documented in any previous investigations.

No	Gender	Age, years	COVID-19-related pneumonia	Vaccination status	Anatomic location	Clinical Finding	Intervention	Cause of death
A	M	46	Positive	Not Vaccinated	Left Lower Limb	CLI	Thromboembolectomy	-
B	M	44	Positive	Not Vaccinated	B/L Lower limb	CLI	Embolectomy + Forefoot amputation	-
C	F	36	Positive	Not Vaccinated	Right Upper Limb	Gangrene	Amputation + Stump Embolectomy	-
D	M	44	Negative	Not Vaccinated	Left Lower Limb	CLI	Embolectomy	-
E	M	56	Positive	Not Vaccinated	B/L Lower limb	CLI	B/L Embolectomy	ARDS
F	M	38	Negative	Not Vaccinated	Right Upper Limb	Gangrene	Above the knee Amputation + Stump Embolectomy	-
G	M	75	Positive	Not Vaccinated	Right Upper Limb	Gangrene	Above the knee Amputation + Stump Embolectomy	ARDS
H	M	50	Negative (Antibody +ve)	Not Vaccinated	Right Upper Limb	Gangrene	Below the knee Amputation + Stump Embolectomy	-
I	M	51	Negative	Not Vaccinated	Right lower Limb	CLI	Embolectomy	
J	F	46	Positive	Not Vaccinated	Left Lower Limb	Gangrene	Amputation + Stump Embolectomy	-
K	M	56	Positive	Not Vaccinated	B/L Lower limb	CLI	B/L Embolectomy	MOF
L	M	39	Negative	Not Vaccinated	Right Upper Limb	Gangrene	Above the knee Amputation + Stump Embolectomy	-
M	F	69	Positive	Not Vaccinated	Right Upper Limb	Gangrene	Above the knee Amputation + Stump Embolectomy	
N	M	53	Positive	Not Vaccinated	B/L Lower limb	CLI	B/L Embolectomy	
O	M	62	Positive	Not Vaccinated	B/L Lower limb	CLI	B/L Embolectomy	-

Table 2 : Distribution of patients based on Clinical findings

We hypothesized that individuals who test positive for COVID-19 may develop a hypercoagulable condition, which may enhance the incidence and duration of native arterial occlusion. Previous research (prior to COVID-19) shown that the overall prevalence of ALI has decreased dramatically over the last decade, and that the presence of a hypercoagulable condition is a rare cause among the general population with ALI. [9] However, compared to the same period in 2020 before COVID-19, we have examined a much higher number of patients with ALI in our early experience.

Despite the fact that young age and female gender have been linked to recognized hypercoagulable illnesses, this hypercoagulability condition was seen in both younger and older patients in our collection, with a male predominance. In our research, we discovered a 6-fold rise in the number of patients with ALLI compared to the same time last year (March 1, 2020 to June 31, 2020) (2 patients versus 12 patients).

Also It was noted during the study that majority of the patients who reported with ALLI were positive for COVID-19 test. In Our patients' hypercoagulability is not caused by well-known blood diseases, but by COVID-19 infection, which may cause native arterial thrombosis. This is only a first impression, but it's a fascinating one. Anecdotally, viral-related ALI has been documented, although it has not been linked to venous thromboembolism or hypercoagulability in investigations. this adds crucial factor to the evidence given by Lam, R. et.al. [10]

Furthermore, Torrealba et al., [11] found that individuals with identified hypercoagulable illnesses had a considerably poorer result. When compared to prior series, the rate of successful revascularization in patients with COVID-19 was surprisingly low, which is similar to the interventions in our present study. [10, 12]

There are currently no data on COVID-19 individuals who present with ALI, nor have the results of those who have been surgically treated been documented. As a result, there is no defined treatment regimen in place. We chose to be much more aggressive because of the clinical and angiographic features, as well as the significant failure rate for these patients, and we quickly raised our successful clinical and technical outcomes. With the goal of preventing early recurring thrombosis, especially in the distal microcirculation, we chose to employ continuous intravenous heparin infusions beginning immediately after the operation, considering the fact that Heparin inhibits thrombus growth both proximally and distally and keeps collateral veins open. [13-15]

Patients with COVID-19 who present with acute limb ischemia are described in terms of patient and clinical features. The majority of males was consistent with previous reports. The vast majority of patients had at least one cardiovascular risk factor, with hypertension and diabetes being the most common. This could explain the role of traditional classical cardiovascular risk factors in ALLI. This emphasizes that the hypercoagulable state caused by COVID-19 infection is mediated by mechanisms other than atherosclerosis and plaque rupture. [14]

Bellosta et al., [15] elaborated the role of The conventional treatment for acute limb ischemia includes immediate revascularization as well as antiplatelet and anticoagulant therapy. With COVID-19-associated acute limb ischemia, revascularization success rates are found to be lower. This is most likely owing to a continuing, widespread hypercoagulable condition. Post-intervention heparin appeared to improve outcomes in individuals with acute limb ischemia. Which is also emphasized in our current study. [16,17]

There were some significant limitations to the current exploratory observational investigation. The first was the tiny number of people that were included in the study. Second, because of pandemic limitations, the follow-up period was short. Third, we lacked reliable data on coagulation parameters to assess hypercoagulability's long-term condition.

VI. CONCLUSION :

The frequency of ALI interventions has grown dramatically in our early COVID-19 experience. This higher frequency, as well as the high failure rate owing to failed revascularization, appears to suggest the presence of a pronounced hypercoagulable condition in these infected individuals, a process that might be initiated by the virus. Our treatment regimen has been strengthened as a result of these observations, as well as data from animal models, by focusing primarily on the use of continuous intravenous heparin. In our experience, adding heparin to a medication seemed to improve its efficacy and, more crucially, was linked to a higher rate of survival.

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