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Original Research Article

A Retrospective Observational Assessment of Acute Lower Limb Ischemia (ALLI) among Patients Infected with COVID-19

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Abstract

Aim: The aim of the present study was to investigate the prevalence of acute lower limb ischemia (ALLI) among patients infected with COVID-19.

Material & methods: We performed a retrospective observational study on 50 patients with acute limb ischemia (ALI) and SARS-CoV-2 infection at department of Radiology The inclusion criteria were: presence of SARS-CoV-2 infection and acute event of vascular disease, i.e., acute limb ischemia.

Results: 50 patients aged 43–86 years old (mean age 62.88 ± 8.52 years) were admitted. There were 35 males (70%) and 15 females (30%). In terms of co-morbidities, patients were obese, had diabetes mellitus, high blood pressure. 46% patients had habit of smoking. The patients were treated by open surgery (42 patients—84%) or by the means of endovascular techniques (8 patients—16%). The amputation-free survival rate was 82% in hospital and 86% at 1-month follow-up.

Conclusion: The application of the standard treatment—open surgery or endovascular revascularization in patients with acute limb ischemia and SARS-CoV-2 infection is the key to success for lower limb salvage. The prolonged administration of anticoagulants (both in the periprocedural period and after discharge) can improve surgical results, limb salvage, and patient survival.

Keywords: Acute Limb Ischemia; Arterial Thrombosis; Coagulopathy; Coronavirus Disease 2019; D-Dimer.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), originated in December 2019 and has caused a worldwide pandemic. [1] Infection with SARSCoV-2 has been shown to have a wide range of clinical presentations from asymptomatic in a large percentage of patients to devastating pulmonary failure, sepsis, and death. [2,3] Through its rapid transmission world-wide and potentially life and limb threatening complications, COVID-19 has become a global pandemic that has implications through a wide range of medical and surgical specialties due to its association with multi-organ failure.

COVID-19 has other complications in the form of blood disorders, one of which is acute limb ischemia (ALI). [4] Complications of ALI due to COVID-19 are reported to be rare, but if they occur, they can have severe outcomes ranging from limb amputation to death caused by sepsis and multiple organ failure. [5] Although ALLI is a rare complication of COVID-19, [6] there have been increasing number of reports of peripheral arterial thrombosis in COVID-19 patients. [7]

ALI is a condition that needs urgent diagnosis and treatment because it results in decreased arterial blood circulation to the limbs. By definition, ALI is a perfusion disorder in the extremities with symptoms lasting less than 2 weeks. Common causes of ALI are embolism, thrombosis, trauma, aneurysm, and arterial dissection. [4,5] Through systemic inflammation and a hypercoagulable state, there seems to be a spectrum of clinical manifestations of limb injury ranging from chilblains and bullae to acute limb-threatening ischemia. Other clinical findings include acral cyanosis, bruising, blood blisters, and dry gangrene. [8] Symptoms can be cutaneous, subcutaneous, or involve the entirety of a digit or a distal limb. Outcomes suggest that some patients are able to achieve revascularization of the affected limb or digit with observation or medical and/or surgical intervention, but other patients succumb to either amputation or death due to the disease.

Hence the aim of study was to assess correlation between ALI severity, patients' comorbidities, and the association of SARS-CoV-2 infection.

Material & Methods

We performed a retrospective observational study on 50 patients with acute limb ischemia (ALI) and SARS-CoV-2 infection at Department of Radiology, Gouri Devi Institute of Medical Sciences and Hospital, Durgapur, West Bengal, India for one year. The inclusion criteria were: presence of SARS-CoV-2 infection and acute event of vascular disease, i.e., acute limb ischemia.

The clinical status of the patients was defined using the Rutherford classification system. [9] SARS-CoV-2 infection was diagnosed with RT-PCR (Reverse-transcriptase polymerase chain reaction) tests [10] for all patients, and they all underwent chest-computed tomography. All patients underwent preoperative blood tests (consisting in blood count, creatin- phosphokinase (CK), urea, creatinine, LDH, CRP, D-dimers, etc.). Complete medical history was recorded. Computed tomography angiography (CT-Angio) was performed to assess the extension of the arterial lesions, according to standards of care for this pathology. The entire cohort underwent transthoracic ultrasound to investigate signs of embolic risk factors. The patients were isolated, and all procedures were performed observing the universal caution regarding the SARS-CoV-2 infection, avoiding cross-contamination, and reducing the risk of viral spread.

All participants in the study read and signed an informed consent. The data were collected under GDPR (General Data Protection Regulation) laws. The study had the agreement from the Hospital Ethics Committee, under the EU GCP Directives, International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and the Declaration of Helsinki. The surgical treatment was individualized for every patient considering the arterial lesions and the extent of peripheral lesions. They were treated surgically or by the means of endovascular techniques.

Open surgery consisted of Fogarty embolectomy performed in the operating room under loco-regional or local anesthesia, and none of the patients required intubation because of COVID-19 pneumonia. The approach was either from the femoral or popliteal artery. All patients received antibioprophylaxis with 3rd generation cephalosporins. Before clamping the arteries, a bolus of 80 UI/kgc intravenous heparin was administered. Endovascular procedures consisted in catheter-directed intra-arterial thrombolysis using Merit Fountain Thrombolysis Catheter and Infusion System® (Merit Medical, South Jordan, UT, USA). The access was either femoral or brachial. After the catheter placement, 10 mL of rt-PA® (Recombinant Tissue Plasminogen Activator—Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany) was directly infused with the infusion system. After that, 40 mL of continuous perfusion was administered through the intra-arterial catheter at a rate of 1 mL/h for no more than 24 h, and simultaneously heparin (250 UI/mL/h) was administered through the sheath in continuous perfusion. After 24 h, control angiography was performed, and additional procedures were performed when needed.

The revascularization procedure was chosen in relation to anatomical and/or morphological considerations, especially in patients with multiple atherosclerotic deposits; in those patients, endovascular treatment was preferred in order to avoid complications, such as plaque dissection, or in cases where it was impossible to insert the embolectomy catheter. Major amputation was defined as above-the-knee or below-the-knee, and minor amputation was considered to refer to either toes or metatarsal amputation. [11]

Preoperatively, all patients received antiplatelet (Aspenter® 75 mg daily) and anticoagulant treatment (intravenous unfractioned heparin in continuous perfusion). Postoperatively, all patients received low-molecular-weight heparin, 1 mg/kgc twice daily. We initiated Rivaroxaban 20 mg daily after 5 days of low-molecular-weight heparin. [12] At discharge every patient was given Rivaroxaban® 20 mg daily for 30 days, and after that 2 × 2.5 mg/zi Rivaroxaban® and antiplatelet (Aspenter® 75 mg) daily. [13]

Statistical Analysis

Data were analyzed with MedCalc Statistical Software version 19 (MedCalc Software bvba, Ostend, Belgium). Data are presented as mean and standard deviation, median and interquartile range [IQR], number, and percentage. Paired t tests were performed between pre- and post-treatment differences on the lower limb viability. Differences were considered statistically significant at $p < 0.05$. Stepwise logistic analysis was performed in order to identify factors associated with death and amputation.

Results

Table 1: Demographics

Total No. of Patients	**50**
Age, years (mean ± SD)	62.88 ± 8.52
Male, *n* (%)	35 (70)
Female *n* (%) BMI, kg/m^2 (mean ± SD) **Comorbidities**	15 (30) 30.62 ± 6.44
Cardiac insufficiency, *n* (%)	18 (36)
Obesity, *n* (%)	36 (72)
Diabetes mellitus, *n* (%)	32 (64)
Dyslipidemia, *n* (%)	43 (86)
High blood pressure, *n* (%)	50 (100)
I, *n* (%)	15 (30)
II, *n* (%)	23 (46)
III, *n* (%)	12 (24)
Chronic obstructive pulmonary disease, *n* (%)	9 (18)
Brain cerebrovascular disease, *n* (%)	9 (18)
Neoplasm, *n* (%)	4 (8)
Risk factors	
Smoking, *n* (%) Ischemia time, hours (median [IQR]) Preoperative antiplatelet treatment, *n* (%) Rutherford classification IIA, *n* (%)	23 (46) 18.59 [5–34] 43 (86) 34 (68)
IIB, *n* (%)	16 (32)

50 patients aged 43–86 years old (mean age 62.88 ± 8.52 years) were admitted. There were 35 males (70%) and 15 females (30%). In terms of co-morbidities, patients were obese, had diabetes mellitus, high blood pressure. 46% patients had habit of smoking.

Table 2: Pre-operative blood parameters

Characteristics	**Range Values**	**Patients' Values**
Leukocyte count (no. x10^3/L), median [IQR] Normal range	4–9.5	8.35 [5.34–14.28]
Neutrophils (%), mean ± SD	45–70%	62.28 ±12.42
Erythrocyte count (no x10^3/L), median [IQR]	4–5.5	3.64 [3.45–4.24]
Monocyte, median [IQR]	0.8–3.8	1.33 [1.09–1.77]
Hemoglobin level (g/dL), median [IQR]	11.5–15	10.70 [10.31–11.40]
Lymphocyte (no. 10), median [IQR]	0.8–3.8	1.33 [1.09–1.77]
Hematocrit (%), mean SD	35–46	34.08
Platelet count, mean SD	150–400	275545
LDH, median [IQR]	120–246	278 [161.3–346.5]
Ferritin level (μg/L), mean SD	20–290	728.9
CRP level (mg/L), mean SD	0–10	68.08
aPTT (s), median [IQR]	25.1–36.5	29.4 [24.4–35.41]
Quick time (s), median [IQR]	9.4–12.5	14.67 [12.68–15.61]
INR, mean SD	0.8–1.07	1.27
VSH (mm/1 h), mean SD	1–15	82.41
AST (U/L), median [IQR]	14–36	23.5 [18–28.25]
ALT (U/L), mean SD	0–35	23.91
D-dimers (ng/mL) mean SD	0–243	957
Urea (mg/dL), median [IQR]	15–36	30 [23–45]
Creatinine (mg/dL), median [IQR]	0.7–1.2	0.89 [0.7–1.42]
Fibrinogen (mg/dL), mean SD	200–393 668	168.3
CK (U/L), median [IQR]	30–170	115 [43.75–508.8]

The pre-operative blood parameters were normal in the patients.

Table 3: Treatment and amputation-free survival rate

Treatment	N	%
Open surgery	42	84
Endovascular techniques	8	16
Amputation-free survival rate		
In-hospital	42	82
One month follow up	43	86

The patients were treated by open surgery (42 patients—84%) or by the means of endovascular techniques (8 patients—16%). The amputation-free survival rate was 82% in hospital and 86% at 1-month follow-up.

Discussion

Blood hypercoagulability is common among COVID-19 patients. In these patients, elevated D-dimers levels are consistently reported (and are associated with the disease worsening). Other coagulation abnormalities that lead to life-threatening complications, such as PT and aPTT prolongation, fibrin degradation products increase, and severe thrombocytopenia, are also present. [14,15] Acute limb ischemia is associated with blood hypercoagulability and can have either embolic or thrombotic causes. [16] Arterial thrombosis in COVID-19 patients can have different forms, from blue-toe syndrome to limb-threatening acute limb ischemia. Only a few patients present within the limb-salvageable interval, and most of them need amputation because of severe gangrene. [17]

50 patients aged 43–86 years old (mean age 62.88 ± 8.52 years) were admitted. There were 35 males (70%) and 15 females (30%). In terms of co-morbidities, patients were obese, had diabetes mellitus, high blood pressure. 46% patients had habit of smoking. The patients were treated by open surgery (42 patients—84%) or by the means of endovascular techniques (8 patients—16%). The amputation-free survival rate was 82% in hospital and 86% at 1-month follow-up. Even with mild symptoms, COVID-19 patients might develop acute limb ischemia as seen in our case. Although acute respiratory distress syndrome (ARDS) is the most common consequence in patients with severe COVID-19, cardiovascular, thromboembolic, inflammatory, and neurologic complications are being reported more recently. Comorbidities such as cardiovascular disease, diabetes mellitus, obesity, smoking, cancer, chronic renal disease, chronic obstructive pulmonary disease, solid organ or hematopoietic stem cell transplantation, and advanced age are the risk factors for developing severe COVID-19 infection. [18,19] Coagulation disorders that lead to thromboembolic events are linked to a poor prognosis. According to the study by Fournier et al [20] conducted in France, COVID patients with arterial thrombosis had a threefold greater mortality. Embolization of a cardiac or aneurysmal thrombus or thrombophilic conditions such as antiphospholipid antibody syndrome, malignancy, or heparin-induced thrombocytopenia are the most common differential diagnoses in a patient with thrombotic abnormality. Similarly, his clinical presentation, laboratory testing, and chest imaging did not indicate the existence of a malignancy, and once COVID-19 was diagnosed, no further workup was done. [21,22] Patients with comorbidities including hypertension, diabetes, chronic respiratory disease, renal disease, and obesity have a higher risk of adverse outcomes. [23]

There are three mechanisms involved in vascular thrombosis associated with the presence of SARS-CoV-2: altered vascular wall, abnormal blood flow because of high viscosity, and the hypercoagulable state of the patient. The relationship between the baseline inflammatory status and the risk of future cardiovascular events is related to CRP values. There are studies stating that CRP is an actual biomodulator of the inflammation within the arterial wall, and that it can alter the behavior of cells in the vessel wall in a way that can promote thrombosis. [24] The amputation-free survival rate derives from a proper revascularization treatment by taking into consideration the extent of vascular lesions and the European guidelines in acute limb ischemia in patients presenting within the revascularization window with a viable lower limb. [25] In some studies, the therapeutic indication is correlated both with ischemia time and morphological aspects of the arteries (i.e., atherosclerotic deposits). [26] Galyfos et al [27] conducted a systematic review on 34 articles regarding acute limb ischemia and SARS-CoV-2 infection, involving 540 patients. Mortality rate among these patients was 31.4%, while in our study, the rate was 13.18% at 1-month follow-up; the amputation rate among the 540 patients in the review was 23.2%, compared with 13.18% in this study. In the systematic review by Galyfos et al [27], the medical treatment was selected in 41.8% of cases, and these had a higher risk of death when compared with any other intervention. With the application of a proper surgical treatment (either open surgery or endovascular) and with a systemic anticoagulant treatment, we think that the patients with acute limb ischemia and SARS-CoV-2 infection who present within the revascularization window can have a good prognosis, despite viral presence as a prothrombotic factor.

Conclusion

The application of the standard treatment—open surgery or endovascular revascularization in patients with acute limb ischemia and SARS-CoV-2 infection is the key to success for lower limb salvage. The prolonged administration of anticoagulants (both in the periprocedural period and after discharge) can improve surgical results, limb salvage, and patient survival.

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