

## Original Article

# Acute Limb Ischemic in COVID-19 Patients after the Several Peaks of Transmission, What Can be Learned?

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**Abstract**

**Background:** Corona Virus Disease 2019 (COVID-19) has been linked to increased incidence of thrombosis. This study aimed to describe the evaluation of COVID-19 patients with ALI (Acute Limb Ischemic) including the incidence, patient characteristics, predisposing factors, and clinical outcomes in our center as an Indonesian tertiary care hospital.

**Methods:** A retrospective review about COVID-19 patients with ALI was conducted from January 2021 to December 2022. Collected data included patient characteristics, anatomical location of ALI, treatments, and outcomes.

**Results:** A total of 13 COVID-19 patients with ALI were admitted. During the treatment of ALI and COVID, 1 (8%) patient underwent amputation, 6 (46%) patients underwent thromboembolism and 6 (46%) other patients were amputated with thromboembolism. There were 3 patients amputated below their knee and 4 patients amputated above their knee. The most affected limbs in our study were inferior extremities (100%).

**Conclusion:** Early recognition and management of COVID-19 patients with ALI is important to reduce morbidity and mortality. The advantage of open thromboembolism was to remove the thrombus, which was expected to improve the blood flow and reduce the amputation level. By conducting earlier interventions, there were better blood flow, less tissue damage, less necrotic tissue, and reduced risk of mortality.

**INTRODUCTION**

The Corona Virus Disease 2019 (COVID-19) pandemic started near the end of 2019. The first case was reported in December 2019 in Wuhan, China. COVID-19 is an infectious disease originating from the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [1]. Over the past few years, COVID-19 has spread globally with several peaks of transmission, including the delta variant in mid-2021 and the omicron variant in early 2022. Since then, COVID-19 transmission in mid-2022 has decreased drastically [2].

The presentation of COVID-19 could be asymptomatic or develop into a rapidly progressive fatal disease, including multi-organ failure [3]. There were several patients with COVID-19 who were reported to have coagulation disorders. High D-dimer, von Willebrand factor antigen and activity, and factor VIII activity were previously reported in patients with COVID-19. Moreover, endothelial dysfunction, inflammation, cytokine release, hypercoagulability, and hypoxia that occur in COVID-19 were linked to increased incidence of thrombosis. Furthermore, a co-existing hypercoagulable state in patients with COVID-19 might be associated with higher mortality [4].

One of the diseases associated with coagulopathy is acute lower extremity ischemia (ALI), which is a vascular emergency that requires immediate intervention. Arterial thrombosis in patients with hypercoagulable states is one of the most challenging of ALI scenarios. The current study showed there were improvements in hospital mortality and early amputation rates related with ALI. However, in the context of a hypercoagulable state, surgical decision-making and related clinical outcomes have been poorly reported [5].

Consequently, it is important to learn more about ALI in COVID-19 patients. Although the number of COVID-19 cases has decreased compared to last year, it should be noted that COVID-19 as an infectious disease could cause ALI through the inflammation process. Likewise, other infectious diseases could cause ALI. The study of ALI cases with COVID-19 can provide knowledge about others infectious diseases that could cause thrombus in humans. This study aimed to describe the evaluation of COVID-19 patients with ALI including the incidence and characteristics, as well as clinical outcomes in our center as an Indonesian tertiary care hospital.

## MATERIAL AND METHODS

### Patients

A retrospective review about COVID-19 patients with ALI was conducted from January 2021 to December 2022. The inclusion criteria were all of the patients who had a positive COVID-19 swab results before experiencing ALI symptoms. The patients with ALI symptoms before having a positive COVID-19 swab result were excluded. Positive COVID-19 swab result in this study was based on either antigen or polymerase chain reaction (PCR) tests.

During the COVID-19 pandemic, the exposure of medical personnel to the patient has been significantly reduced. Considering Indonesia is a developing country, most diagnosis is typically based on patient history and clinical examination. Patients with symptoms of respiratory tract infection including fever, cough, and dyspnea will undergo antigen or PCR testing for COVID-19 screening. Patients with ALI are diagnosed from history taking with complaints of pain, cold feet, tingling, muscle cramps, pale color/color changing (necrosis) in less than two weeks, while physical examination will reveal any decrease or loss of pulsation in the affected arteries, decrease in function (*Fungsio Laesa*), and gangrene. The computerized tomography (CT)-angiography, peripheral tomography, arteriography, Doppler ultrasound, and D-Dimer examinations are not performed routinely because of limited financial resources, manpower, and tools. Other blood factors are not checked routinely due to the high expense and lack of coverage.

### Treatment

The patients who were confirmed with COVID-19 and ALI were treated with standard management of patients with COVID-19, including isolation and administration of anti-COVID-19 drugs/antiviral agents. Treatment for ALI depends on clinical conditions ranging from heparin administration to amputation according to Rutherford's criteria. In detail, patients with clinical presentation of Rutherford II were given heparin and embolization, while patients with Rutherford III underwent amputation. The revascularization procedure was performed openly to reduce the level of amputation. Heparin administration starts from 10 IU/kg/hour, and dosages were increased up to 1.5-2 times depending on the patient's condition. Heparin is administered to patients with Rutherford II, III, and post-operative patients.

### Follow-up

After the patient received treatments for COVID-19 and ALI, the follow-up and evaluations were conducted until their condition of COVID-19 and ALI improved or worsened which determined whether the patient was discharged or not (outcome: survived or died).

### Statistical Analysis

Data were collected using Microsoft Excel 2020 (Microsoft Corp., Redmond, WA USA) and analyzed using SPSS 23 (IBM Corp., Armonk, NY USA). Descriptive data were presented as median with range or mean  $\pm$  standard deviation (SD). Meanwhile,

the category data were presented as numbers or percentages. *P*-values were listed in tables to determine the homogeneity of a data. The incidence of ALI in COVID patients was calculated using the Fisher and Friedman test. The patient's end point was the condition of the patient who survived when they suffered from COVID and ALI with *p*-value  $<0.05$  considered statistically significant.

## RESULTS

### Patient Characteristics and Operative Data

Patient characteristics are described in Table 1. A total of 13 patients had confirmed COVID-19 and suffered from ALI with Rutherford categories varying from I to III at our center from January 2021 to December 2022. There were 13,095 patients with COVID-19 in our center during January 2021 to December 2022. The incidence of ALI in COVID-19 patients in our center was 0.1%. Most of the COVID-19 patients with ALI were male. All of the patients complained of pain as the chief complaint.

There were 13 patients admitted to the hospital with serum levels: hemoglobin 12.8 (7.2-15.8) g/dl, hematocrit 38.1 (22.1-48.4) %, and platelets 284 (149-611)  $10^3/\mu\text{L}$ . During the treatment of ALI and COVID-19, 12 (92%) patients underwent thromboembolectomy, 6 (46%) patients were amputated with thromboembolectomy, and 6 (46%) other patients underwent only thromboembolectomy. One patient had a patent blood flow, therefore, thromboembolectomy was not performed.

We performed amputation in 7 (53%) patients, involving 6 (46%) patients who were amputated with thromboembolectomy, and 1 (8%) other patient who was amputated without thromboembolectomy. From the 7 patients who underwent amputation, there were 3 amputated below the knee and 4 patients amputated above the knee. The one patient who underwent amputation without thromboembolectomy was amputated below their knee. Mean length of treatment was  $7.5 \pm 8.3$  days without any mortality during the treatments. Other operative data are shown in Table 2.

### Risk Factors of ALI in COVID-19

Risk factors of ALI in COVID-19 are shown in Table 3. Table 4 shows patients with COVID-19 tended to have the factors that

**Table 1:** Patient Characteristics

Characteristic	Value (%)	Median (Range)	P Value
Male	7 (54%)		0.03
Age (Years old)	13 (100%)	59 (35-75)	0.00
ALI Criteria	13 (100%)		0.00
Rutherford I	0 (0%)		0.00
Rutherford IIA	0 (0%)		0.00
Rutherford IIB	9 (69%)		0.00
Rutherford III	4 (30%)		0.04
Affected Extremity	13 (100%)		
Superior Unilateral	0 (0%)		
Superior Bilateral	0 (0%)		
Inferior Unilateral	12 (92%)		0.337
Bilateral	1 (7%)		0.00

ALI: acute limb ischemia.

**Table 2:** Operative Data

Examination	Value (%)	Median (Range)	P-Value
Hemoglobin (g/dl)	13(100%)	12.8 (7.2-15.8)	0.00
Hematocrit (%)	13(100%)	38.1 (22.1-48.4)	0.00
Thrombocyte (K/mm <sup>3</sup> )	13(100%)	284 (149-611)	0.00
APTT (second)	13(100%)	31.5 (22.4-44)	0.34
Amputation	1 (8%)		0.34
TE	6 (46%)		0.08
Amputation + TE	6 (46%)		0.08
Heparin	100 (100%)		
LOS (day/s)	13 (100%)	7.5 ± 8.3	0.07
Mortality	0 (0%)		

TE: Thromboembolotomy, LOS: Length of stay, APTT: Activated Partial Thromboplastin Clotting Time.

**Table 3:** Risk Factors of ALI in COVID-19

Factors	P-Value
Male	0.01
Age	0.00
Rutherford II A	0.00
Rutherford II B	0.05
Rutherford III	0.00
Hemoglobin	0.00
Hematocrit	0.00
Thrombocyte	0.00
Unilateral Inferior	0.32
Bilateral Inferior	0.00
Unilateral Superior	0.00
Bilateral Superior	0.00
COVID-19	1

ALI: acute limb ischemia.

**Table 4:** Friedman Rank Test of COVID-19 patients with ALI

Rutherford Classification	Friedman Rank Test	P-Value
IIB	1.69	0.01
III	1.31	0.01

ALI: Acute Limb Ischemia

increased the risk of ALI, namely Rutherford IIB increased by 1.69, while Rutherford III increased by 1.31.

## DISCUSSION

COVID-19 tends to induce secondary inflammation reactions which lead to a hypercoagulation state. Many patients with COVID-19 infection present with thrombocytopenia injury and dysfunction, elevated levels of von Willebrand factor, and elevated D-dimer levels [6]. One study about histopathology of patients with COVID-19 stated that there were viral elements present within endothelial cells with an accumulation of inflammatory cells followed by endothelial and inflammatory cell death. These phenomena indicate that SARS-CoV-2 infection indirectly induces endotheliitis. Furthermore, apoptosis and pyroptosis have important roles to induce endothelial cell injury in patients with COVID-19. Those phenomena predispose patients to the increasing risk of ALI [7].

The incidence of ALI in COVID-19 patients in our center was less than other studies. They reported 0.54% from November-December 2020 [8]. Meanwhile, we recorded data from January

2021-December 2022 which included the various variants of COVID-19. The differences in data might have occurred because our center is a central referral hospital, and COVID-19 patients with mild symptoms are treated at other health facilities. Subjects with ALI without any operative procedure tend to be treated in primary/secondary health facilities. In addition, the initial treatment of patients with COVID-19 at admission involves heparin according to the therapeutic protocol. This reduces the risk of hypercoagulability, thromboembolic events, and decreases the level of amputation.

There was no significant gender difference in COVID-19 patients with ALI [9]. In our study, most of the patients were male, which matches a review of 20 cases of ALI in COVID-19 patients that occurred mainly in men (90%) [4]. Guan et al., reported that 76% of patients who suffered ALI with COVID-19 were men [6]. On the other hand, another study conducted by Ilonzo et al. showed 57% of patients who suffered ALI with COVID-19 were women [9].

Many studies reported a very wide age range starting from 39 years old. It was reported that thrombotic disorders can also occur at a young age [10]. The median age of patients with COVID-19 in our study had a similar result with other results reported by Etkin et al. [11], and Bellosta et al. [4]. In contrast, patients with comorbid diseases including coronary disease, kidney disease, diabetes, and dyslipidemia showed low rates of ALI. This finding suggests that patients without comorbidities had the same risk of vascular complications [10].

Most studies about Rutherford classification mainly involved patients who presented with IIA or IIB, accompanied by a slight incidence of Rutherford stage III [4,9,12]. Bellosta et al. reported ALI Rutherford stage IIA in 2 patients (10%), stage IIB in 15 patients (75%), and stage III in 3 patients (15%) [4].

The hemoglobin levels in our study were lower compared to the results in the study conducted by Bellosta et al. [4]. The median level of hematocrit was similar with the case report conducted by Sighn et al. that reported hematocrit of the patient was 38.2% followed by hemoglobin of 12.1 g/dl [13]. Thrombocytes reviewed by Bellosta et al. were  $239 \pm 82 \times 10^3/\text{mm}^3$ , which was different from the findings of our study [4]. In a study of consecutive cases with COVID-19, patients with very low platelets only occurred in those with severe COVID-19. Thrombotic complications still persisted in patients with or without low platelet levels. Thus, thrombocytopenia is not an important predictor of the outcome or the progression of the diseases [14].

The most affected limbs were inferior extremities in our center, and another study found similar findings as our study. Bellosta et al. [4], and Etkin et al. [9], reported the most affected limbs were the lower extremities, with 52% and 71%, respectively. In our center, there was no interim mortality. In contrast, Etkin et al., and Bellosta et al., reported the mortality rates were as much as 40-46% [5,11]. We performed embolization to remove the thrombus and treatment included an anticoagulant to reduce the risk of thrombus. The amputations were done to reduce the risk of infection and sepsis when the clinical condition of the patients was not supporting the limb salvage.

## CONCLUSIONS, LIMITATIONS, & RECOMMENDATIONS

Early recognition and management of COVID-19 patients with ALI is important to reduce the patient morbidity and mortality. The advantage of open thromboembolectomy was to remove the thrombus, which was expected to improve the blood flow and reduce the amputation level. By conducting earlier interventions, there were better blood flow, less tissue damage, less necrotic tissue, and reduced risk of mortality.

Our study was conducted using retrospective descriptive review methods. We treated patients according to standard hospital service, so there was no intervention or control patient in our study. This study was limited to only one hospital, while a multi-center study is highly recommended.

Even though the incidence of COVID-19 has already decreased, it is important to raise the awareness of health workers about infectious diseases that could increase the risk of developing ALI. This phenomenon should be considered in other infectious diseases which could also increase the risk of ALI through the mechanism of endothelial dysfunction accompanied by hypercoagulability states.

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