VDM Vascular Disease Management

ORIGINAL RESEARCH

Acute Limb Ischemia as a Complication of COVID-19

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Keywords

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Abstract

Background: COVID-19 is a viral infection caused by a new variant of the coronavirus, SARS- CoV-2. One of the many complications of COVID-19 is blood hypercoagulability, which can result in acute limb ischemia (ALI). ALI is characterized by a sudden perfusion abnormality that requires immediate evaluation and treatment. This study was conducted to present ALI as a complication of hypercoagulability caused by COVID-19 in a hospital in Surabaya, Indonesia. **Case Presentation:** This study presents a series of 4 cases from patients diagnosed with COVID-19 as well as ALI complications who were treated at RSUD Dr. Soetomo hospital in Surabaya. The authors highlight the duration from the onset of COVID-19 symptoms until the onset of complaints that lead to ALI. The result shows equal distribution of gender, with 2 men and 2 women. The age distribution of all cases is over 40 years. The duration of time from being diagnosed with COVID-19 until the occurrence of ALI is similar in all 4 cases. All 4 cases were categorized as having COVID-19 with severe symptoms accompanied by pneumonia, and all cases had comorbidities. One out of 4 patients died (25%). **Conclusions:** ALI results from hypercoagulopathy as a complication of COVID-19 infection. As a result, hypercoagulopathy must be evaluated, and patients with COVID-19 who are self-isolating must be taught to report their concerns during self-isolation so interventions can be done to reduce morbidity and mortality.

Introduction

COVID-19 is a viral infection caused by a new variant of the coronavirus, SARS- CoV-2. It was first discovered at the end of 2019 in Wuhan, China[1], quickly spreading around the world and causing a global pandemic. As of July 2021, COVID-19 has infected more than 182 million people and killed more than 4 million worldwide.[2] The main symptom of COVID-19 is respiratory disorders ranging from mild to severe and life-threatening.[3]

There are reports that 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.[1]

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]

This case series differs from the general etiology of ALI, which is due to hypercoagulopathy as a complication of COVID-19. The authors present a case report of 4 patients diagnosed with COVID-19 and having ALI complications who were treated at RSUD Dr. Soetomo hospital in Surabaya, Indonesia. The authors highlight the duration from the onset of symptoms of COVID-19 until the onset of symptoms that lead to ALI.

Case Presentation

Case 1

A 45-year-old man was admitted to RSUD Dr. Soetomo with a significant complaint of pain in the left leg, which had been present for 3 days before admission. The pain was felt from the groin to the tip of the toe and did not go away with rest. The complaint was accompanied by difficulties moving the left leg, and the leg changing color to purplish hue and feeling cold. Twelve days before the admission to the hospital, the patient was diagnosed as COVID-19-positive. Fever, cough, myalgia, cephalgia, anosmia, and ageusia were among the symptoms with a positive antigen examination. The patient was placed in self-isolation at home while taking symptom-relieving medicine. The patient had uncontrolled diabetes mellitus, no history of hypertension, no history of trauma, and no abnormal heart rhythms.

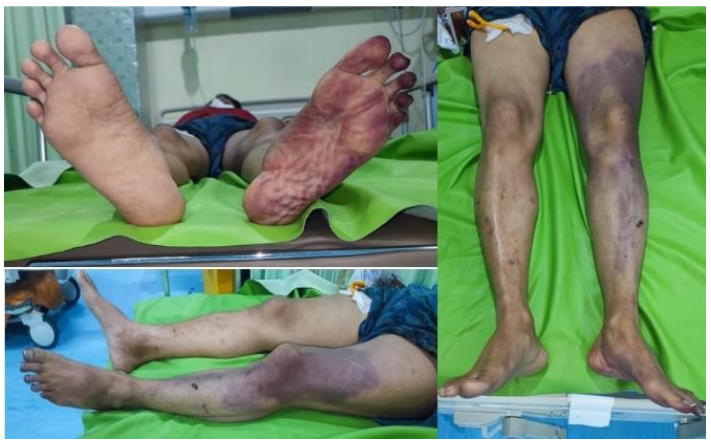

Figure 1. The left lower leg had regional skin darkening at the level of the femoral region, necrotic toes, was cold to the touch, had a motor strength of 3/5, and there was no pulsation on the posterior tibial artery, popliteal artery, and femoral artery.

On physical examination, vital signs and heart and lung exams were within normal ranges. However, the patient's overall health was weak. The left lower leg had regional skin darkening at the level of the femoral region, necrotic toes, was cold to the touch, had a motor strength of 3/5, and there was no pulsation on the posterior tibial artery, popliteal artery, and femoral artery (**Figure 1**). Physical testing and vascular status of the right lower leg yielded normal results. Laboratory test results included: hyperglycemia, 512 mg/dL; HbA1c, 13.7%; leukocytosis, 22,800; D-dimer, 35.050; and fibrinogen, 295.8 mg/dL. Heparin (15,000 U), ceftriaxone (1 g/12 hours IV), insulin for blood sugar management, enoxaparin, and pavipiravir were administered to the patient.

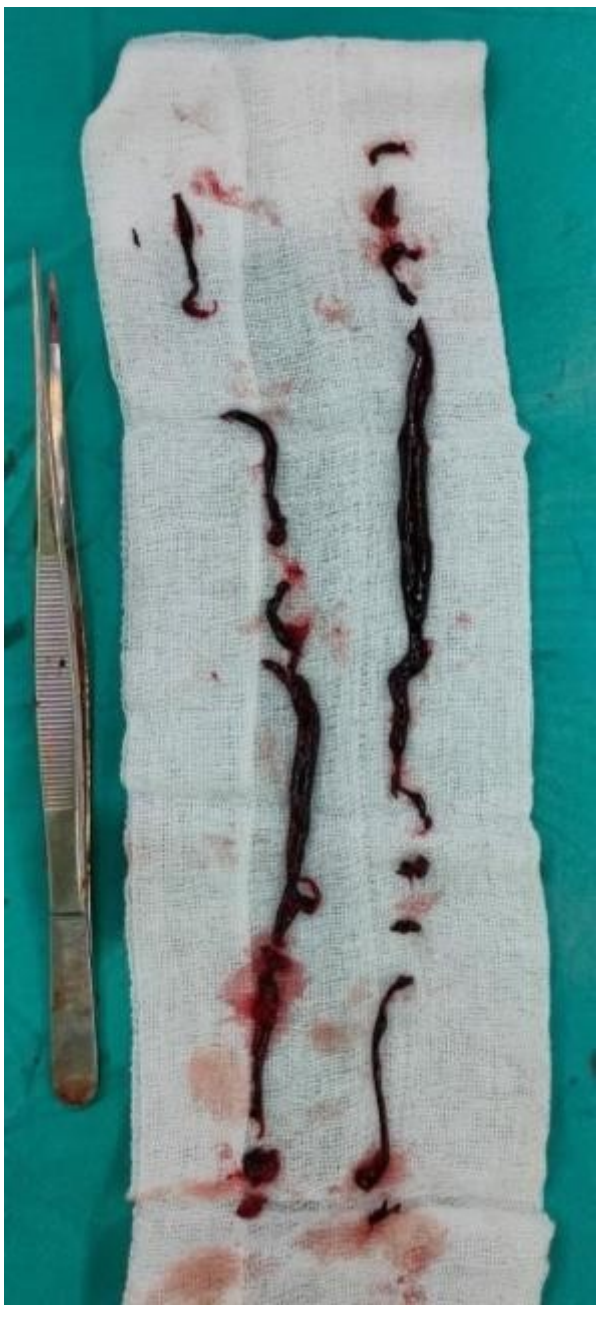

Figure 2. Left femoral artery thrombectomy.

Surgical treatment involved above-the-knee amputation and left femoral artery thrombectomy (**Figure 2**). The patient was discharged after 17 days of hospitalization with no adverse reactions.

Case 2

A 53-year-old male was admitted to the RSUD Dr. Soetomo emergency department (ED) with a fever and shortness of breath that had worsened 2 days before admission. The patient was receiving treatment at home and practicing self-isolation after receiving a COVID-19 diagnosis 2 days before admission. The first signs of complaints, including heartburn, fever, myalgia, and cough, appeared 4 days before admission. Complaints about the tip of the right toe appeared on day 11 after COVID-19 was confirmed, in the form of severe pain described as being stabbed at the tip of the right toe, numbness, and coldness to the touch; the patient had difficulty walking because it became more painful when walking. The patient's medical history included uncontrolled hypertension, smoking cessation for the preceding 10 years, no history of diabetes, no history of trauma, and an abnormal cardiac rhythm. Physical examination revealed that the patient's overall health was fine. Physical examination found hypertension (150/70 mm Hg), tachypnea (24 breaths/min), and oxygen desaturation (SpO_2 93%). Bilateral coarse crackles were mild.

The right toe's tip felt cold, the front third of the foot's sole developed a purplish red rash, and the right toenail appeared slightly bluish but without necrotic tissue (**Figure 3**). The tibialis posterior artery and dorsal pedis artery had no pulsation, while the femoral artery pulse and popliteal artery pulse were normal in the right lower leg's vascular condition. The left lower leg's vascular condition and physical

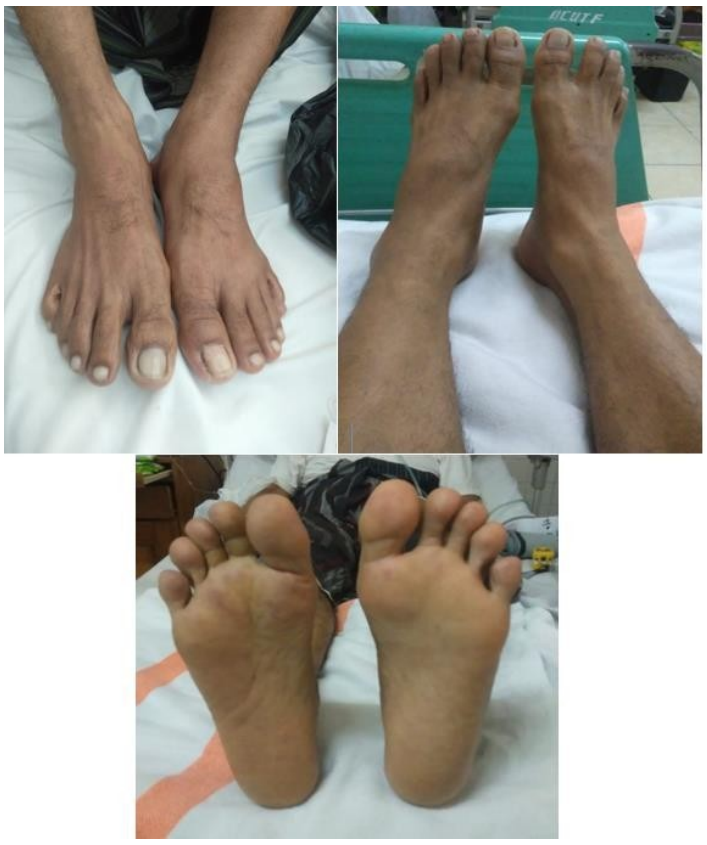

Figure 3. The front third of the foot's sole developed a purplish red rash, and the right toenail appeared slightly bluish but without necrotic tissue.

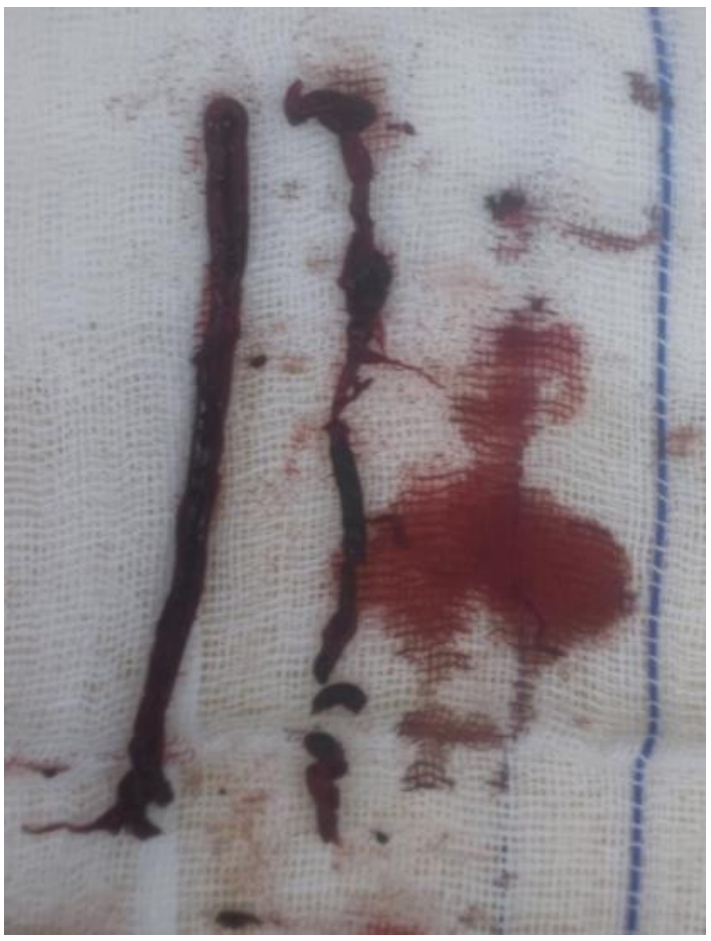

Figure 4. Thrombectomy was performed on the right femoral, tibialis anterior, and tibialis posterior arteries.

Figure 5. The right lower limb was found to be anemic, with a motor status of 0/5; necrotic digits 1 through 5; demarcation

testing were within normal range. Both lower limbs had appropriate levels of motor strength. Dyslipidemia, a rise in D-dimer of 2.910, and an increase in liver function enzymes were discovered during the laboratory examination conducted at the time of the complaint. The patient received antiviral therapy with favipiravir, pentoxifylline, and heparin (15,000 U). Thrombectomy was performed on the right femoral, tibialis anterior, and tibialis posterior arteries (**Figure 4**). On the 21st day of treatment, the patient was discharged with no complaints of pain or discoloration and a slight numbness in the tip of the right toe.

Case 3

A 59-year-old woman was referred to RSUD Dr. Soetomo with a major complaint that her right leg was stiff and changed in color. The patient was on the 21st day following the confirmation of COVID-19. The patient stated that her right leg started to feel weak and was hard to move on the 10th day following the confirmation of COVID-19. Fever and coughing complaints were present at the time of the COVID-19 diagnosis, and the patient was subsequently placed in self-isolation and given symptom-relieving medications. The patient had a history of uncontrolled hypertension, no history of diabetes, no heart issues, and no history of trauma.

The patient's vital signs were within normal range, but her overall health was feeble. No abnormalities were discovered during heart and lung tests. The right lower limb was examined to determine its localized status. It was found to be anemic, with a motor status of 0/5; necrotic digits 1 through 5; demarcation at the level of the femoral region; and cold to the touch (**Figure 5**). No pulsation was found on the anterior tibialis, dorsal pedis, popliteal, and femoral arteries. It was discovered that the contralateral leg's localization status was within normal ranges. The patient's laboratory blood tests included D-dimer, 9.150 and hypoalbuminemia, 3.3 g/dL. Heparin (10 units/kg/day) was administered to the patient as nonoperative care before femoral artery thrombectomy was performed, followed by above-the-knee amputation of the right leg (**Figure 6**). Due to sepsis and multiple organ failure, the patient passed away on the 6th day of intensive care.

Case 4

A 47-year-old woman was admitted to the ED of RSUD Dr. Soetomo with pain in her left hand that had been blue for 1 day before admission. The pain was felt on the tip of the hands and palms. The complaint was accompanied by a change in skin color to dark blue, a numb left hand up to the left elbow, and a chilly sensation in the left hand. The discomfort was unaffected by activity. The patient expressed frustration at how challenging

at the level of the femoral region; and cold to the touch.

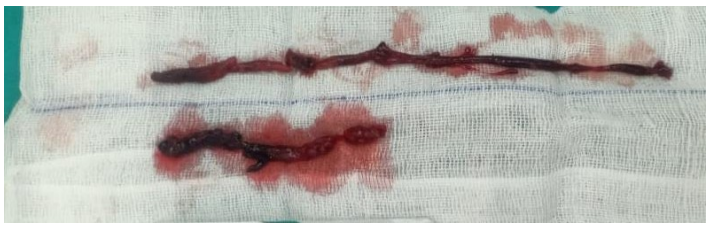

Figure 6. Femoral artery thrombectomy was performed.

and heavy it was to move the fingers on the left hand. She reported having shortness of breath 3 days before admission and cough, weakness, dizziness, and fever for the past 10 days. The patient was confirmed to be COVID-19 positive with a polymerase chain reaction swab at admission. She had a history of uncontrolled diabetes and toxic nodular goiter euthyroid phase; she also had normal blood pressure, did not smoke, and had no history of trauma.

Figure 7. The fingertips of the left hand were bluish and cold to the touch.

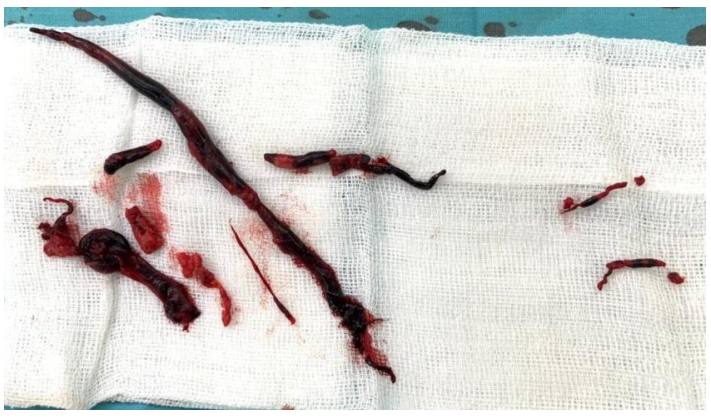

Figure 8. The patient underwent thrombectomy on the radial artery, ulnar artery, and brachialis artery.

On physical examination, the patient's general condition appeared weak. Respiratory rate was 24 times/minute, with oxygen saturation of 89% on free air. The heart and lungs were found to be within normal ranges. Examination of the left upper limb found that the fingertips of the left hand were bluish and cold to the touch (**Figure 7**). The vascular status of the left hand was found to have no palpable pulse on the radial artery, ulnar artery, and brachialis artery. The right hand's local and vascular conditions were both within normal ranges. The patient had an elevated C-reactive protein of 16.3 mg/L; hyperglycemia, 282 mm Hg; hypercoagulability, 6,040; leukocytosis, 13,600; and respiratory failure type 1, P/F ratio 191. The patient was treated with oxygenation, heparinization, an antiviral, an anticoagulant, glucose control medication, and antibiotics. She underwent thrombectomy on the radial artery, ulnar artery, and brachialis artery (**Figure 8**) and was discharged on day 30 of treatment.

Discussion

Since the end of 2019 until present, there has been a global pandemic known as COVID-19, caused by the SARS-CoV-2 virus. The World Health Organization reported that as of July 2021, SARS-CoV-2 had infected 182 million people worldwide.[2] The signs and symptoms of COVID-19 differ from person to person, with the respiratory system being the primary target of the disease. Symptoms range from asymptomatic to severe, life-threatening symptoms. The most common systemic symptoms are arthralgia, myalgia, fever, and malaise.[6] Symptoms of the respiratory system in patients infected with COVID-19 include coughing, rhinorrhea, dyspnea, and respiratory failure. Approximately 15% of patients with COVID-19 will experience severe symptoms, and about 5% will require intensive care due to respiratory failure.[7,8]

COVID-19 has manifestations and complications to other organs or body systems outside the respiratory system, although this is less common. Other systems that can be affected by COVID-19 include the digestive system, nervous system, integumentary system, and other systems that have nonspecific symptoms, such as the vascular system.[6,7,9] There have been numerous cases of patients who were positive for COVID-19 and had hypercoagulopathy, a condition closely related to the incidence of venous and arterial thrombosis. Complications include deep vein thrombosis, stroke, and ALI.[6,8]

The pathophysiology of hypercoagulopathy in patients with COVID-19 is the presence of angiotensin-converting enzyme (ACE)-2 receptors on endothelial cells, which are the entry sites for viruses that lead to endothelial dysfunction.[10] Furthermore, endothelial dysfunction will cause the procoagulant system to become activated, including platelet aggregation, tissue factor activation, an increase in von Willebrand factor, and factor VIII. This series of activations helps in the formation of thrombin and fibrin clots. Thrombin then stimulates inflammation, activates the neutrophil extracellular trap, and stimulates

the endothelium to recruit monocytes via protease-activated receptors. Recruitment of neutrophils and monocytes will increase the expression of tissue factors and the coagulation cascade that causes thrombus formation.[10-13]

The state of hypercoagulopathy in patients with COVID-19 has several terms, such as COVID-19 associated hemostatic abnormalities and COVID-19 associated coagulopathy, which have the same meaning, namely the hypercoagulable state in patients with COVID-19.[12] D-dimer is the most consistent marker of hypercoagulopathy, among other markers such as platelet count, prothrombin time, and fibrinogen. D-dimer is a product of fibrin degradation, and elevation in D-dimer value is associated with thrombus events, although it does not explicitly inform where the thrombus occurred. Research comparing D-dimer values in patients with COVID-19 discovered that high D-dimer values are linked to higher death and morbidity rates.[12]

ALI is a condition where there is a sudden decrease in arterial blood flow to the limbs with a duration of symptoms less than or equal to 2 weeks from the onset of symptoms. The main etiologies of ALI are embolism, arterial thrombosis, aneurysm, arterial dissection, and artery trauma.[15] Atrial fibrillation is the most frequent heart condition to induce emboli, accounting for more than 90% of cases.[4]

A study by Bellosta et al[14] in Italy reported a significant increase in the incidence of ALI as a secondary complication of hypercoagulopathy of COVID-19 compared to 1 year earlier when the COVID-19 pandemic had not yet spread.[7] Until now, Indonesia did not have data on the prevalence of ALI as a complication of COVID-19. Based on the data at our hospital, when the presentation of this serial case took place in August 2021, we treated 4 cases of ALI as a complication of COVID-19 from a total of 10,645 patients with COVID-19 who were treated during the pandemic.

The main symptoms of ALI are known as the 6 Ps: pain, pallor, paralysis, pulse deficit, paresthesia, and poikilothermia. Not every symptom is present when the patient first arrives. The sign distinguishing ALI from acute or chronic limb ischemia is that the patient has a history of intermittent claudication and risk factors for peripheral arterial disease such as smoking, hypertension, obesity, diabetes mellitus, and kidney failure.[4] Clinical manifestations in ALI patients are influenced by the location, degree, and duration of the occlusion; collateral circulation; and metabolic changes due to tissue ischemia.

Typical clinical signs are ischemia located distal to the occlusion site.[15] In this case series, 3 out of 4 patients came late to the hospital. In Case 2, the patient's complaints occurred when the patient was treated for COVID-19 isolation at the hospital. The 3 other cases came to the hospital when there was a change in the limbs in the form of a bluish color and neurological disorders such as paralysis. Based on history, 3 of the 4 patients at that time were undergoing self-isolation at home and were afraid to come to the hospital; in Case 1 and Case 3, the delay was accompanied by the full capacity of the referral hospital so that 2 out of 4 cases had tissue necrosis and underwent amputation.

Table. Characteristics of COVID-19 Patients With Acute Limb Ischemia

	Case 1	**Case 2**	**Case 3**	**Case 4**
Age (years)	45	53	59	47
Gender	Male	Male	Female	Female
Comorbidity	Diabetes type II	Hypertension	Hypertension	Diabetes type II
Smoking history	Yes	Yes	No	No
COVID-19 symptoms	Fever, cough, headache, myalgia, ansomia	Fever, cough, myalgia, epigastric pain	Fever, cough, difficulty breathing	Fever, difficulty breathing, cough, malaise, headache

ALI symptoms	Limb pain, cold feet, difficulty moving, numb, change in skin color	Limb pain, pale, cold feet, numb	Limb pain, cold feed, numb, difficulty moving, color change to bluish skin	Limb pain, cold fingertips, color change to bluish skin, difficulty moving, numb
ALI onset	Day 12	Day 11	Day 10	Day 10
Pneumonia	Yes	Yes	Yes	Yes
D-dimer	35.090	2.910	9.150	6.040
Fibrinogen	295.8	348.2	556	566.1
PT	14.4	9.8	14.6	10.8
aPTT	21.5	22.8	27.9	20.3
Rutherford classification	III	IIA	III	IIA
Operation	Amputation + thrombectomy	Thrombectomy	Amputation + thrombectomy	Thrombectomy
Outcome	Outpatient	Outpatient	Deceased	Outpatient

ALI = acute limb ischemia; PT = prothrombin time; aPTT = activated partial thromboplastin time.

Based on the patient characteristics in the **Table**, the authors obtained data from the 4 cases on the length of time since the first COVID-19 symptoms until the ALI complaint appeared; the time difference was similar. The first case was on the 12th day, the second on the 11th day, the third on the 10th day, and the fourth on the 10th day. These results are similar to clinical observations conducted by Li Taisheng et al in China.[16] According to the study, the second episode happened 7 to 14 days after the onset of the first symptoms. This results from the presence of viremia in the target organs of the digestive system, lungs, and tissues that carry ACE-2 receptors, such as vascular endothelial cells.[16] Several study reports said the incidence of hypercoagulopathy was more common in COVID-19 infections with severe symptoms.[17,18] Patients with COVID-19 and comorbid disorders such as diabetes mellitus, hypertension, cardiovascular disease, kidney disease, and obesity are more likely to experience ALI complications than those without such conditions.[19] All 4 patients in this report had concomitant conditions and were classified as having severe symptoms and pneumonia.

Conclusions

ALI results from hypercoagulopathy as a complication of COVID-19 infection. Patients typically come late to the hospital due to a combination of factors, including the patient's self-isolation during the attack, anxiety about seeking medical attention at the hospital during the pandemic, and the referral hospital's capacity due to the second wave of COVID-19. Therefore, it is necessary to evaluate hypercoagulopathy and educate patients who undergo self-isolation to report their complaints during self-isolation so actions can be taken to prevent morbidity and mortality. ■

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no financial relationships or conflicts of interest regarding the content herein.

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REFERENCES

1. Shao T, In-Bok Lee C, Jabori S, Rey J, Duran ER, Kang N. Acute upper limb ischemia as the first manifestation in a patient with COVID-19. *J Vasc Surg Cases Innov Tech.* 2020;6(4):674-677. doi:10.1016/j.jvscit.2020.08.003

2. World Health Organization. Therapeutics and COVID-19: living guideline. 2023. https://app.magicapp.org/#/guideline/nBkO1E

3. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *J Adv Res.* 2020;24:91-98. doi:10.1016/j.jare.2020.03.0054. Sidawy A, Perler B. *Rutherford's Vascular Surgery and Endovascular Therapy.* 9th ed. Elsevier; 2019.

5. Brunicardi F. *Schwartz's Principles of Surgery.* 11th ed. McGraw Hill Education; 2019.

6. Grant MC, Geoghegan L, Arbyn M, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): a systematic review and meta analysis of 148 studies from 9 countries. *PLoS One.* 2020;15(6):e0234765. doi:10.1371/journal.pone.0234765

7. Singhania N, Bansal S, Nimmatoori DP, Ejaz AA, McCullough PA, Singhania G. Current overview on hypercoagulability in COVID-19. *Am J Cardiovasc Drugs.* 2020;20(5):393-403. doi:10.1007/s40256-020-00431-z

8. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA.* 2020;323(13):1239-1242. doi:10.1001/jama.2020.2648

9. Topcu AC, Ariturk C, Yilmaz E. Acute limb ischemia in a COVID-19 patient. *Thrombosis Update.* 2021;2:100031. doi:10.1016/j.tru.2020.100031

10. Kichloo A, Dettloff K, Aljadah M, et al. COVID-19 and hypercoagulability: a review. *Clin Appl Thromb Hemost.* 2020;26:107602962096285. doi:10.1177/1076029620962853

11. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thromb Res.* 2020;194:101-115. doi:10.1016/j.thromres.2020.06.029

12. Ortega-Paz L, Capodanno D, Montalescot G, Angiolillo DJ. Coronavirus disease 2019–associated thrombosis and coagulopathy: review of the pathophysiological characteristics and implications for antithrombotic management. *J Am Heart Assoc.* 2021;10(3):e019650. doi:10.1161/JAHA.120.019650

13. Kohansal Vajari M, Shirin M, Pourbagheri-Sigaroodi A, Akbari ME, Abolghasemi H, Bashash D. COVID-19-related coagulopathy: a review of pathophysiology and pharmaceutical management. *Cell Biol Int.* 2021;45(9):1832-1850. doi:10.1002/cbin.11623

14. Bellosta R, Luzzani L, Natalini G, et al. Acute limb ischemia in patients with COVID-19 pneumonia. *J Vasc Surg.* 2020;72(6):1864-1872. doi:10.1016/j.jvs.2020.04.483

15. Björck M, Earnshaw JJ, Acosta S, et al. Editor's Choice – European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Acute Limb Ischaemia. *Eur J Vasc Endovasc Surg.* 2020;59(2):173-218. doi:10.1016/j.ejvs.2019.09.006

16. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. *Emerg Microbes Infect.* 2020;9(1):687-690. doi:10.1080/22221751.2020.1741327

17. Mestres G, Puigmacià R, Blanco C, Yugueros X, Esturrica M, Riambau V. Risk of peripheral arterial thrombosis in COVID-19. *J Vasc Surg*. 2020;72(2):756-757. doi:10.1016/j.jvs.2020.04.477

18. Mietto C, Salice V, Ferraris M, et al. Acute lower limb ischemia as clinical presentation of COVID-19 infection. *Ann Vasc Surg.* 2020;69:80-84. doi:10.1016/j.avsg.2020.08.004

19. Veerasuri S, Kulkarni SR, Wilson WR, Paravastu SCV. Bilateral acute lower limb ischemia secondary to COVID-19. *Vasc Endovascular Surg*. 2021;55(2):196-199. doi:10.1177/1538574420954301