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Acute Limb Ischemia among COVID-19 Patients in Hospital Kuala Lumpur

Karthigesu Aimanan[1], Nurul Nadiah Nazurah Mohd Ali[1], Mohd Nurhisham Azmi Abdul Rahman[2], Putra Mas Pian[1], Kumaraguru V. K. Pillay[1], Firdaus Hayati[3,4]*, Hanif Hussein[1]

[1]Department of Surgery, Kuala Lumpur Hospital, Ministry of Health Malaysia, Kuala Lumpur, Malaysia; [2]Department of Surgery, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia; [3]Department of Surgery, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia; [4]Department of General Surgery, Hospital Universiti Malaysia Sabah, Universiti Malaysia Sabah, Kota Kianbalu, Sabah, Malaysia

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***Correspondence:** Firdaus Hayati, Department of Surgery, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia. E-mail: m_firdaus@ums.edu.my
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Abstract

BACKGROUND: Acute arterial thromboembolism among the novel coronavirus 2019 (COVID-19) patients is worrying as it can result in significant thrombotic events.

AIM: The research aimed to determine the clinical results of COVID-19-infected patients who had acute limb ischemia (ALI) during the COVID-19 epidemic.

METHODS: ALI patients who had a positive COVID-19 were included in the observational cohort study, which was conducted at a single center. The primary outcomes were 30 days mortality, limb salvage, and successful revascularization.

RESULTS: From May to October 2021, data from 21 ALI subjects who had positive COVID-19 were analyzed. Of the 21 included subjects, 10 were male (48%). Their mean age was 65 ± 5 years. In 9 subjects (42%), revascularization was done. Four (19%) of the 21 persons died while they were hospitalized. Twelve patients underwent major amputation, and among them, one patient died after a month of hospitalization for COVID-19-related pneumonia. Among the 12 patients that underwent amputation, 10 of them presented with ALI during the 1st week of COVID-19 illness. Only one patient developed acute limb ischemia despite being on heparin thromboprophylaxis.

CONCLUSION: Despite attempts at revascularization, ALI associated with COVID-19 has high mortality and high rates of limb loss. In our experience, major amputation is required in up to a third of patients. This poor result appears to confirm that these infected individuals have a marked hypercoagulable condition. However, adhering to the treatment protocol of heparin thromboprophylaxis confers a benefit in this patient group.

Introduction

There are several known symptoms of the novel coronavirus 2019 (COVID-19), ranging from asymptomatic carriers to those has upper respiratory signs. In extreme cases, the virus may cause sepsis, acute respiratory distress syndrome, and even death. There is growing evidence that virus-infected individuals seem to have virus-induced hypercoagulability that leads to serious thrombotic occurrences. Historically arterial thromboembolism has been described with respiratory viruses such as Middle-East respiratory syndrome coronavirus, “severe acute respiratory syndrome:” SARS-CoV-1 and SARS-CoV-2 [1], [2], [3]. However, thrombotic problems are being observed more often in COVID-19 patients than in those who had the prior pandemics. Thought to involve endothelial dysfunction, endotheliitis, and deregulation of the clotting cascade, the mechanism of thrombosis is still not fully understood [2].

Patients with COVID-19 may develop thromboembolism in several ways, most commonly with venous thromboembolism, but also with ischemic complications related to arterial thrombosis of extremity, cerebral, coronary, and visceral arteries. The occurrence of ALI among COVID-19 patients who need hospitalization varies from 3 to 15%. When compared to the rate of ALI in the general people, this number is 3 times higher. The severity of infection was found to have a negative impact on the reported result. Evidence from published case series shows that limb salvage efforts were made in less than half of individuals with COVID-19 with ALI; up to 15% required primary amputation [4], [5], [6], [7]. Multiple factors might contribute to this incidence likely due to the disease severity, higher prevalent use of steroids, type of vaccination, and the usage of other medications. The aim of this study is to review the prevalence, clinical manifestation, treatment, and prognosis of acute arterial thrombosis in patients with COVID-19 at a tertiary center.

Methods

The Department of Vascular Surgery and the Department of Medicine at "Hospital Kuala Lumpur in Kuala Lumpur, Malaysia," conducted this prospective cohort study. From May to October 2021, a total of 21 COVID-19 and acute arterial thromboembolism patients were admitted to the hospital. They were assessed for 30-day mortality of ALI including the overall amputation-free survival of ALI, risk of developing acute limb ischemia among patients on steroid treatment for COVID-19, and identification of laboratory markers as an early predictor of ALI among hospitalized persons for COVID-19.

Patients undergoing PCR (polymerase chain reaction) testing within 30 days of diagnosis for COVID-19 infections that have been verified in the laboratory and those with signs and symptoms of ALI <2 weeks, and confirmed by the vascular team were recruited. Patients with chronic respiratory symptoms without an acute component occurring within 2 weeks, patients with COVID-19 testing negative while having respiratory symptoms, and patients with these conditions and those with dermatologic conditions mimicking ALI were excluded from the study. We gathered information on the patient's comorbidities, demographics, laboratory indicators, medicines, anatomical sites, and clinical manifestations of thromboembolism. Interventions such as the specific treatment and clinical outcomes also were gathered. These patients were followed up at the surgical clinic on discharge.

Results

From May to October of 2021, a total of 21 individuals were brought to the hospital with acute arterial thromboembolism and COVID-19 (Table 1). The patients' mean age was 65, and 48% of them were male. Among them, 11 (52%) were Malays, 7 (34%) were Indians, and the rest were Chinese. Six patients were referred from the emergency department and the remaining 15 patients were referred from other nearby hospitals. Only one patient out of 21 patients was free from any medical conditions. Diabetes and hypertension were the highest comorbidities with 62% and 66% each. Seven (31.8%) patients were on antiplatelet and 6 (27.2%) patients were on warfarin even before the onset of acute limb ischemia. None of them was on steroids before the COVID-19 infection.

Table 1: Demographics and comorbidities

Characteristics	n = 21, n (%)
Median age	65 ± 5 (36–81)
Gender (% male)	10 (48)
Race	
Malay	11 (52)
Chinese	3 (14)
Indian	7 (34)
Median BMI	-
Comorbidities	
Hypertension	15 (71)
Diabetes	16 (76)
Atrial fibrillation	2 (10)
Ischemic heart disease	6 (29)
History of stroke	4 (19)
Chronic kidney disease	3 (14)
Peripheral vascular disease	5 (24)
Smokers	3 (14)
Malignancy	-
Home medications	
Antiplatelet	7 (33)
Warfarin	6 (29)

BMI: Body mass index.

PCR was used as the confirmatory test in all patients and CT value was used to determine the infectivity of COVID-19. All of them had CT values below 40. Three (16%) of them had CT values below 30 and the remaining showed CT values above 30. A total of 13 (62%) subjects developed ALI within the first 7 days of illness. Meanwhile, 11 (52%) of the patients had symptoms of acute arterial ischemia and were later identified as having COVID-19 while 10 (48%) developed acute limb ischemia during admission for COVID- 19. Six (28%) patients developed acute limb ischemia after a week to 1 month of COVID infection. Only two patients presented with acute limb ischemia after more than a month of COVID infection. CAT score was used to classify the disease severity of patients throughout their stay in the ward. Eight patients were in CAT score 1; three patients in CAT score 2; three patients in CAT score 3; four patients in CAT score 4; and three patients were in CAT score 5.

A total of 11 (52%) patients were not on any steroid throughout the treatment for COVID-19. Dexamethasone, prednisolone, and methylprednisolone were the steroids used in our hospital. Only one patient was on the steroid for more than 2 weeks due to the severity of COVID-19. Three (14%) patients had completed COVID-19 vaccination. The D-dimer result was only available for 11 (52%) patients. Elevated D-dimer was noted only in 1 (9%) patient in CAT 1 category whereas 5 (45%) in CAT 3 and above category. Five out of six of these patients presented with Rutherford 3 of acute limb ischemia and underwent amputation.

Rutherford's Stages IIa, IIb, and Stage III were the ALI stages at admission for 4 (19%), 8 (38%), and 9 (43%) of the patients, respectively (Table 2). Twelve (57%) patients did not undergo revascularization. Due to acute pneumonia caused by COVID-19, 3 (or 25%) of them were in a moribund condition. The remaining 9 (75%)

Table 2: Outcome of acute limb ischemia

Outcome/intervention	n (%)
Level of ischemia on referral	
Rutherford 2a	4 (19)
Rutherford 2b	8 (38)
Rutherford 3	9 (43)
Revascularization	
Thrombectomy	2 (22)
Thrombectomy+Endovascular revascularization	3 (33)
Endovascular revascularization	4 (45)
Amputation	12 (57)
Imaging for diagnosis	
CT angiogram	8 (38)
US duplex	6 (28)

CT: Computed tomography, US: Ultrasonography.

subjects were presented with a Rutherford 3 state of ischemia. Twelve patients underwent major amputation and among them, one patient died after a month of hospitalization for COVID-19-related pneumonia. Among the 12 patients that underwent amputation, 10 of them presented with ALI during the 1st week of infection. Only one patient developed acute limb ischemia despite being on heparin thromboprophylaxis. All together four patients died throughout their stay in the hospital (Table 3). None of them underwent imaging to confirm diagnosis and revascularization.

The distribution of ischemia included aortoiliac (28%), femoral above knee (43%), and popliteal below-knee arteries (29%). None of them exhibited concurrent arterial thrombus in other anatomical sites. Four individuals (19%) also had deep vein thrombosis concurrently. Eight patients (38%) had a CT angiogram as a diagnostic test and six had a duplex ultrasound (28%). The other seven patients' diagnosis of acute ischemia was made based on their outward clinical manifestations since they were too unstable to be transported for imaging.

Discussion

Although the prevalence of ALI has reduced overall and the hypercoagulable condition continues to be a rare cause of limb ischemia, COVID-19 patients have a higher than average risk of thromboembolic consequences, ranging from 35 to 45% [8]. There is an even greater risk of arterial and venous thromboembolism in critically sick patients, which is linked to a high death rate. Although the estimated mortality in non-infected groups with ALI ranged from 5% to 9% in the literature, our research indicated that ALI was related to a death rate of 19% [9], [10]. This relative rise in arterial thrombotic occurrences during the pandemic may be due to various factors, including lockdown-related delays in emergency department presentation, older people, or fear of visiting hospitals due to a high risk of contamination [11]. Many findings also suggest that these thrombotic episodes take place later on in the illness. However, in our review, thrombotic events mostly happen during the 1st week of infection. A COVID-19 diagnosis was made in 52% of patients who first had symptoms of ALI.

Case series and individual case reports were used to gather information on the prevalence and features of arterial thromboembolic consequences in COVID-19 patients. Based on this, the distribution of thromboembolic events comprised brain ischemia at 10%, upper 14% and lower 71% extremities ischemia, and 4% bowel ischemia [12]. Twelve percent of patients had thrombus in multiple locations. However, in this review, there was no incidence of thromboembolic in other anatomic locations than lower limbs. Imaging of the patients presented with acute limb ischemia in this review showed only mild atherosclerotic disease. This is consistent with the literature study, which implies that a significant number of arterial thromboses in viral infected individuals may occur across healthy or mildly infected arteries.

The steroid is a potent anti-inflammatory drug widely being used in hospitalized COVID-19-infected persons. In a comprehensive study, Judith *et al*. found that corticosteroids had a positive impact on short-term mortality and minimized the requirement for mechanical breathing [13]. Despite the beneficial effects of steroids, historically, there were many reports on the risk of hypercoagulability with steroid usage [14], [15], [16]. The hypercoagulability effect is highest during the initiation and weans off on discontinuation. Steroid-induced effect during this period was achieved by increasing levels of clotting factors and fibrinogen [17]. However, in this review, we do not find any significant association between the type of steroid and the severity of thromboembolic problems in COVID-19.

Multiple laboratory abnormalities, such as higher D-dimer levels, reduced antithrombin levels, elevated fibrin-degradation products, increased fibrinogen, and decreased partial thromboplastin time, have been noticed in COVID-19 patients. These laboratory indicators should also be taken into account when estimating the patients' thrombotic risk. Elevated D-dimer and fibrinogen levels were noticed by Nicole *et al*. in a case series as a predictor of a high risk of thrombotic effects from COVID-19 [18]. All of the patients in our evaluation experienced a thrombotic problem, which pointed to a group with greater mortality risk. This might explain why we were unable to determine a limit for D-dimer. A high NLR has been linked in past research to an increased risk of infection progression [19]. It has been proposed that the virus affects T cells and that subsequent sequelae may have a vital role in the formation and spread of clots. Procalcitonin and the severity of COVID-19 illness have also been linked in studies, however, the underlying mechanism is yet unknown [20].

In our center, we adhered to the local guideline on thromboprophylaxis for COVID-19 patients with CAT

Table 3: Risk factors for mortality of patients with acute limb ischemia in COVID-19 infection

Age	Gender	Medical conditions	Previous medications	Day of illness on referral	COVID-19 vaccination	Lower extremity, thrombosis/embolism	Rutherford classification of ALI	Amputation	Cause of death
58	Female	DM, HPT, IHD, CKD, PVD	Cardiprin, Warfarin	8	No	Popliteal below knee	3	No	MOF
72	Male	None	None	12	No	Popliteal below knee	3	No	ARDS
63	Female	DM, HPT, PVD	None	3	No	Popliteal below knee	2A	Yes	MOF
67	Male	DM, HPT, CVA, IHD	Cardiprin	26	Yes	Popliteal below knee	3	No	ARDS

CKD: Chronic kidney disease, DM: Diabetes mellitus, HPT: Hypertension, IHD: Ischemic heart disease, PVD: Peripheral vascular disease, ALI: Acute limb ischemia, ARDS: Acute respiratory distress syndrome.

3 and above. In addition, the WHO guidelines suggest preventive doses of subcutaneous unfractionated heparin twice a day or daily low-molecular-weight heparin to prevent venous thromboembolism in severely infected persons. In this review, most of the patients presented within the 1st week of illness and showed that thromboprophylaxis has not been associated with the prevention of acute limb ischemia. According to the literature, ALI may also develop in individuals who are already taking thromboprophylaxis, and this result has often been seen.

When an acute thrombotic episode and a virus infected patient, the choice to act must be carefully considered. The threshold for intervention will be determined by the person's respiratory condition, the level of ischemia, and the prognosis overall. The probability of death after the COVID-19 virus has been recorded at varying rates, although it has consistently been 3.7% [12]. However, several earlier reports indicate that individuals with ALI in the context of COVID-19 are at significant mortality risk. Despite just a few subjects having extreme COVID-19 contamination at diagnosis, the death rate for arterial thrombosis in our group was significant at 19%. Here, we have shown that patients who come with acute limb ischemia symptoms early on in the course of COVID-19 pneumonia have a better prognosis than individuals who present later. However, this benefit does not confer to limb salvage in this group of patients.

Anticoagulation and palliative treatment were provided to persons who were terminally sick, and amputation was done in cases of non-salvageable limb ischemia, depending on the signs and overall seriousness of the condition [12]. Less often did Rutherford 2b patients get thrombolytic treatment, and surgical thrombectomy was the primary surgical procedure used in these patients. There is currently no information available on COVID-19 individuals who present with ALI, and surgical treatment results have not been documented either. Thus, there is no existing therapy procedure. The outcome of successful revascularization in the available literature is also not great ranging from 10 to 40%. Interestingly, Bellosta *et al*. have reported the highest rate of successful revascularization in their review which is 76% [7]. Furthermore, there were a high number of patients for revascularization in this report which was 17 out of 20 patients. However, there were no details on COVID-19 duration of illness in this review. In our review, patients presenting during the 1st week of COVID-19 illness have a higher chance of surgical intervention. However, this does not confer to an increase in limb salvage outcomes.

Conclusion

Despite attempts at revascularization ALI associated with COVID-19 have high mortality and high rates of limb loss. Major amputation is required in up to a third of patients. This poor result appears to confirm that these infected individuals have a marked hypercoagulable condition. However, adhering to the treatment protocol of heparin thromboprophylaxis confers a benefit in this patient group.

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