



# The Impact of COVID-19 on Prognosis of Acute Limb Ischemia

## Akut Ekstremitte İskemisi Prognozunda COVID-19 Etkisi

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### ABSTRACT

**Objective:** To validate the hypercoagulability state of coronavirus disease-2019 (COVID-19) disease on the prognosis of patients with acute peripheral arterial thrombosis.

**Methods:** Patients presenting to emergency services with symptoms of acute limb ischemia were divided into two groups. COVID-19 positive patients were named group 1. All patients were treated according to the indications of the acute limb ischemia classification. COVID-19 positive patients were also treated with the pandemic protocols. The study was designed retrospectively, and data were collected from patient records.

**Results:** One hundred twenty-four patients were evaluated. D-dimer levels were higher in group 1. Fifty-eight of group 1 and 39 of group 2 patients underwent emergent surgery for thrombectomy. Three patients from group 2 needed intensive care, but only one was intubated. Eighteen of group 1 and seven of group 2 patients needed fasciotomies. After revascularization surgery, seven patients from group 1 and two patients from group 2 had ongoing ischemic symptoms (p-value <0.05). Amputation was inevitable for them. Six patients from group 1 had acute myocardial infarction. Twelve patients from group 1 and three patients from group 2 needed haemodialysis for acute renal failure. Eleven patients died in the intensive care unit from group 1, with no deaths in group 2.

**Conclusion:** Severe COVID-19 infection induces a highly prothrombotic state. The prevalence of acute limb ischemia is high and is associated with adverse clinical outcomes.

**Keywords:** COVID-19, hypercoagulability, acute arterial thrombosis, prognosis

### ÖZ

**Amaç:** Koronavirüs hastalığı-2019 (COVID-19) hastalığının hiperkoagülabilité durumunun, akut periferik arter trombozu olan hastaların prognozu üzerindeki etkisini doğrulamaktır.

**Yöntemler:** Acil servise akut ekstremitte iskemisi semptomlarıyla başvuran hastalar iki gruba ayrıldı. COVID-19 pozitif hastalar grup 1 olarak adlandırıldı. Tüm hastalar, akut ekstremitte iskemisi sınıflandırmasına göre tedavi edildi. COVID-19 pozitif hastalar ayrıca pandemi protokollerine göre tedavi edildi. Çalışma geriye dönük olarak tasarlanmış olup, veriler hasta kayıtlarından toplanmıştır.

**Bulgular:** Yüz yirmi dört hasta değerlendirildi. Grup 1'de D-dimer seviyeleri daha yüksekti. Grup 1'de 58, grup 2'de ise 39 hasta acil olarak trombektomi için cerrahi müdahale gördü. Grup 2'den üç hasta yoğun bakım ünitesine alındı, ancak sadece birisi entübe edildi. Grup 1'de 18, grup 2'de ise 7 hasta fasiotomiye ihtiyaç duydu. Revaskülarizasyon cerrahisinden sonra, grup 1'den 7 hasta ve grup 2'den 2 hasta devam eden iskemisi semptomları gösterdi (p-değeri <0,05). Bu hastalar için amputasyon kaçınılmaz oldu. Grup 1'de 6 hasta akut miyokard infarktüsü geçirdi. Grup 1'de 12 hasta ve grup 2'de 3 hasta akut böbrek yetmezliği nedeniyle hemodiyaliz aldı. Grup 1'de yoğun bakım ünitesinde 11 hasta hayatını kaybetti, grup 2'de ise ölüm olmadı.

**Sonuç:** Şiddetli COVID-19 enfeksiyonu, yüksek derecede prokoagülan bir durumu tetikler. Akut ekstremitte iskemisi prevalansı yüksektir ve kötü klinik sonuçlarla ilişkilidir.

**Anahtar kelimeler:** COVID-19, hiperkoagülabilité, akut arteriyel tromboz, prognoz

### INTRODUCTION

Since March 2020, the global coronavirus disease-2019 (COVID-19) pandemic has brought increased attention to thrombosis in affected patients. Hypercoagulability is a crucial

aspect of the disease, with numerous studies establishing a strong link between COVID-19 and coagulopathy (1-3). Notable alterations have been observed in fibrinolysis markers, including D-dimer, fibrinogen, and fibrin degradation

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products (FDP), as well as coagulation parameters such as prothrombin time (PT) and antiphospholipid antibodies (APLAs, anticardiolipin IgA, anti- $\beta$ 2-glycoprotein I IgA, and IgG) (1-3). Dysregulated coagulation and fibrinolysis play a significant role in COVID-19 severity and mortality. Elevated levels of D-dimer, PT, and FDP are associated with more severe disease progression (1,2). Although respiratory complications remain the hallmark of COVID-19, studies indicate that elevated D-dimer levels, accompanied by acute limb ischemia, correlate with higher mortality (1,2). These findings suggest that COVID-19 induces a distinct coagulation disorder. Autopsies of COVID-19 patients reveal the presence of fibrin thrombi within small vessels and capillaries, along with extensive extracellular fibrin deposits (3,4). Patients suffering from acute peripheral arterial occlusion face greater complications due to the pandemic, with hypercoagulability being a key contributor to poor prognosis. Symptoms such as pallor, numbness, and paresthesia become more pronounced, followed by pain and a reduced quality of life. This study aims to elucidate the thrombophilic impact of COVID-19 on the prognosis of patients with acute peripheral arterial occlusion.

## MATERIALS AND METHODS

### Study Design and Patient Selection

This retrospective case-control study was conducted to identify potential risk factors for acute limb ischemia in COVID-19 patients. Data were extracted from electronic hospital records, including demographic characteristics such as age, body mass index, sex, medical history, and treatment regimens (Table 1).

A total of 144 patients over 18 years old, admitted to our hospital between March 1, 2020, and December 31, 2020, with acute limb ischemia symptoms, were assessed. Peripheral vascular Doppler ultrasound was used for arterial evaluation, with intravenous contrast-enhanced computed tomography (CT) employed when further diagnostics were required. After excluding 20 patients without acute limb ischemia, 124 cases met the study criteria. Patients were classified into two groups based on COVID-19 status. COVID-19 was diagnosed using polymerase chain reaction (PCR) testing on nasopharyngeal swabs. Patients with negative PCR results but positive CT findings indicative of COVID-19 were also classified as COVID-19 positive. Additional clinical data, including laboratory findings (hemoglobin, blood cell counts, coagulation parameters, cardiac biomarkers, and creatinine levels) and radiologic assessments, were collected. Eighty patients tested positive for COVID-19 (Group 1), while forty-four tested negative (Group 2). Patients were further categorized according to the Rutherford classification for acute limb ischemia (5).

### Treatment Approach

All patients received anticoagulant and antiaggregant therapy, with surgery performed when indicated. Patients classified as Rutherford Class 2b underwent urgent thrombectomy. Group 1 patients received COVID-19 treatment as per the Turkish Ministry of Health guidelines, along with medications for peripheral vascular disease. Therapeutic interventions included iloprost, cilostazol, low molecular weight heparins (LMWH) at therapeutic doses, and acetylsalicylates, while comorbid conditions were managed accordingly. COVID-19 severity was categorized per the Chinese Management Guidelines for COVID-19 into general, severe, and critical illness based on clinical and radiological findings.

### Data Collection

This study adhered to the ethical principles of the Helsinki Declaration and was approved by the Ethics Committee of Sakarya University Medical Faculty (approval no: E-71522473-050.01.04-645, date: 03.13.2020).

### Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 26 and Microsoft Excel version 16.0. Demographic

**Table 1. Patient characteristics**

	Group 1 n/percent	Group 2 n/percent	p-value
Age, year (mean)	63.4	57.2	>0.05
Male sex	51 (63%)	26 (26%)	>0.05
BMI	29	28	>0.05
Hypertension	62 (77%)	33 (73%)	>0.05
DM	51 (63%)	17 (38%)	>0.05
Hyperlipidemia	43 (54%)	16 (35%)	>0.05
Smoking	50 (62%)	33 (73%)	>0.05
CAD	47 (58%)	22 (50%)	>0.05
COPD	37 (46%)	22 (50%)	>0.05
AF	14 (17%)	5 (11%)	>0.05
Concomitant DVT	9 (11%)	2 (3%)	<0.05
Malignancy	4 (3.2%)	0 (0%)	None
Complaints			
Extremity pain	80 (100%)	44 (100%)	>0.05
Numbness	48 (61%)	19 (47%)	>0.05
Pallor	47 (60%)	24 (58%)	>0.05
Paralysis	17 (24%)	2 (5%)	<0.05
Exposure COVID-19	44 (52%)	12 (26%)	<0.05

BMI: Body mass index, DM: Diabetes mellitus, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, AF: Atrial fibrillation, DVT: Deep vein thrombosis, COVID-19: Coronavirus disease-2019

Table 2. Laboratory values			
	Group 1	Group 2	p-value
Total number	80	44	
WBC, ×10/L	11.7 (9.1-17.7)	10.5 (8.9-15.6)	>0.05
Neutrophil count, ×10/L	9.6 (6.7-14.4)	8.9 (7.5-12.2)	>0.05
Lymphocyte count, ×10/L	2.1 (1.8-2.2)	1.8 (1.5-2.3)	>0.05
Neutrophil to lymphocyte ratio	11.1 (7.3-19.4)	9.4 (7.3-11.1)	>0.05
Hemoglobin, g/dL	11.2±2.3	12.4±2.8	>0.05
Platelet count, ×10/L	244.6 (214.6-274.1)	257.64 (231.6-289.2)	>0.05
Prothrombin time, seconds	17.1 (16.2-19.1)	15.8 (14.1-17.2)	>0.05
aPTT, seconds	35.5 (33.7-44)	34.3 (32.4-41.1)	>0.05
CPK, U/L	167.1 (65.4-233.4)	145.7 (64.4-221.1)	>0.05
Average in-hospital D-dimer, mg/mL	21.93 (18.25-26.97)	17.28 (11.62-22.88)	>0.05
First D-dimer, mg/mL	19.88 (9.79-32)	16.79 (9.79-23.6)	>0.05
Fibrinogen, mg/dL	401 (320-529)	526.2 (341.6-589.1)	>0.05
CRP, mg/dL	14.2 (5.24-26.1)	12.3 (5.24-18.2)	>0.05
Lactate dehydrogenase, U/L	448 (388.5-522.5)	416.2 (343.7-492.5)	>0.05
WBC: White blood cell, aPTT: Activated partial thrombin time, CPK: Creatine phosphokinase, CRP: C-reactive protein			

data distributions were assessed using ANOVA and Tukey tests. Normally distributed data were expressed as mean ± standard deviation, while non-normally distributed data were presented as median and interquartile range. A p-value <0.05 was considered statistically significant.

## RESULTS

Both groups had similar age distributions. However, a significant difference was noted in the incidence of deep venous thrombosis, which was observed in Group 1 but absent in Group 2 ( $p<0.05$ ). Comorbidities such as type 2 diabetes, hyperlipidemia, smoking, and chronic obstructive pulmonary disease were present in varying proportions but did not yield statistically significant differences. Most ischemic events occurred in the lower extremities (89%), with a small proportion of bilateral involvement (3%) exclusively in Group 1. D-dimer levels were significantly elevated in Group 1 both at admission and during hospitalization (Table 2). Primary patency rates were 100% in Group 2 but dropped to 88% in

Group 1 following thrombectomy ( $p<0.05$ ). Amputation rates were also higher in Group 1. Intensive care unit admissions, inotropic support, and intubation rates were significantly greater among COVID-19 patients. The mean hospital stay was substantially longer for Group 1 ( $24\pm 8$  days) compared to Group 2 ( $8\pm 4$  days,  $p<0.05$ ).

## DISCUSSION

Thrombosis has emerged as a major clinical challenge, particularly in COVID-19 patients. Since April 2020, numerous studies have highlighted the increased thrombotic risk associated with severe acute respiratory syndrome-coronavirus-2 infection. COVID-19 triggers both venous and arterial thrombosis (6-11), with acute limb ischemia becoming increasingly recognized during the pandemic (8-11). Early and meticulous assessment of COVID-19 patients presenting with non-specific symptoms is crucial for timely thrombosis diagnosis. Doppler ultrasound serves as an effective diagnostic tool for evaluating both arterial and venous limb pathologies. Notably, bilateral lower limb ischemia was only observed in COVID-19 patients. The severity of COVID-19 significantly influences peripheral arterial thromboembolism prognosis, as systemic complications further worsen outcomes. Additionally, corticosteroids used in treatment may exacerbate thrombophilia (3). Conventional management strategies for acute limb ischemia appear inadequate in COVID-19 patients, necessitating the early initiation of anticoagulation with LMWH. Surgical success rates remain suboptimal, with increased complications and amputation rates (8-11). Thus, rigorous monitoring of ischemic symptoms is essential in COVID-19 patients.

## CONCLUSION

Severe COVID-19 is characterized by a hypercoagulable state, predisposing patients to arterial, venous, and microvascular thrombosis. The prevalence of acute limb ischemia is notably high in COVID-19 patients, leading to poorer clinical outcomes, reduced therapeutic success, and higher complication rates.

### Ethics

**Ethics Committee Approval:** This study adhered to the ethical principles of the Helsinki Declaration and was approved by the Ethics Committee of Sakarya University Medical Faculty (approval no: E-71522473-050.01-04-645, date: 03.12.2020).

### Footnotes

#### Authorship Contributions

Concept: B.P., Design: B.P., S.S., H.E., Data Collection or Processing: B.P., Writing: B.P., S.S., H.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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