

# Ischemic Necrosis of Lower Extremity in COVID-19: A Case Report

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Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an acute infectious disease that spreads mainly via the respiratory route. Elderly patients or those with underlying diseases are more seriously affected. We report a case of COVID-19 infection in a geriatric patient with arteriovenous thrombosis of the right lower limb. Despite persistent anticoagulant therapy, the patient's arterial thrombosis continued to progress and presented with ischemic necrosis of the lower extremity. After amputation in this case, the levels of D-dimer and inflammatory cytokine increased progressively, and he presented with acute myocardial infarction, which progressed rapidly to multisystem organ failure. However, whether coronavirus can directly cause the damage of the cardiovascular system and thrombosis needs further investigation.

**Key words:** COVID-19, SARS-CoV-2, Thrombosis, Coronavirus, Wuhan

## Introduction

In December 2019, there was an outbreak of SARS-CoV-2 infection disease in Wuhan, China<sup>1</sup>. On February 11, 2020, the World Health Organization has termed this disease as the coronavirus disease 2019 (COVID-19) and declared it as pandemic on March 11, 2020. COVID-19 is highly contagious and has rapidly spread to many countries around the world. By May 14, 2020, there were 4,248,389 confirmed cases with 294,046 related deaths<sup>2</sup>.

Wuhan Union Hospital is one of the hospitals in China designated for the treatment of critically ill COVID-19 patients. During the outbreak, we treated several COVID-19 patients in Wuhan Union Hospital. We now report the first operative amputation case of COVID-19 that manifested ischemic necrosis in the world.

## Case Report

A 70-year-old man who resided in Wuhan, China, felt the first symptoms of chest discomfort on January 17, 2020, and had chest x-rays that showed mild pulmonary infection. At that time, he did not have diarrhea, cough, or subjective fever. He refused to be hospitalized, and he took oral anti-infective drug by himself at home. He did not have direct exposure to the Huanan seafood market in Wuhan, but he had a history of left lung cancer surgery 4 years ago. There was no tumor metastasis or recurrence. He had no history of previous arteriovenous thromboembolic disease, hypertension, diabetes, or heart disease. On January 27, 2020, he suffered from muscle pain and bruise in the lower right limb. Gradually, he developed fatigue, anorexia, and ecchymosis of the right lower limb and was then hospitalized in a local community hospital on February 3, 2020. Despite antibiotic treatment in the community hospital, his condition con-

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tinued to deteriorate. On February 8, 2020, he was transferred to the Wuhan Steel Hospital. An ultrasound examination showed the presence of multiple emboli at the right femoral artery and superficial femoral artery. Laboratory tests revealed that D-dimer was 22.43 mg/L (normal <0.5 mg/L). The chest computed tomography (CT) images showed multiple infectious lesions in both lungs with partial fibrosis, highly suspicious of SARS-CoV-2 infection (see [Supplementary Fig. 1](#)). Further laboratory testing using novel coronavirus nucleic acid test confirmed this case as positive COVID-19. On February 8, 2020, enoxaparin sodium (4000 IU once every 12 h subcutaneous injection) was used for antithrombotic treatment (see [Supplementary Fig. 2A](#)). However, after 12 days of antithrombotic and antiviral treatment, his arterial circulation was not restored. On February 19, 2020, the ultrasound examination showed thrombosis in the middle and lower segments of the common femoral vein in the right lower limb.

On February 20, 2020, the patient was transferred to our Wuhan Union Hospital. On admission, he reported cough and expectoration. However, the phlegm culture was all negative. Physical examination revealed obvious, bluish-purple swelling, and pain to palpation of the lower right limb, but the pulsation of the right dorsalis pedis arteries disappeared ([Fig. 1](#)). On February 21, 2020, an inferior vena cava filter was done via the left common femoral vein to prevent pulmonary thrombosis before surgery by a vascular surgeon. Afterward, lower right limb amputation was conducted under general anesthesia.

Postoperatively, the patient stayed in an intensive care unit, and enoxaparin sodium (4000 IU once daily by subcutaneous injection) was commenced for deep vein thrombosis (DVT) prophylaxis (see [Supplementary Fig. 2B](#)). His consciousness was clear and his vital signs were normal. On day 2 postoperative, he was transferred to a general quarantine ward. On day 3 after surgery, his axillary body temperature was 36.3°C–38.4°C; heart rate, 64–72 beats/min; respiratory rate, 15–20 breaths/min; blood pressure, 99/145–65/88 mmHg; and arterial oxygen saturation (SaO<sub>2</sub>) 95%–98% (nasal oxygen breath, 3 L/min). On day 4 postoperative, he developed chest oppression and nausea. The SaO<sub>2</sub> was 94% (nasal oxygen breath, 5 L/min), and respiratory rate was 20–23 breaths/min. On day 6 postoperative, his symptoms had not improved, and he developed bloody sputum ([Fig. 2](#)). The SaO<sub>2</sub> decreased to 88%–98% (non-invasive ventilation, 10 L/min). On day 7 postoperative, his hypoxemia and shortness of breath worsened. Arterial blood gas analysis indicated an oxygenation index of 40 mmHg, an SaO<sub>2</sub> of 67%, and a pH of 7.28. He was immediately

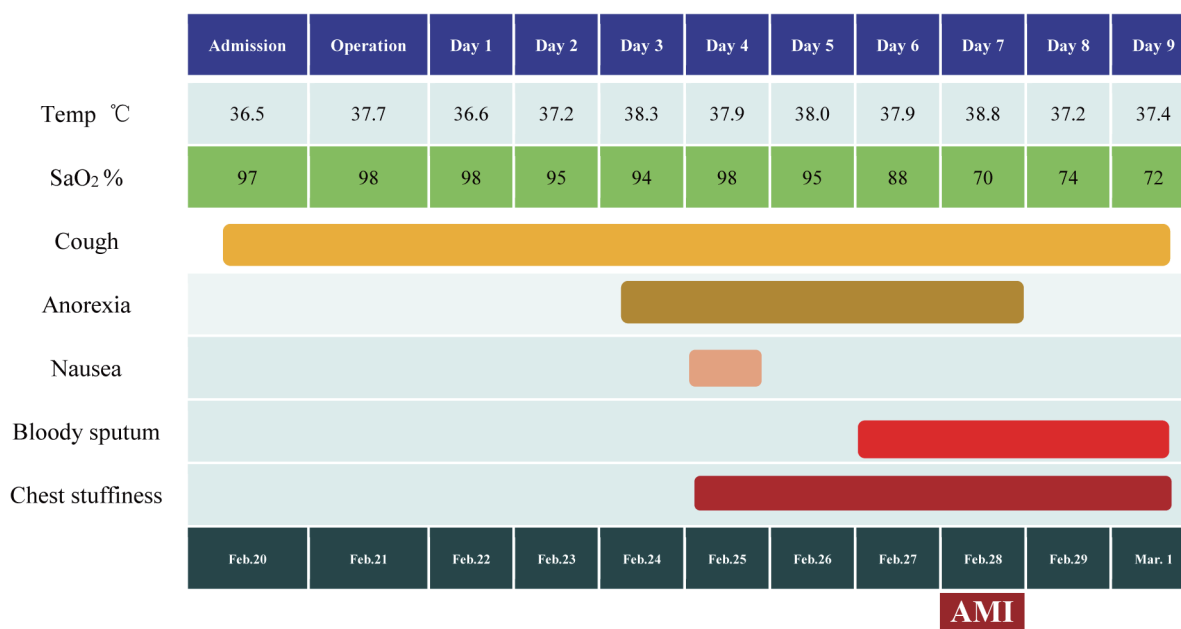


**Fig. 1.** Lower right limb of the patient, showing that the lower limb is bluish-purple with apparent swelling (Photo taken at on admission)

given invasive ventilation. Electrocardiogram showed atrial fibrillation and acute myocardial infarction. Hypersensitive troponin I level was 10025.4 ng/L (normal ≤ 26.2 ng/L), brain natriuretic peptide level was 508.9 pg/mL (normal ≤ 100 pg/mL), and echocardiogram demonstrated an ejection fraction of 43%. Despite receiving invasive ventilation, his SaO<sub>2</sub> decreased to 74%–85%. The condition progressed rapidly to multisystem organ failure (MSOF), including acute heart failure, acute kidney injury, acute liver failure, and acute hypoxic respiratory failure ([Table 1](#)). On day 9 postoperative, his SaO<sub>2</sub> decreased to 60%–66%. He was immediately given chest compression and adrenaline injection. Unfortunately, the rescue was not successful, and the patient died on March 1, 2020.

## Discussion

COVID-19 has become a serious global health problem. The most common symptoms of SARS-



**Fig. 2.** Maximum Body Temperatures, Minimum oxygen saturation and Symptoms by Day of hospitalization  
AMI: acute myocardial infarction.

**Table 1.** Laboratory findings of the patient on admission to Wuhan Union Hospital

	Normal range	Feb 20 (pre-op)	Feb 22 (1 day post-op)	Feb 23 (2 day post-op)	Feb 25 (4 day post-op)	Feb 26 (5 day post-op)	Feb 28 (7 day post-op)	Feb 29 (8 day post-op)	Mar 1 (9 day post-op)
White blood cell count, × 10 <sup>9</sup> /L	(3.5-9.5)	9.83	6.22	11.31	11.42	11.58	11.67	5.76	8.24
Lymphocyte count, × 10 <sup>9</sup> /L	(1.1-3.2)	1.32	0.52	1.37	0.68	0.64	0.45	0.81	0.48
CRP, mg/L	(0-8)	79.08	65.79	79.08	122.24	132.75	151.4	151.82	189.95
Procalcitonin, ng/mL	(0-0.05)			0.16	0.17	0.21	0.65	15.77	37.5
IL-6, pg/mL	(0-7)						336.2		
D-dimer, ug/mL	(0-0.5)	6.55	5.67	>8	5.19	2.85	7.62	>8	>8
Fibrinogen, g/L	(2-4)	5.6	5.25	5.32	6.07	5.75	6.16	4.53	3.9
PT, s	(11-16)	14.5	14.1	13.6	14.5	14.8	15.7	19	18.1
APTT, s	(27-45)	57.2	51.5	42.8	44.1	43.5	40.4	47.9	49.4
Platelet count, × 10 <sup>9</sup> /L	(125-350)	282	233	224	275	249	271	215	60
Aspartate aminotransferase, U/L	(8-40)	65	82	65	63	28	34	488	840
Alanine aminotransferase, U/L	(5-40)	68	92	68	73	39	27	232	367
Creatinine, umol/L	(57-111)	62.3	59	62.3	62.1	54.9	46.1	173.8	207.3
Urea nitrogen, umol/L	(2.9-8.2)	4.5	5.09	4.5	4.48	3.4	66.4	10.1	12.86
Hypersensitive troponin I, ng/L	(0-26.2)	5.9	25.7	22.4			1002.5	>50000	>50000
BNP, pg/mL	(0-100)	122.4	88.5	235.2			508.9	1641.5	>5000
COVID-19 IgM, AU/mL	(0-10)								41.46
COVID-19 IgG, AU/mL	(0-10)								118.36

C-reactive protein (CRP), Interleukin-6 (IL-6), Prothrombin time (PT), Activated partial thromboplastin time (APTT), Brain natriuretic peptide(BNP)

COV-2 infection are fever, cough, and myalgia or fatigue. Most patients had normal white blood cell counts but leukopenia, elevated levels of C-reactive protein (CRP), and abnormal chest CT images show-

ing ground glass opacity<sup>1, 3</sup>). As shown in this case, the elderly patient demonstrated most of the common symptoms but afebrile in the early stage.

SARS-CoV-2 can be transmitted by droplets, via

direct contact, and possibly by aerosols. Thus, operating room personnel should wear personal protective equipment (PPE), including disposable cap, goggles, face shield, N95 mask, disposable latex gloves, and waterproof boot. To avoid cross contamination, the operation should be conducted in a negative-pressure surgery room. PPE and respirators should be discarded before leaving the operating room.

Studies indicated that DVT and pulmonary embolism in SARS patients who were infected by another coronavirus was 20.5% and 11.4%, respectively<sup>4</sup>. It has been clinically recognized that COVID-19 patients are prone to thrombotic dysfunction, and COVID-19 patients, especially those with severe symptoms, had a higher D-dimer value and risk of thrombosis<sup>1, 3, 5, 6</sup>. Furthermore, COVID-19 patients may exhibit many risk factors of thrombosis such as blood concentration, vascular endothelial injury, blood hypercoagulation, bed rest, advanced age, and history of surgery. In this case, the elderly patient first developed chest discomfort and lung infection 10 days before thrombosis symptom occurred in the lower extremity. Despite 12 days of persistent anticoagulant therapy in the hospital, the patient's arterial thrombosis continued to progress, and he was presented with ischemic necrosis of the lower extremity. Therefore, we speculate that there is a high correlation between COVID-19 infection and thrombosis.

Recent studies have demonstrated that SARS-CoV-2 uses the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) for host cell entry<sup>7</sup>. ACE2 protein is highly expressed in cardiovascular tissues<sup>8</sup>. According to the Diagnosis and Treatment Program of 2019 New Coronavirus Pneumonia (trial seventh version), the vascular pathological changes of COVID-19 were mainly partial vascular endothelial shedding, vascular intimal inflammation, and thrombosis<sup>9</sup>. Additionally, the endotheliitis has been reported to be correlated with SARS-CoV-2 infection, which may promote the development of thrombosis in COVID-19<sup>10, 11</sup>. This patient suffered from a sudden worsening of condition on the fourth day after operation, followed by abnormal electrocardiogram (atrial fibrillation and acute myocardial infarction) and then extremely high hypersensitive troponin I level. Therefore, it appears that SARS-CoV-2 could attack cardiovascular tissue directly or indirectly via inducing inflammation storm.

Previous studies have shown that CRP and procalcitonin (PCT) are correlated and can successfully predict mortality in patients with community-acquired pneumonia (CAP)<sup>12</sup>. D-dimer levels are elevated in patients with CAP and are associated with the severity of CAP and clinical outcomes<sup>13</sup>. As shown in

this case, the level of D-dimer, CRP, and PCT increased progressively after surgery and the patient progressed rapidly with acute respiratory distress syndrome and acute myocardial infarction, which was eventually followed by MSOF. Furthermore, recent research has shown that increased amounts of proinflammatory cytokines in serum were associated with disease severity in COVID-19<sup>1</sup>. In SARS patients, the cytokine storm was associated with pulmonary inflammation and extensive lung damage<sup>14</sup>. Therefore, elevations of D-dimer and inflammatory cytokine might account for the sudden progression of disease in this patient. His serum cytokine IL-6 had a 50-fold increase (Table 1). Additionally, surgery represents a major stress event for the patient, which may aggravate the body's inflammatory response. Those probably indicated poor prognosis of this patient.

In conclusion, the pathogenesis of this patient's lower limb arterial thrombosis is unknown. Whether the coronavirus can directly cause thrombosis needs further investigation. However, COVID-19 infection not only can induce various proinflammatory immune mediators that might damage the lungs but also is enough to activate the coagulation system. This case highlights the importance of timely diagnosis of COVID-19 and appropriate management of thrombosis.

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## Declaration of Interests

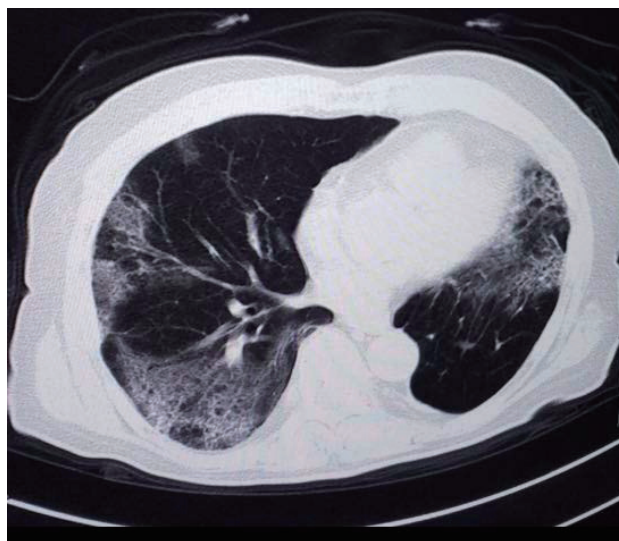
The authors declare that they have no competing interest.

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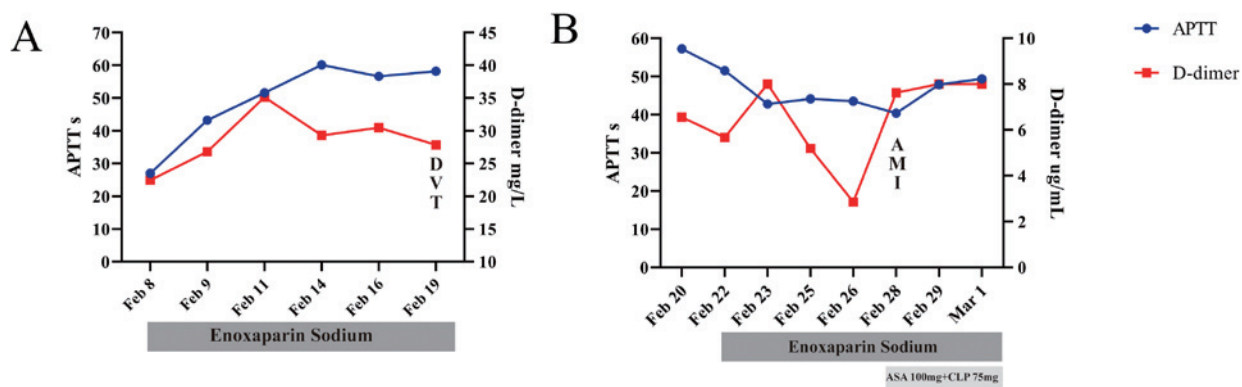
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**Supplementary Fig. 1.** Transverse chest CT images showing bilateral ground-glass opacity on day 13 after symptom onset



**Supplementary Fig. 2.** The antithrombotic course demonstrates changes over time in APTT and D-dimer

A. Antithrombotic therapy and changes in APTT and D-dimer in other hospital. B. Antithrombotic therapy and changes in APTT and D-dimer in our hospital. DVT: deep vein thrombosis, APTT: activated partial thromboplastin time, ASA: aspirin, CLP: clopidogrel, AMI: acute myocardial infarction.