2020

Acute Arterial Thromboembolism in Patients with COVID-19 in the New York City Area

Y. Etkin
Zucker School of Medicine at Hofstra/Northwell

A. M. Conway
Zucker School of Medicine at Hofstra/Northwell

J. Silpe
Northwell Health

K. Qato
Zucker School of Medicine at Hofstra/Northwell

A. Carroccio
Zucker School of Medicine at Hofstra/Northwell

See next page for additional authors

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

ELSEVIER

Clinical Research

Acute Arterial Thromboembolism in Patients with COVID-19 in the New York City Area

Yana Etkin, Allan M. Conway[1], Jeffrey Silpe, Khalil Qato, Alfio Carroccio, Pallavi Manvar-Singh, Gary Giangola, Jonathan S. Deitch, Luis Davila-Santini, Jonathan A. Schor, Kuldeep Singh, Firas F. Mussa, and Gregg S. Landis, Hempstead

Background: Coronavirus disease 2019 (COVID-19) predisposes to arterial and venous thromboembolic complications. We describe the clinical presentation, management, and outcomes of acute arterial ischemia and concomitant infection at the epicenter of cases in the United States.

Methods: Patients with confirmed COVID-19 infection between March 1, 2020 and May 15, 2020 with an acute arterial thromboembolic event were reviewed. Data collected included demographics, anatomical location of the thromboembolism, treatments, and outcomes.

Results: Over the 11-week period, the Northwell Health System cared for 12,630 hospitalized patients with COVID-19. A total of 49 patients with arterial thromboembolism and confirmed COVID-19 were identified. The median age was 67 years (58−75) and 37 (76%) were men. The most common preexisting conditions were hypertension (53%) and diabetes (35%). The median D-dimer level was 2,673 ng/mL (723−7,139). The distribution of thromboembolic events included upper 7 (14%) and lower 35 (71%) extremity ischemia, bowel ischemia 2 (4%), and cerebral ischemia 5 (10%). Six patients (12%) had thrombus in multiple locations. Concomitant deep vein thrombosis was found in 8 patients (16%). Twenty-two (45%) patients presented with signs of acute arterial ischemia and were subsequently diagnosed with COVID-19. The remaining 27 (55%) developed ischemia during hospitalization. Revascularization was performed in 13 (27%) patients, primary amputation in 5 (10%), administration of systemic tissue-plasminogen activator in 3 (6%), and 28 (57%) were treated with systemic anticoagulation only. The rate of limb loss was 18%. Twenty-one patients (46%) died in the hospital. Twenty-five (51%) were successfully discharged, and 3 patients are still in the hospital.

Conclusions: While the mechanism of thromboembolic events in patients with COVID-19 remains unclear, the occurrence of such complication is associated with acute arterial ischemia which results in a high limb loss and mortality.

Type of Research: Retrospective analysis of the largest reported single health system experience with COVID-19 presenting with acute arterial thrombosis from the United States' epicenter of the infection.

Key Findings: COVID-19 is a risk factor for acute arterial thrombosis and carries poor prognosis in terms of mortality and morbidity.

Take Home Message: Patients with confirmed COVID-19 are at increased risk for thromboembolic complications and early diagnosis, and treatment is critical. Despite all attempts for life and limb salvage, the overall outcome is largely driven by the patient's physiologic state at presentation.

Table of Contents Summary: We report the clinical presentation, management, and outcomes of acute arterial ischemia and concomitant infection at the epicenter of cases in the United States.

Source of Funding: None.

Conflict of Interest: The authors confirm that there are no conflicts of interest.

Allan M. Conway is a co-first author.

[1]*Division of Vascular and Endovascular Surgery, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.*

Correspondence to: Yana Etkin, MD, Division of Vascular and Endovascular Surgery, Zucker School of Medicine at Hofstra/Northwell, 1999 Marcus Avenue, Suite 106, Lake Success, NY 114042, USA; E-mail: yetkin@northwell.edu

Ann Vasc Surg 2020; ■: 1–5
https://doi.org/10.1016/j.avsg.2020.08.085

Manuscript received: June 9, 2020; manuscript accepted: August 16, 2020; published online: ■ ■ ■

INTRODUCTION

In December 2019, a series of pneumonia cases of unknown origin were identified in Wuhan, China.[1] The pathogen has since been identified as a novel enveloped RNA beta-coronavirus that has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] The first confirmed case of coronavirus disease 2019 (COVID-19) in the United States was reported in Washington State in January 2020.[3] Although the typical presentation involves viral pneumonia causing severe respiratory deterioration, a hypercoagulable state has been observed in many patients with SARS-CoV-2 and is a predictor of a worse prognosis.[1,4,5]

COVID-19 may predispose to both arterial and venous thromboembolic complications.[6] The cumulative incidence of thrombotic complications in critically ill patients with COVID-19 was 31% despite systemic thromboprophylaxis, including 27% venous thromboembolisms and 4% arterial thrombotic events.[6] Arterial thromboembolic complications may have devastating consequences, including limb loss, premature intubation, multiorgan dysfunction, stroke, and death.

The purpose of this study was to review the incidence, clinical presentation, management, and outcomes with 46 consecutive cases with acute arterial thrombosis in patients with confirmed COVID-19.

METHODS

A study was conducted at 7 hospitals within Northwell Health, the largest academic health system in New York State, serving approximately 11 million persons. All patients with confirmed COVID-19 infection and acute arterial thrombosis from March 1, 2020 to May 15, 2020 were entered into a Research Electronic Data Capture tools hosted at Northwell Health.[7] These patients were identified based on retrospective review of prospectively maintained database of all inhospital consultations. Research Electronic Data Capture is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The Northwell Health Institutional Review Board approved this case series as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent.

Data collected included patient demographic information, comorbidities, anatomical location, and clinical presentation of thromboembolism, treatment, and clinical outcomes. Race and sex data were collected by self-report in prespecified fixed categories. The Northwell COVID survival calculator was used to assess for expected mortality. This tool was constructed using multivariate regression with L1 regularization (LASSO) to predict survival during hospitalization, based on outcomes of 5,233 patients with COVID-19 hospitalized at Northwell Health. Patient age, serum blood urea nitrogen, Emergency Severity Index, red cell distribution width, absolute neutrophil count, serum bicarbonate, and glucose were identified as the optimal predictors of survival by multivariate LASSO regression.[8]

All statistics were performed as a descriptive analysis. Continuous variables were expressed as medians and interquartile ranges. Categorical variables were summarized as counts and percentages.

RESULTS

During the study period, the Northwell Health System cared for 12,630 hospitalized patients with COVID-19. The initial characteristics of 5,700 patients from Northwell are presented elsewhere.[9] This case series presents indepth results on 49 patients with acute arterial thromboembolisms and COVID-19 were not presented in that article. The median age was 67 years, and 76% were men (Table I). Based on Northwell COVID-19 survival calculator, median-predicted mortality at the time of vascular evaluation was 37% (IQR = 11−94). Thirteen patients (27%) were severely ill and were intubated before onset of ischemia. The median D-dimer level was 2,673 (IQR = 723−7,139), and 83% of patients had D-dimer greater than 1,000 ng/mL. Twenty-two (45%) patients presented with signs of acute arterial ischemia and were subsequently diagnosed with COVID-19. Twenty-seven patients (55%) developed ischemia during hospitalization after an average of 6 ± 4.5 days.

The distribution of ischemia included upper (14%) and lower (71%) extremity, mesenteric (4%), and cerebral (10%). Six patients (12%) had concomitant arterial thrombus in multiple anatomic locations (Table II). Sixteen percent had concomitant deep vein thrombosis. Computed tomography angiogram was diagnostic in 25 patients (51%) and duplex ultrasound in 19 (39%). The remaining 5 patients were too unstable for transport to imaging, and the diagnosis was based on clinical signs of acute ischemia.

Table I. Demographics and comorbidities[a]

Characteristics	$N = 49$ (%)
Median age (IQR), year	67 (58−75)
Gender (%male), *n* (%)	37 (76)
Race, *n* (%)	
Caucasian	17 (35)
African American	9 (18)
Hispanic	17 (35)
Asian	6 (12)
Median BMI (IQR), kg/m^2	28 (25−32)
Comorbidities, *n* (%)	
Hypertension	26 (53)
Diabetes mellitus	17 (35)
Chronic obstructive pulmonary disease	3 (6)
Heart disease	8 (16)
Chronic kidney disease	2 (4)
Hypercholesterolemia	12 (24)
Peripheral vascular disease	2 (4)
Atrial fibrillation	7 (14)
Smoking	9 (18)
Active smokers	2 (4)
Ex-smokers	7 (14)
Malignancy	7 (14)
Multiple comorbidities	22 (45)
No past medical history	13 (27)
Home medications	
Antiplatelets	14 (29)
Anticoagulants	7 (14)

Race and ethnic group were reported by the patient or were determined by family or physician if patient was non-communicative.
[a]Percentages may not total 100 because of rounding. IQR denotes interquartile range.

Of the 35 patients with lower extremity ischemia, 9 received open thrombectomy, 2 endovascular thrombectomy, and 5 primary amputations. Of the 2 patients with mesenteric ischemia, 1 underwent open thrombectomy and 1 endovascular thrombolysis. A total of 28 patients (57%) were treated with systemic anticoagulation, 3 (7%) received a single weight-based dose of recombinant tissue plasminogen activator, of those, 19 (61%) were deemed too unstable for surgical interventions.

The rate of limb loss was 18%, and overall, inhospital mortality was 46%. Mortality in patients with lower limb ischemia was 50%, and in patients with mesenteric ischemia, it was 100%. Twenty-five patients (51%) were successfully discharged from hospital, and 3 (6%) remain hospitalized at the time this manuscript was prepared.

Table II. Symptoms and anatomic location of the thromboembolism[a]

Symptoms and location of arterial occlusion	*N* (%)
Lower extremity ischemia	35 (71)
Aortoiliac	8/35 (23)
Femoral above knee	12/35 (34)
Popliteal below knee	15/35 (43)
Upper extremity ischemia	7 (14)
Upper arm (subclavian, axillary and brachial)	4/7 (57)
Forearm (ulnar and radial)	3/7 (43)
SMA thrombosis with bowel ischemia	2 (4)
Renal artery thrombosis	5 (10)
Splenic artery thrombosis	3 (6)
CVA with carotid artery thrombosis	5 (10)
Asymptomatic with thoracic aortic thrombus	1 (2)
Thrombosis in multiple locations[b]	6 (12)

[a]Percentages may not total 100 because of rounding.
[b]Concomitant thrombus in the SMA, renal arteries, and lower and upper extremity arteries. SMA denotes superior mesenteric artery and CVA cerebrovascular accident.

DISCUSSION

SARS-CoV are an emerging and reemerging source of global pandemic (e.g., SARS, Middle East respiratory syndrome (MERS), and COVID-19) which have caused significant morbidity and mortality, most notably in the last several months. Although the typical presentation involves viral pneumonia with severe respiratory deterioration,[4] abnormal coagulation occurs in many patients with COVID-19 population and is a predictor of worse prognosis[1,5,10,11] Furthermore, COVID-19 may predispose to both arterial and venous thromboembolic complications.[6,12−14] To our knowledge, this report represents the largest case series of acute arterial ischemic complications in patients with COVID-19 to date. Of 12,630 patients who were hospitalized in our system with COVID-19, 49 patients were diagnosed with acute arterial ischemia and 16% of them had concipient venous thromboembolisms. Acute arterial ischemic events were noted as the presenting symptom in 45% of our patients suggesting that a diagnosis of COVID-19 should be considered in any patient presenting with arterial ischemia. It remains unclear if any of the thromboembolic events in our series were a result of paradoxical embolism in the setting of a patent foramen ovale. The routine use of echocardiography with agitated saline was avoided due to the concern for aerosolization of the virus.

Our patients were predominantly men over the age of 65 years with multiple comorbidities which

is compatible with other reports from China and the United States,[9,15] which demonstrated increase prevalence of severe COVID-19 infection and worse outcomes in this subset of patients. The overall mortality in our cohort was significantly higher (46%) than 21−26% reported in other studies of hospitalized patients with COVID-19.[9,15] We also observed worse outcomes in patients with acute lower limb ischemia with mortality of 50% as than 5−9% reported in a non-COVID-19 population.[16,17] Mortality from acute mesenteric ischemia is between 22% and 50%,[18,19] far lower than the 100% rate observed in our series. However, it is difficult to draw any meaningful conclusions based on our data due to very small sample size. This difference in mortality further supports the fact that hypercoagulable state in patients with SARS-COV-2 is a predictor of worse prognosis.

Inflammation secondary to viral infection has been a key component leading to a procoagulant state; this phenomenon is secondary to a myriad of factors including tissue factor−dependent activation of the coagulation cascade secondary to endothelial cell injury and dysfunction, elevated levels of von Willebrand factor, and toll-like receptor activation of proinflammatory cytokines.[20] Historically, SARS-CoV-1 and MERS-CoV also exhibited similar prothrombotic complications, as well as thrombocytopenia.[21] Furthermore, disseminated intravascular coagulation was a prevalent complication in many of the fatal MERS-CoV cases.[22] Many patients with COVID-19 infection present with thrombocytopenia and elevated D-dimer levels, which are augmented in the most severe forms of the disease.[23] Nonsurvivors of COVID-19 have been shown to have higher D-dimer and fibrin degradation product levels, with longer prothrombin times, associated with coagulation dysfunction. In our cohort, all patients had elevated D-dimer levels and 83% of patients had D-dimer greater than 1,000 ng/mL. We observed 77% mortality in patients with D-dimer levels over 5,000 ng/mL. Elevated D-dimer levels reiterate the acquired hypercoagulability in these patients as well as inflammatory state. With further research, these levels may help to predict which patients with COVID-19 will develop thromboembolic complications and subsequently worse outcomes.

Previous coronavirus and influenza epidemics have suggested that viral infections can trigger acute coronary syndromes, arrhythmias, and exacerbation of heart failure.[24,25] Huang and et al. reported 12% incidence of acute cardiac injury in patients with COVID-19. In this series, 16% of patients had preexisting cardiac disease and 14% had history of arrhythmias. Given the baseline cardiovascular disease, the development of arrhythmias, and the hypercoagulable states in patients with SARS-CoV-2 infection, the potential to develop thromboembolic disease is understandably high.

LIMITATIONS

This study has several limitations. It is a retrospective descriptive review with no direct comparison with patients without COVID-19 infection (control group). We were not able to investigate a direct cause-effect mechanism and that was not the intention of this review. With the limited number of cases, it is also difficult to assess risk factors for disease distribution and outcomes. In addition, some patients remained in the hospital, and the outcomes were unknown at the time of data cutoff. Finally, this series is likely an under-representation of the true incidence of acute arterial thromboembolic events in patients with COVID-19, as both asymptomatic cases, and acute arterial ischemic events in moribund patients were likely never diagnosed.

CONCLUSION

In this series of patients with COVID-19 and acute arterial ischemia, presentation varied from asymptomatic to nonsalvageable. Prognosis was largely driven by the overall physiologic condition of the patient at presentation and also by duration of symptoms and was generally poor. The limb loss rate was high at 18%, and overall mortality was 46%. Eighty-three percent of patients had elevated D-dimer levels greater than 1,000 ng/mL. In patients with COVID-19, hypercoagulability is likely related to an inflammatory cascade with cytokine storm secondary to sepsis, possible disseminated intravascular coagulation, and excessive activation of the coagulation cascade. Arterial thromboembolic complications carry devastating consequences of limb loss, multiorgan dysfunction, and death. A diagnosis of COVID-19 should be considered in any patient presenting with arterial ischemia.

The Northwell COVID-19 Research consortium.

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497−506.

2. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565–74.
3. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382:929–36.
4. Cheng VCC, Lau SKP, Woo PCY, et al. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev 2007;20:660–94.
5. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med 2020;58:1116–20.
6. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–7.
7. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:145–7.
8. Levy TJ, Richardson S, Coppa K, et al. A predictive model to estimate survival of hospitalized COVID-19 patients from admission data. medRxiv, 2020. doi:10.1101/2020.04.22.20075416.
9. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020;323:2052–9.
10. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
11. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:1233–4.
12. Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med 2020;382:e60.
13. Marone EM, Rinaldi LF. Upsurge of deep venous thrombosis in patients affected by COVID-19: preliminary data and possible explanations. J Vasc Surg Venous Lymphat Disord 2020;8:694–5.
14. Bellosta R, Luzzani L, Natalini G, et al. Acute limb ischemia in patients with COVID-19 pneumonia. J Vasc Surg 2020.
15. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.
16. Eliason JL, Wainess RM, Proctor MC, et al. A national and single institutional experience in the contemporary treatment of acute lower extremity ischemia. Ann Surg 2003;238:382–9.
17. Hemingway J, Emanuels D, Aarabi S, et al. Safety of transfer, type of procedure, and factors predictive of limb salvage in a modern series of acute limb ischemia. J Vasc Surg 2019;69:1174–9.
18. Schermerhorn ML, Giles KA, Hamdan AD, et al. Mesenteric revascularization: management and outcomes in the United States, 1988-2006. J Vasc Surg 2009;50:341–348.e1.
19. Ryer EJ, Kalra M, Oderich GS, et al. Revascularization for acute mesenteric ischemia. J Vasc Surg 2012;55:1682–9.
20. Subramaniam S, Scharrer I. Procoagulant activity during viral infections. Front Biosci (Landmark Ed) 2018;23:1060–81.
21. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol 2020;127:104362.
22. Al-Abdallat MM, Payne DC, Alqasrawi S, et al. Hospital-associated outbreak of middle east respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description. Clin Infect Dis 2014;59:1225–33.
23. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
24. Madjid M, Miller CC, Zarubaev VV, et al. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34 892 subjects. Eur Heart J 2007;28:1205–10.
25. Madjid M, Connolly AT, Nabutovsky Y, et al. Effect of high influenza activity on risk of ventricular arrhythmias requiring therapy in patients with implantable cardiac defibrillators and cardiac resynchronization therapy defibrillators. Am J Cardiol 2019;124:44–50.