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COVID-19 Pneumonia Hospitalizations Followed by Re-Presentation for Presumed Thrombotic Event



To the Editor:

VTE is an important, dangerous, and sometimes fatal complication of coronavirus disease 2019 (COVID-19).^{1,2} Thrombosis, including ischemic heart disease and stroke, contributes to the overall disease burden in all non-COVID patient populations worldwide, accounting for approximately one in four deaths.³

Current guidelines recommend chemical prophylaxis in all patients with COVID-19 who are admitted to the hospital; however, after discharge, recommendations are not addressed.⁴ The benefit of extending VTE prophylaxis after discharge has been observed to be safe and effective in some high-risk populations.⁵⁻⁸ Simple

laboratory makers, which include D-dimer and C-reactive protein (CRP), can be especially important in choosing who may benefit from extended VTE prophylaxis.⁹⁻¹² To date, there have been no randomized studies to study extending VTE prophylaxis in the COVID-19 patient population.

This series describes clinical observations at a large academic hospital center in New York City that are related to increased rates of thrombotic events in patients re-presenting to health care within a short timeframe after an index COVID-19 admission. These patients re-presented with presumed thromboembolic complications, both arterial and venous. Most of these cases resulted in acute and rapid decline at re-presentation that led to death. These observations have raised our concern regarding a continued hypercoagulable state in patients with COVID-19, despite clinical stability that exists after hospitalization; patients with certain risk factors may benefit from extended VTE prophylaxis.

Methods

Re-presentation data exists currently under our institution quality improvement. We reviewed all patients with confirmed COVID-19 who were discharged and then re-presented to any of our hospital or ED facilities located in the New York metropolitan area between the dates of March 3 and April 10, 2020. We reviewed the hospital records and

filtered for patients who were presumed to have a DVT, pulmonary embolism, limb ischemia due to arterial thrombosis, acute coronary syndromes due to coronary thrombosis (ST elevation myocardial infarction), or acute stroke. However, given the under-diagnosis of these events, we also included rapidly evolving hemodynamic instability with elevated D-dimer at time of re-presentation.

Results

We identified nine patients who were discharged from an inpatient stay and returned with concern for a thrombotic event based on clinical review and laboratory findings. Thrombotic events accounted for the second most common reason for presentations after discharge during the monitored time. There were 1975 all-hospital discharges during the time period. There were 68 adult medical re-presentations: pneumonia-bacterial or pneumonia-viral (n = 37), thrombotic events (n = 8), cardiac, not myocardial infarctions (n = 5), syncope (n = 4), acute respiratory distress syndrome (n = 3), urinary tract infections (n = 3), septic shock (n = 2), altered mental status (n = 2), pancreatitis (n = 1), failure to thrive (n = 1), electrolytes (n = 1), and renal failure (n = 1). All patients were readmitted, except one

case of a 68-year-old man who re-presented to the ED, was sent home, and died the same day. We included this patient, because there was no evidence of infection on evaluation in the ED, his hypoxia had improved, and his complaint on re-presentation was acute fatigue and near syncope.

Of the nine patients, three were women, and six were men. The median age of patients was 74 years old (± 6.4 years). On average, patients were overweight: BMI, 28.7 kg/m² (± 6.3 kg/m²). Patients had varied past medical histories. The most common co-morbidities included hyperlipidemia (55.6%), obesity (33.3%), hypertension (33.3%), diabetes mellitus (22.2%), chronic kidney disease (22.2%), and arrhythmia (22.2%). Two people did not have any diagnosed co-morbidities. The

average CRP before discharge was 111±96 mg/L, and the average D-dimer before discharge was 403±253 ng/mL. Both markers significantly trended up between discharge and re-presentation. There was a high mortality rate as eight of the nine patients died during readmission or within 24 hours of presentation to the ED (Table 1). All patients received chemical DVT prophylaxis during their initial hospitalization. During re-presentation, all patients who were admitted for > 24 hours before death were given full-dose anticoagulation; two patients died within 24 hours and had received only prophylactic dose heparin. There were no observed bleeding events, and no patients required transfusion.

Discussion

The incidence of thrombosis in COVID-19 has been reported so far to be as high as 25% to 31%, with VTE making up the largest proportion.^{2,13} The precise mechanism of thrombosis remains unclear. Immune dysregulation and hyper-inflammatory states may lead

to endothelial dysfunction and the initiation of the thrombotic cascade.^{2,13,14} Autopsy findings of patients with severe acute respiratory syndrome coronavirus 2 have demonstrated circulating megakaryocytes, fibrin deposition, and microvascular injury in multiple organs that support this theory.¹⁵ Although classic disseminated intravascular coagulation has also been identified in certain patients with COVID-19, the incidence of this is seemingly rare.^{1,16} Instead, patients with COVID-19 more often experience a coagulopathy with elevations in D-dimer, prolonged prothrombin time, and activated partial thromboplastin time but high fibrinogen and lack of bleeding, which is not typical for disseminated intravascular coagulation.¹⁶

Elevated D-dimer, prolonged prothrombin time, and prolonged activated partial thromboplastin time have been identified as independent predictors of death in COVID-19.¹⁴ This may represent either overt thrombosis or dysregulated systemic inflammation and requires further study.

TABLE 1] Patient Demographics, Laboratory Values, and Hospitalization Timeline

Age, y	Sex	At Index Admission			Days Between Admissions, No.	At Re-presentation		Evidence of Thrombosis During Re-presentation	Death (Cause)
		Length of Stay, d	Last C-Reactive Protein, mg/L	Last D-Dimer, ng/mL		C-Reactive Protein, mg/L	D-Dimer, ng/mL		
81	F	4	3	450	3	173	858	NSTEMI, decreased EF	Y (ARDS, withdrawal)
85	M	3	39	757	7	142	9,334	New RBBB and RAD	Y (cardiogenic, shock)
69	M	1	147	118	4	258	181	NSTEMI	Y (ARDS, shock)
75	F	4	54	699	6	118	>10,000	Never evaluated for VTE	Y (shock)
68	M	7	206	586	1	Never evaluated for VTE	Y (unknown)
71	M	4	255	...	7	173	428	Stroke	Y (ARDS, shock)
69	F	2	13	121	3	100	273	NSTEMI, decreased EF	Y (cardiogenic, shock)
69	M	2	3	386	...	Never evaluated for VTE	Y (ARDS, shock)
80	M	3	170	350	8	39	4,681	Bilateral LE DVT	N

CRP = C-reactive protein; EF = ejection fraction; F = female; LE = lower extremity; LOS = length of stay; M = male; N = no; NSTEMI = non ST segment myocardial infarction; RAD = right axis deviation; RBBB = right bundle branch block; Y = yes.

Several different anticoagulants have been used as DVT prophylaxis both in hospital and after discharge.^{5,17,18} Given the lack of knowledge surrounding thrombus formation, increase in platelet aggregation, increased megakaryocytes, and fibrin deposition, the class of drug for thromboprophylaxis and duration of treatment in COVID-19 remains unknown. The pathophysiologic findings to date arguably can be construed to support the use of anticoagulant, antiplatelet agents, or possibly both. Current society recommendations support the consideration of extended prophylaxis in certain high-risk patients but lack the ability to further define the cohort.¹⁹

Our method of data extraction lends to underreporting of posthospitalization thrombosis. Although we were able to capture all re-presentations within our own institution, we were not able to identify re-presentations to other institutions or death out of the hospital. Thus, we are not able meaningfully to comment on prevalence. Additionally, we do not know each individual's bleeding risk, which would play a significant role in choosing whether to extend DVT prophylaxis to the outpatient setting.

Despite these limitations, we identified nine patients who were clinically stable when discharged from the hospital and likely went on to experience thrombotic complications. The patients were all >68 years of age; most of them had elevated D-dimer at discharge, and all of them had some immobility because they were confined to home after discharge, given the current travel restrictions and quarantine instructions. Furthermore, no patient had both normal CRP and D-dimer at time of discharge, which is likely common in this patient population. Every patient with data showed both markers increased at the time of re-presentation. All patients re-presented within eight days of discharge, which echoes prior studies that depict that the highest risk for thrombosis after hospitalization for a medical illness occurs within nine days.²⁰ This shows that the postdischarge thrombosis risk in COVID-19 seems to behave similar to other medical admission thrombosis.

We believe this case series is a call for further studies regarding extended prophylaxis in this patient population. In line with previous trials of extended thromboprophylaxis in at-risk medically ill patients, the continued use of prophylactic anticoagulation or antiplatelet agents beyond the initial hospital stay may be required until complete recovery from the illness.^{5,6,17,18} Further research is necessary to identify

which patients would benefit most, which medications should be used and the duration of therapy.

Further studies are needed to assess the true incidence of postdischarge thrombotic events and to evaluate anticoagulation strategies in patients with COVID-19.

Shari B. Brosnahan, MD

Alok Bhatt, MD

Jeffery S. Berger, MD

Eugene Yuriditsky, MD

Eduardo Iturrate, MD

Nancy E. Amoroso, MD

New York, NY

AFFILIATIONS: From the Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine (Drs Brosnahan, Bhatt, and Amoroso), the Leon H. Charney Division of Cardiology, Department of Medicine (Drs Berger and Yuriditsky), and the Department of Medicine (Dr Iturrate), New York University Langone Health

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CORRESPONDENCE TO: Shari B. Brosnahan, MD, Division of Pulmonary, Critical Care, and Sleep Medicine, New York University Langone Medical Center, 550 First Ave, Tisch Hospital- 15 W, New York, NY 10016; e-mail: Shari.Brosnahan@nyulangone.org

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