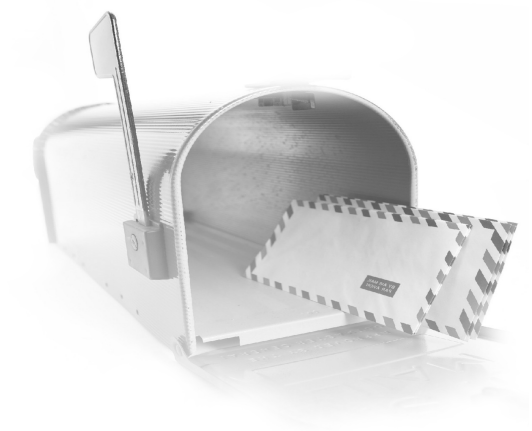

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Letters to the Editor

Pulmonary embolism rate in patients infected with SARS-CoV-2

TO THE EDITOR: Coronavirus disease 2019 (COVID-19) commonly presents with cough, fever, dyspnea, and myalgia [1]. Many patients develop severe complications, including thrombosis. The initial presentation of pulmonary embolism (PE) is similar to that of COVID-19 infection. An early study of patients with COVID-19 in the intensive care unit (ICU) demonstrated a 31% rate of venous thrombosis, 85% of which was PE [2]. A meta-analysis by Henrina *et al.* [3] analyzed 1,237 pooled patients from eight studies and found that venous thromboembolism was associated with higher mortality, need for ICU admission, and mechanical ventilation. To better understand the incidence of PE in a more general population of patients with upper respiratory symptoms suspicious of COVID-19 infection or PE, we studied the incidence of pulmonary embolism in patients presenting to our institution with upper respiratory symptoms during the height of the pandemic. We correlated this with COVID-19 infection status and other clinical characteristics to better understand the association with pulmonary embolism.

Under our Internal Review Board (IRB)-approved protocol (protocol number AAAS9652 approved 3/16/2020 to study patients between 2/28/2020–04/08/2020), we retrospectively queried our radiology record system, Catalyst, to identify reports of patients with a computed tomography angiogram (CTA) for the evaluation of pulmonary embolism during this time period. One hundred and thirty-four patients were identified; however, upon chart review, eight of these patients did not have all of the clinical data available; therefore, 126 patients were included in the study. Demographics and clinical information were obtained via chart review, including if patients were confirmed to have COVID-19 by a reverse transcription polymerase chain reaction test, information on comorbid conditions, highest D-dimer level during hospitalization (reported in μg/mL fibrinogen equivalent units), and clinical course of their disease, including outcomes and treatments. Chest CT scans were reviewed to assess for PE and for the presence or absence of consolidation. Consolidation was defined as a dense opacity in the pulmonary parenchyma that obscured blood vessels in the region. Clinical information regarding DVT, active cancer, and recent surgery was obtained for patients with PE.

Table 1. Demographics and clinical characteristics of COVID-19-positive and COVID-19-negative patients.

	COVID-19-Positive (%)	COVID-19-Negative (%)	*P*
N of patients	51	75	
Average age (range)	52.5 (23–86)	55.6 (24–84)	0.30
Male sex	29 (57)	24 (32)	<0.01
Oxygen saturation, % (range)	94.1 (66–100)	96.7 (88–100)	<0.01
Consolidation	34 (67)	21 (28)	<0.01
DM	7 (14)	12 (16)	0.92
HTN	16 (31)	29 (39)	0.52
Highest D-dimer (range)	5.3 (0.2–20.0)	3.3 (0.3–20.0)	0.20
Positive PE	10 (20)	14 (19)	0.92
PE and DVT	1 (10)	4 (29)	0.27
PE and recent surgery	1 (10)	1 (7)	0.80
PE and cancer	0 (10)	1 (7)	∞

Abbreviations: DM, diabetes mellitus; DVT, deep vein thrombosis; HTN, hypertension; PE, pulmonary embolism.

Student's t-tests and chi-squared tests were used for continuous and categorical variables, respectively, to evaluate differences between the COVID-19-positive and -negative groups and differences in patients with or without pulmonary embolism. Multivariable logistic regression analysis was employed to evaluate the characteristics associated with pulmonary embolism.

Of the 126 patients who met the inclusion criteria for this study, 51 tested positive for SARS-CoV-2 infection and 75 tested negative. Table 1 shows the demographic and clinical information for patients who were COVID-19-positive and COVID-19-negative. Twenty-four of the 126 patients had a PE, a rate of 19%, comprised of 10 COVID-19-positive patients (20%), and 14 COVID-19-negative patients (19%). There was no significant difference in the rate of pulmonary embolism between patients who were COVID-19-positive versus those who were COVID-19-negative. There was also no difference in the average age, rate of comorbid hypertension (HTN), diabetes mellitus (DM), or highest D-dimer between groups.

There was a slight preponderance of male patients who tested positive for COVID-19 infection, which may have been related to sample size. There was a significantly lower average oxygen saturation on presentation in COVID-19-positive patients, likely due to several cases of severely low oxygen saturation in this population. There was a significantly increased rate of consolidation on chest CT in COVID-19-positive patients.

Certain clinical conditions predispose to pulmonary embolism. In patients with PE, we evaluated active cancer, DVT, and recent surgery to assess whether PE may have been provoked by a comorbid condition and whether these associations differed according to COVID-19 status. Table 1 also demonstrates comorbid conditions in patients found to have PE; 1/10 COVID-19-positive and 4/14 COVID-19-negative patients had concomitant DVT, 1/10 COVID-19-positive and 1/14 COVID-19-negative patients had recent surgery, and 0/10 COVID-19-positive and 1/14 COVID-19-negative patients had active cancer. There was no significant difference in any of these comorbid conditions between patients who were COVID-19-positive and those who were COVID-19-negative.

Table 2 shows the multivariable logistic regression analysis of patients with and without pulmonary embolism, demonstrating no difference in the rate of COVID-19 infection. Age, sex, presenting oxygen saturation, and comorbid HTN and DM were not associated with an increased rate of pulmonary embolism. The presence of consolidation on chest CT was associated with a higher risk of PE (OR 34.7, P=0.02). Patients with a higher D-dimer also had a higher risk of PE (OR 1.2, P=0.01). Fig. 1 demonstrates a patient with COVID-19 infection with bilateral consolidations and a pul-

Table 2. Multivariable analysis with outcome of PE. Patients with consolidation had a higher risk of PE [OR 34.69, 95% CI (1.8, 664.31), P=0.02]; patients with higher d-dimer also had a higher risk of PE [OR 1.15, 95% CI (1.03, 1.29), P=0.01].

	(-) PE	(+) PE	OR	95% CI	*P*
N of patients	102	24			
Average age	54.8	52.7	0.98	0.92–1.1	0.73
Male sex	44 (43%)	9 (38%)	0.80	0.13–5.0	0.82
Oxygen saturation, %	95.6	95.7	1.00	0.9–1.1	0.96
Consolidation	40 (40%)	14 (58%)	34.70	1.8–664.3	0.02
DM	13 (13%)	6 (25%)	2.60	0.4–18.0	0.34
HTN	38 (37%)	7 (29%)	2.10	0.3–16.0	0.48
COVID-19	41 (40%)	10 (42%)	0.25	0.0–2.0	0.19
Highest D-dimer (average)	2.9	10.8	1.20	1.0–1.3	0.01

Abbreviations: COVID-19, coronavirus-2019; DM, diabetes mellitus; HTN, hypertension.

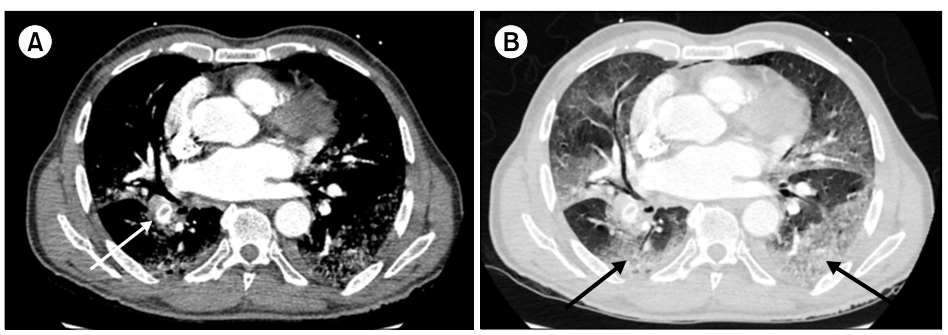

Fig. 1. This figure demonstrates an acute pulmonary embolism (white arrow) in a COVID-19 infected patient in soft tissue **(A)** and lung **(B)** windows. Pulmonary disease is characterized by peripheral and lower lobe predominant ground glass opacities (black arrows), typical of COVID-19 infection.

monary embolus.

Research has shown that D-dimer levels correlate with worse outcomes in COVID-19 (Pernia *et al.*, manuscript under review). We found that elevated D-dimer levels correlated with the incidence of PE, yet there was no increased incidence of PE on chest CT in patients who were COVID-19-positive compared to those who were COVID-19-negative. The role of microthrombi in COVID-19 infection has been controversial but is increasingly recognized as being important in disease pathophysiology. The first reported cases of COVID-19 infection did not identify pulmonary microthrombi [4], which was corroborated by subsequent autopsy [5] and biopsy studies [6]. However, using ultrasound-based minimally invasive autopsies, a study from Brazil demonstrated that the majority of patients had pulmonary microthrombi in arterioles in both damaged and preserved regions of the lung. This group also found secondary signs of coagulation cascade activation, including endothelial tumefaction and large numbers of megakaryocytes [7]. The disparity in pathologic findings may have been due to the limited number of patients and the method of pulmonary parenchymal sampling in studies lacking pulmonary microthrombi. Together, these studies suggest that microthrombi may be the cause of elevated D-dimer levels and perfusion abnormalities in these patients. Given the lack of randomized trials assessing anticoagulation in COVID-19 infection, widespread use of general venous thromboembolism prophylaxis guidelines for hospitalized patients has also been employed [8].

Studies have demonstrated an increased incidence of thrombotic events in patients with COVID-19 [2, 9], and the low rate of PE demonstrated in our study was an unexpected finding. In thrombosis, as well as in diabetes research, distinction is made between microvascular and macrovascular thrombosis. This distinction is also applicable in COVID-19 infection. Clinical imaging of microthrombi is challenging given the limits of resolution in diagnostic radiology [10]. Dual-energy CT is a technique that uses differences in beam attenuation at different energies to assess material densities within tissue. It has been used to demonstrate differences in pulmonary perfusion secondary to pulmonary embolism. A recent study published in Lancet Infectious Diseases using dual-energy CT to assess patients with COVID-19 infection demonstrated striking perfusion abnormalities in the absence of visualized pulmonary embolism [11]. Widespread use of dual-energy CT to assess pulmonary perfusion in patients with COVID-19 may provide important clinical information in the absence of pulmonary embolism on chest CT.

The limitations of our study include the fact that it was a single center study. Given the widespread nature of the pandemic and numerous early reports of increased thrombotic events, clinicians may have changed their ordering practices during this time period. The data available for this retrospective study allowed us to assess the rate of pulmonary embolism in patients with COVID-19 versus those with similar symptoms without COVID-19. A prospective study may have provided additional information as to whether these patients went on to develop pulmonary emboli at a later time point. However, given that these limitations equally affected the COVID-19-negative and -positive populations, it is unlikely that they would have introduced significant differences in the conclusions drawn from these data.

Our study demonstrated no difference in the rate of pulmonary embolism in patients with COVID-19 compared to patients presenting with similar symptoms without COVID-negative. Mounting evidence suggests that patients with severe COVID-19 have diffuse microthrombotic disease resulting in pulmonary parenchymal infarcts. Further studies testing this hypothesis will provide evidence to strengthen the guidelines for treating microthrombotic disease in patients with COVID-19 infection.

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COVID-19 in a patient with chronic myelomonocytic leukemia: a twisting tale

TO THE EDITOR: Chronic myelomonocytic leukemia (CMML) is a rare disease characterized by persistent clonal monocytosis. Specific features of CMML, such as autoimmunity and a tendency to mount a brisk leukemoid reaction, could be potentially relevant during the COVID-19 pandemic [1]. In this report, we describe a case of CMML with COVID-19 and discuss the relevant evidence-based management considerations.

A 30-year old man was diagnosed with CMML-2 at our hospital in December 2019. Bone marrow (BM) examination showed marked granulocytic hyperplasia, monocytosis, 5% blasts, and the absence of dysplasia (Fig. 1A). BM biopsy showed grade-1 reticulin fibrosis. Peripheral blood (PB) showed 6% blasts. Whole exome sequencing of PB revealed the following mutations (mutant allele, %): FLT3-TKD (30.7%), ASXL1 (49%), SETBP1 (51%), NRAS (4.4%), and CBL (10%). Treatment with hydroxyurea (30 mg/kg/day) resulted in a ~50% reduction in spleen size and reasonably controlled total leucocyte counts (TLC) to ~30–40×10^9/L. In June 2020, he presented with a 2-week history of low-grade fever, joint pain, fatigue, and abdominal discomfort. An abdominal examination revealed significant hepatosplenomegaly. CBC showed a hemoglobin level of 7.9 g/dL, TLC of 451×10^9/L (14% monocytes, absolute lymphocyte count/ALC- 10×10^9/L, and 7% myeloblasts), and platelets- 27×10^9/L. BM revealed 5–6% blasts, showed marked granulocytic hyperplasia, dysplasia, and evidence of toxic granules and vacuolation in the granulocytic series suggestive of leukemoid reaction (Fig. 1B). Antinuclear antibodies were positive. A direct anti-globulin test was negative. The ELISA-based PB cytokine profile revealed elevated levels of IL-6 (12.0 pg/mL, normal < 7 pg/mL) and TNF-α (1153.0 pg/mL, normal < 29.4 pg/mL), and normal levels of IL-1β level. Coagulogram showed prolonged PT (INR-1.62) and APTT (46 sec, control < 34 sec), both of which failed to correct in the mixing study. Lupus anticoagulant was negative. Factor assay showed reduced Factor X activity (31%, normal range, 50–100%), suggesting an acquired factor X inhibitor. The fibrinogen level and activity of other clotting factors were normal. D-dimers were elevated. The patient denied any history of surgery. Infection screening, including viral markers, HIV, blood cultures, and work-up for malaria, typhoid, and tuberculosis, was unremarkable. COVID-19 testing of nasopharyngeal and oral samples by RT-PCR was negative on 10-7-2020. Therefore, an autoimmune etiology was considered for leukemoid reaction, an acquired factor X inhibitor, and the pro-inflammatory state. The hydroxyurea dose increment worsened the thrombocytopenia and failed to achieve an organ response. The factor X inhibitor disappeared after leucoreduction with hydroxyurea. Considering the patient's young age, good performance score, and progressive disease, we started FLT3-mutated AML-like intensive chemotherapy (IC) with '7+3' plus midostaurin on 15–7-2020. On day-7, the patient had febrile neutropenia (FN) and diarrhea, due to neutropenic enterocolitis (NEC). FN and NEC were treated with broad-spectrum antibiotics and empirical antifungals. Midostaurin (50 mg BID) and G-CSF were started from day-8 onwards. Infection screening, including assessing procalcitonin, serum galactomannan, blood and stool cultures, and stool for Clostridium difficile toxin were negative. Due to intense myelosuppression, midostaurin was withheld on day-14. The patient complained of cough on day-14, due to which we performed CT of the chest and abdomen. The CT scan was clear, except for a few tiny lung nodules. On day-15, the patient experienced worsening respiratory distress and hypoxemia (SpO_2-85% despite 90% FiO_2). On the same day, CBC showed absolute lymphopenia, a sudden surge in neutrophils (10-fold increase), and a 5-fold increase in neutrophil: lymphocyte ratio (NLR). Considering the possibility of G-CSF-induced acute respiratory distress syndrome (ARDS), G-CSF administration was stopped. A repeat COVID-19 test on the nasopharyngeal sample on day-15 using RT-PCR was positive. The patient was shifted on mechanical ventilation in the intensive care unit and was treated with dexamethasone, hydroxychloroquine, and azithromycin in addition to supportive care, including platelet transfusions. The patient succumbed to respiratory failure on day-16. Anti-COVID-19 therapies such as Remdesivir, convalescent plasma, or anti-cytokine drugs could not be administered due to non-availability. The complete clinical course of the patient is shown in Fig. 1C.

Hyperleucocytosis (TLC > 100×10^9/L) at diagnosis is uncommon in CMML, but occasionally manifests during leukemoid reaction [2, 3]. Patients with proliferative CMML have