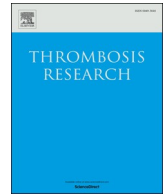




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Letter to the Editors-in-Chief

Venous thromboembolism and coronavirus disease 2019 in an ambulatory care setting - A report of 4 cases



The clinical manifestations of coronavirus disease 2019 (COVID-19) vary widely from asymptomatic to life-threatening illness. According to early data from China, an estimated 80% of infected patients with clinical disease experience mild symptoms, such as fever, dry cough, myalgia, diarrhea or fatigue [1]. Subsequently, it was assumed that these patients can be managed entirely at home. The same data material proposed that around 20% of patients develop severe or critical disease, with pneumonia being the most frequent manifestation [1].

It has been established that coagulation abnormalities are common features in inpatients with COVID-19. These include elevated D-dimer, fibrinogen and fibrin degradation products (FDPs), prolonged prothrombin time, and activated partial thromboplastin time. Elevated D-dimer, fibrinogen and FDPs support the presence of a hypercoagulable state in these patients. Moreover, markedly elevated D-dimer levels have been shown to be a poor prognostic factor in hospitalized patients [2]. Several recent publications have reported a high VTE incidence among patients admitted to an intensive care unit (ICU), ranging from 20 to 40%, despite the administration of thromboprophylaxis [3–5]. This has prompted the use of higher doses of thromboprophylaxis in several institutions. Subsequently, these findings, as well as the coagulation abnormalities present in COVID-19 patients, support the presence of a hypercoagulable state.

The International Society on Thrombosis and Haemostasis (ISTH) and the American Society of Hematology now recommend using pharmacological thromboprophylaxis in all hospitalized patients with COVID-19, if the risk of thromboembolic events outweighs the risk of bleeding [6,7].

As of today, almost all reports addressing VTE in COVID-19 patients have included hospitalized patients, and particularly ICU admitted patients [3–5,8–10]. In this case series, we report four cases of VTE in COVID-19 outpatients (Table 1). All patients have provided written consent for publication.

1. Case 1

A 55-year old male was referred to the hospital with suspected deep vein thrombosis (DVT) after two days of unilateral pain and swelling of the left lower extremity. He had a family history of DVT. The patient had recently been experiencing fever and myalgia for two weeks, during which time he had been almost entirely bedridden. However, the symptoms had been gradually improving during the last four days.

Clinical examination revealed tenderness on calf compression and on palpation along the deep veins of the thigh. There was a 1 cm difference in the leg circumference. Laboratory tests revealed an elevated D-dimer level. Compression ultrasonography (CUS) revealed no DVT, but because of high clinical suspicion the patient was scheduled for repeat CUS one week later. A nasopharyngeal swab for SARS-CoV-2 PCR was secured due to his flu-like symptoms revealing a positive

result. Repeat CUS one week later confirmed the presence of a DVT in the left leg, and anticoagulation with apixaban was initiated.

2. Case 2

A 39-year old male had been in home isolation for 27 days after he tested positive for SARS-CoV-2. His initial symptoms were fever, cough and diarrhea. He had been entirely bedridden during most of this time. He had been gradually improving until the last two days prior to presenting to the hospital, when he started experiencing increased dyspnea and pleuritic chest pain.

On examination, the patient was febrile (temperature of 38.4 °C), had a pulse rate of 95/min, respiratory rate of 21/min, and blood pressure of 135/98 mmHg. His oxygen saturation was 95% on room air. Lung auscultation was normal and biochemical markers did not point towards a bacterial pneumonia. There were no signs of DVT. Seen in context with an elevated D-dimer level and a moderate pretest clinical probability, a computed tomography pulmonary angiogram (CTPA) was warranted, which showed bilateral pulmonary embolism (PE) with proximal extension to the lobar arteries. The patient was subsequently admitted to the hospital but was discharged the following day with prescribed apixaban.

3. Case 3

A 57-year-old male was brought to the emergency room (ER) four weeks after testing positive for SARS-CoV-2. His symptoms initially consisted of a moderate fever, dyspnea, dry cough and headache. His chronic back pain worsened during the infection and he was immobilized for the last two weeks prior to admission. Two days before admission, he experienced worsening of his condition with fever, rigors and left-sided chest and shoulder pain aggravated by inspiration.

On examination the patient was hemodynamically stable (blood pressure 142/75 mmHg; pulse rate 65/min). He was slightly hypoventilating (respiratory rate 10/min) with an oxygen saturation of 96% on room air. Arterial blood gas analysis revealed slight hypoxemia with a PaO₂ 10,3 kPa. Troponin I levels were within normal range. There were normal clinical findings, with no signs of DVT. Based on respiratory symptoms, a moderately elevated pretest clinical probability for PE, and an elevated D-dimer, a CTPA was performed showing a filling defect in the left lower lobe consistent with PE. Treatment with apixaban was initiated, and the patient was discharged the same day.

4. Case 4

A 55-year old male presented with a three-week history of diarrhea, dry cough, dyspnea and fatigue. Nearly one week prior to admission, he sought medical advice from a general practitioner and received

Table 1
Clinical and biochemical characteristics of the four patients.

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	56	39	57	55
Gender	Male	Male	Male	Male
Weight (kg)	91	110	100	100
BMI	27,2	36,3	29,3	29,9
Comorbidity & VTE risk factors	Varicose veins, family history of VTE	DCM, hypertension	OSA, asthma, chronic back pain	Asthma, hypertension
Duration of symptoms before diagnosis of VTE (days)	≈ 14	≈ 30	≈ 30	≈ 21
Duration of immobilization (days)	≈ 14	≈ 10	≈ 21	≈ 14
Clinical probability of VTE according to Wells' criteria	Moderate	Moderate	Moderate	High
Type of VTE	DVT	PE	PE	PE
CRP (< 5 mg/L)	12	35	50	77
Thrombocytes (150–450 × 10 ⁹ /L)	295	192	223	297
D-dimer (< 0,5 mg/L FEU)	8,2	2,6	2,1	> 20
PT-INR (0,8-1,2)	–	0,9	1,1	1,1

FEU: Fibrinogen Equivalent Unit. BMI: Body Mass Index, calculated as weight in kilograms divided by height in meters squared. OSA: Obstructive sleep apnea. DCM: Dilated cardiomyopathy.

Immobilization: Confined to bed/couch/chair > 50% of the day.

Amoxicillin for suspected lower respiratory tract infection. Due to increasing dyspnea and new-onset hemoptysis, he was referred to the ER.

On examination his blood pressure was 126/87 mmHg, respiratory rate 24/min, and oxygen saturation was 82% on room air. Lung auscultation revealed bilateral coarse crepitations. There were no signs of DVT. Arterial blood gas analysis showed a severe respiratory failure (PaO₂ 6,5 kPa). Due to his high-risk profile and markedly elevated D-dimer, a CTPA was performed. CTPA revealed bilateral PE extending to the lobar arteries, as well as bilateral consolidations and ground-glass opacifications. Nasopharyngeal swab confirmed SARS-CoV-2 infection. Treatment with therapeutic dose dalteparin was initiated. The patient gradually improved over the following days without the need for ventilatory support and was discharged to a rehabilitation facility on edoxaban after 7 days.

Østfold hospital, Norway, has a catchment area of 320,000 inhabitants and provides health services to the entire population of the Østfold province in Norway. As of April 30th, 2020, 384 patients have been diagnosed with COVID-19 in Østfold province with all being diagnosed at the Østfold hospital's laboratory. Of these, 64 (17%) patients were admitted and treated as inpatients, including 13 (20%) in the ICU, of whom 12 required assisted ventilation. Of all admitted patients, VTE occurred only in one patient, despite receiving thromboprophylaxis, 18 days into his stay in the ICU.

Our case series clearly illustrates that VTE does not occur only in critically ill and immobilized inpatients, and that outpatients in home isolation are also at risk of developing VTE. This is also highlighted by a study done in Milan, Italy, where 50% of the diagnosed thromboembolic events were diagnosed within 24 h of admission to hospital [9]. In general, our four patients were relatively young (39–57 years) males, were moderately obese (BMI 27–36), had low comorbidity profile and had no major risk factors for VTE. All were, however, bedridden for 1.5 to 3 weeks prior to diagnosis, except for case 3, who had to sit upright due to his back pain. Case 2 and 3 both presented at the ER in the early stages of the outbreak, prior to reports on the potential increased risk of VTE associated with COVID-19 infection. They reported a similar history with a secondary exacerbation, and there were no clinical or biochemical markers suggesting a bacterial superinfection. They both had an elevated D-dimer level, raising suspicion of an underlying PE. Case 4, on the other hand, presented later in the outbreak. He gradually declined at home over weeks and had a severe respiratory failure upon presentation at the hospital. His markedly elevated D-dimer level raised the suspicion of a PE and hence the need to perform a CTPA, as a bacterial infection was initially suspected. However, knowledge about the risk of developing a VTE may also have contributed to raising the suspicion of a PE in this case.

Several publications report a relatively high incidence of VTE in hospitalized patients with COVID-19 infection, particularly in ICU treated patients. A French study comparing a cohort non-COVID-19 Adult Respiratory Distress Syndrome (ARDS) to COVID-19 ARDS patients showed significantly higher rates of thrombotic complications, mainly PE, in COVID-19 ARDS than in non-COVID-19 ARDS (2.1% vs 11.7%, $p < 0.008$) [5]. This may indicate that the disease itself induces a hypercoagulable state, possibly through the interplay between the severe inflammatory drive and the coagulation system leading to thrombo-inflammation and its consequences including dysregulation of the coagulation/fibrinolytic systems, neutrophils recruitment, platelet and endothelial cell activation.[2,11] Although the mechanisms underlying this hypercoagulable state are not fully understood, it is likely that this thrombo-inflammatory status, together with the stasis caused by immobilization, causes the increased risk of venous thrombosis. It has been postulated that the high incidence of VTE seen in COVID-19 patients may partially be explained by pulmonary thrombosis in situ. None of our patients diagnosed with PE showed signs of DVT, and an additional lower extremity compression ultrasound (CUS) was consequently not performed to establish the presence of a concurrent DVT.

Our report suggests that patients who are observed at home are also at risk of developing VTE. Thus, these patients should be informed about the potential risk of acquiring VTE during a COVID-19 infection, and that worsening dyspnea and/or leg swelling should prompt immediate contact with their primary care providers to conduct the proper work-up for VTE. D-dimer is best documented to exclude VTE if negative, however, it has been shown to be one of the most important prognostic factors in admitted COVID-19 patients. Obtaining D-dimer may also need to be considered as a standard baseline test in all patients with confirmed COVID-19 infection, and later on during the follow-up of home- confined, bedridden patients.

Obviously, we cannot advocate thromboprophylaxis in all COVID-19 patients in an ambulatory care setting based on this case series. Our patients were mainly bedridden during their home confinement, nevertheless, we do not know to what extent immobilization has contributed to VTE. Since immobilization is an established risk factor of VTE, it is plausible that this tendency is more pronounced in the hypercoagulable state caused by COVID-19. Therefore, non-hospitalized patients should be contacted and assessed on a regular basis with regards to their degree of mobility. Alternatively, we would suggest considering prophylactic anticoagulation in patients largely immobilized during the course of the disease, provided they are not at high risk of bleeding.

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