BRIEF COMMUNICATION

Pulmonary embolus in patients with COVID-19: an Australian perspective

Danielle H. Robinson 1, Hari Wimaleswaran2,3,4 Christine F McDonald2,3 Mark E. Howard2,3,4 and Abbey Willcox1,5

Departments of 1Clinical Haematology, and 2Respiratory and Sleep Medicine, Austin Health, 3Institute for Breathing and Sleep, 4Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, and 5Australian Centre for Blood Diseases, Monash University, Melbourne, Victoria, Australia

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Abstract
Pulmonary embolus (PE) is a known complication of coronavirus disease 2019 (COVID-19). The diagnosis of PE in our hospitalised patients with COVID-19 correlated with more severe disease and occurred despite the use of routine thromboprophylaxis. Higher D-dimers were seen on admission in patients who developed PE and rose at PE diagnosis, suggesting a role for D-dimer in risk stratification.

While pulmonary embolus (PE) is known to occur in hospitalised critically unwell patients, data have emerged indicating this risk may be higher in those hospitalised with coronavirus disease 2019 (COVID-19) and remains high in this group despite prophylactic anticoagulation.1 Similar to findings in other critically unwell patient populations, PE prevalence is also higher in patients with COVID-19 admitted to critical care units1–3 when compared with general wards.

Some of the earliest studies originating from China demonstrated that elevated D-dimer levels in patients with COVID-19 correlated with poorer patient outcomes,4 and that levels are often higher in patients admitted to critical care units.5 Additionally, associations between the development of PE and elevated D-dimer levels in patients with COVID-19 have been described.6–8

Conjecture remains regarding the pathophysiology of pulmonary thrombosis in COVID-19, and whether these dots represent in situ immune-mediated thrombosis secondary to endotheliitis or a true embolic phenomenon.9,10 Furthermore there is uncertainty around ideal venous thromboembolism (VTE) prophylaxis in COVID-19 infected patients and in particular whether they need ongoing chemical thromboprophylaxis on discharge from hospital.11

We performed a retrospective analysis of patients with COVID-19 hospitalised at Austin Health, a large tertiary metropolitan hospital, from 19 March to 27 August 2020. This study was conducted in accordance with the Austin Health Human Research Ethics Committee.

Inclusion criteria included age ≥18 years and a positive polymerase chain reaction test for SARS-CoV-2 from a nasopharyngeal swab. For patients who were transferred to subacute hospital sites or had multiple admissions related to COVID-19, the first admission was considered the index admission. Similarly, duration of hospital stay related only to that index admission. The National Institutes of Health (NIH) guideline was used to calculate severity of COVID-19.12

The primary outcome was the incidence of PE during admission or up to 6 months post-discharge following hospitalisation with COVID-19 (none of whom was discharged on VTE prophylaxis).

C-reactive protein (CRP), D-dimer and ferritin blood levels were extracted from electronic medical records at hospital presentation, PE diagnosis and follow up. Follow up occurred in a dedicated COVID-19 respiratory outpatient clinic at 8 weeks and 6 months post-discharge.

Data were analysed with one-way analysis of variance using Tukey’s multiple-comparison post-test or paired
Forty-eight patients were admitted with severe/critical COVID-19. Of this group, five (10%, 95% confidence interval (CI) 3.5–22.7) patients developed a PE either during their index admission (n = 3) or on representation to hospital (n = 2) (Table 1). The PE diagnosis occurred at a median 15 (12–33) days after COVID-19 diagnosis. Of the two patients who were diagnosed with PE on representation to hospital, one had been transferred to a subacute rehabilitation hospital only 24 h prior to their PE diagnosis. The other patient had been successfully discharged into the community after their index admission and had not been readmitted to any hospital prior to their representation with PE.

All patients, except for the patient diagnosed with PE on day of admission to hospital, received VTE prophylaxis (enoxaparin 40 mg daily) prior to the development of thrombosis of an average 13 days duration. One patient developed a clot in the main branch of the pulmonary arterial vasculature. The remaining four patients developed segmental (n = 2) and subsegmental PE (n = 2). PE was diagnosed via computed tomography pulmonary angiogram for all patients and all patients received apixaban (loading then 5 mg twice daily) as anticoagulation post-diagnosis.

Only one patient, who had developed bilateral sub-segmental PE, had a lower limb Doppler ultrasound that demonstrated a deep vein thrombosis.

Of the patients who developed PE, 80% were admitted to ICU, with a median hospitalisation duration of 14 (12–25) days and median ICU admission duration of 4 (3–9) days.

The 43 patients with severe/critical COVID-19 who did not develop PE had a median hospitalisation duration of 9 (7–16) days; of the 42% requiring ICU support, their median duration of ICU admission was 4 (3–11) days.

Those patients who developed PE had higher levels of CRP and D-dimer on presentation to hospital, and these levels had further increased at the time of PE diagnosis (Table 2). Collectively patients with severe/critical COVID-19 had higher presentation CRP compared with non-severe group (median 18.8 vs 95.0, $P < 0.005$, 95% CI 30.12–108.7). However, there was no difference in CRP at presentation between patients with severe/critical disease who went on to develop PE compared to those who did not (median 87.4 vs 157.0, $P = 0.39$, CI −129.4 to 38.13). Similar findings were seen with ferritin levels (Table 2). However, patients who developed PE had higher D-dimer at presentation than those with non-severe disease (median 2237 vs 751, $P = 0.02$, 95% CI 569–6781) and those with severe/critical disease who did not develop PE (median 2237 vs 760, $P = 0.007$, 95% CI 850–6330). In those who went on to develop PE, there was a trend towards higher D-dimer at PE diagnosis when compared to their presentation D-dimer; however, given the small numbers this did not reach statistical significance (D-dimer at initial presentation: median 2237, range 1293–14 023; D-dimer at time of PE diagnosis: median 10 157, range 1020–27 757).

| Characteristic | PE during index admission | PE on representation to hospital |
|----------------|---------------------------|----------------------------------|
| **Age (years)** | 72 Male 84.9 | 70 Male 128 |
| **Gender**     | 41 Male 83.5 | 59 Female 74.6 |
| **Weight (kg)**| 58 Male 102 | 72 Male 84.9 |
| **Duration of hospital stay (days)** | 10 | 14 |
| **Duration of ICU stay (days)** | NA | 3 |
| **No. days post COVID-19 diagnosis when event occurred** | 11 | 33 |
| **No. days after admission when event occurred** | 7 | 13 |
| **No. days post-discharge when event occurred** | 12 | 36 |

ICU, intensive care unit.
At 8 weeks follow up there was no clear difference in inflammatory markers between the groups; however, all groups had CRP that remained higher than the laboratory-defined upper range of normal. It was also notable that patients with severe/critical disease who had not developed PE (and thus not discharged on anticoagulation) had persistently elevated D-dimer levels beyond the upper range of normal out to 8 weeks.

Discussion

Despite an increasing body of data surrounding the diagnosis of PE in COVID-19 patients, uncertainty remains around the underlying pathophysiology, as well as optimal dose and duration of thromboprophylaxis.

In keeping with international experience, suggesting that PE is more prevalent in those requiring critical care support, we have demonstrated a relationship between the severity of COVID-19 disease and PE.\textsuperscript{1–3,6,13} A systematic review and meta-analysis of over 33 970 patients with COVID-19 and VTE found a wide disparity between studies in risk of VTE and PE, but overall a prevalence of PE of 3.5% (95% CI 2.2–5.1) in non-ICU patients and 13.7% (95% CI 10.0–17.9) in ICU patients.\textsuperscript{14} In our single-centre study the rate of PE was similar (10%) in patients with severe/critical illness from COVID-19. While it is apparent that COVID-19 causes a prothrombotic phenotype, it remains unclear whether COVID-19 related thrombotic events represent true embolic phenomena or immunothrombosis in situ secondary to endothelial inflammation. SARS-CoV-2 invades pulmonary vascular endothelium via angiotensin-converting enzyme 2 receptors, and along with the cytokines released by activated inflammatory cells and activated platelets and complement, can result in localised immune-mediated thrombosis.\textsuperscript{15} Central artery thrombosis more likely represents true embolic events,\textsuperscript{10} while thrombosis occurring in the more distal segmental and subsegmental vasculature may be more reflective of immune-mediated coagulation.\textsuperscript{16}

While our patient population developed PE all along the pulmonary vasculature, they occurred more commonly distally, echoing autopsy findings on a limited number of COVID-19 patients that demonstrated distal microthrombi within the lungs suggestive of immunothrombosis.\textsuperscript{17}

D-dimer, a fibrin degradation product, has repeatedly been demonstrated to be associated with thrombosis and COVID-19 outcomes.\textsuperscript{6} The patients in our study who developed PE had markedly elevated D-dimer levels on admission compared with those who did not develop PE (even those in the severe/critical disease group) and similarly there was a trend towards a comparative rise in the D-dimer at the time of PE diagnosis when considered relative to presentation levels. This suggests D-dimer may be an effective biomarker in risk stratification for intensification of thromboprophylaxis from the time of hospital admission and reinforces that D-dimer remains a helpful tool in PE diagnosis when considered relative to presentation levels.

All patients in our study received standard thromboprophylaxis at the time of PE diagnosis. The risk of thrombosis in COVID-19 appears to remain elevated despite thromboprophylaxis, raising questions around the optimal dose and duration in this cohort. The role of risk stratifying based on clinical scores of severity or biomarkers such as D-dimer with intensification of thromboprophylaxis in higher risk patients has been discussed. There remains little evidence to inform such practice, although the Dutch National Institute for Public Health recommends using D-dimer thresholds to define COVID-19 patients for whom therapeutic low-molecular-weight heparin is recommended.\textsuperscript{18} Differing doses of thromboprophylaxis are currently being evaluated in international studies.
Our patient group developed PE relatively late in their illness (median day 15) compared to some international studies, raising questions whether patients may benefit from extended prophylaxis beyond their hospital admission. Notably, patients who had severe disease and were not diagnosed with PE had elevated D-dimer and CRP out to 8 weeks. While we can only speculate as to the implications of this, it suggests a persistent inflammatory pro-thrombotic milieu in these patients. Of note, 65% of severe/critical COVID-19 patients received dexamethasone and only one patient from the entire cohort received tocilizumab as COVID-19 therapy, which has the potential to cloud interpretation of elevated CRP and other markers of inflammation at the later time point of 8 weeks. The recommendations regarding extended thromboprophylaxis on hospital discharge have become increasingly unclear, given limited evidence for the use of heparin prophylaxis in other types of thrombotic microangiopathy, the potential for increased bleeding with intensified thromboprophylaxis and the many conflicting guidelines. Recent data suggest that the risk of PE post-discharge from hospital with COVID-19 may be no greater than other medical admissions; however, the British Thoracic Society guidelines suggest that patients who have had critical COVID-19 be considered for extended thromboprophylaxis.

Our study highlights scope for further research into the aetiology of PE in the higher risk severe and critically unwell COVID-19 patients, the optimal dose and duration of thromboprophylaxis and defining biological markers for those who may benefit from intensification of anticoagulation.

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