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ORIGINAL ARTICLE

Low rates of venous thromboembolism in hospitalised COVID-19 patients: an Australian experience

Jeremy Ong,[1] Patricia Walker,[1] Kasha P. Singh,[2] Emma Bishop[2] and Kay Htun[1]

Departments of [1]Haematology, and [2]Infectious Diseases, Peninsula Health, Melbourne, Victoria, Australia

Key words
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Correspondence
Jeremy Ong, Department of Haematology, Peninsula Health, 2 Hastings Road, Frankston, Vic. 3199, Australia.
Email: jeremy.yk.ong@gmail.com

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Abstract

Background: Venous thromboembolic (VTE) complications appear common in hospitalised COVID-19 patients, particularly among critically ill patients in intensive care units. However, there is significant heterogeneity in the reported use of thromboprophylaxis.
Aims: The primary objective was to determine rates of symptomatic VTE in hospitalised COVID-19 patients. Secondary objectives were to assess adherence to an institutional risk-adapted thromboprophylaxis guideline, and rates of bleeding complications.
Methods: A retrospective, single-centre, cohort study was performed in consecutive hospitalised COVID-19 patients over a 6-month period (March to August 2020). Enoxaparin was used as thromboprophylaxis in all patients without a contraindication, with dose adjusted according to disease severity, weight and renal function.
Results: Among 86 hospitalised COVID-19 patients, no VTE were identified. Eighty-one (94%) patients received anticoagulation, with 90% adherence to institutional thromboprophylaxis guidelines. Four bleeding events occurred, with one clinically relevant non-major bleeding event and three minor bleeding events.
Conclusion: Low rates of VTE were identified in hospitalised COVID-19 patients using a risk-adapted thromboprophylaxis protocol.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), rapidly became a worldwide health emergency in 2020. Coagulation abnormalities and venous thromboembolic (VTE) complications, both pulmonary embolisms (PE) and deep vein thromboses (DVT), are common in hospitalised COVID-19 patients.[1] The risk appears highest among critically ill patients in intensive care units (ICU), with an estimated prevalence of 20%.[1–4] However, there is significant heterogeneity in the use of anticoagulation for thromboprophylaxis and routine ultrasound screening for lower limb DVT. In contrast to early reports, several large retrospective studies have not demonstrated the same high risk of VTE among COVID-19 patients.[5–7]

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In response to the initial reports of frequent VTE complications, clinical guidelines were established for the diagnosis, prevention and treatment of VTE in COVID-19 patients.[8] Based on these guidelines, our health service developed an institutional thromboprophylaxis protocol in hospitalised COVID-19 patients (Fig. 1). The primary aim of this study was to determine our local rates of symptomatic VTE in hospitalised COVID-19 patients receiving thromboprophylaxis.

Methods

Patients

A retrospective study was performed of consecutive hospitalised patients with COVID-19 admitted to Peninsula Health, located in Victoria, Australia from March 2020 to August 2020. COVID-19 was confirmed in all patients with a positive reverse-transcription polymerase chain reaction test for SARS-CoV-2 on a nasopharyngeal or

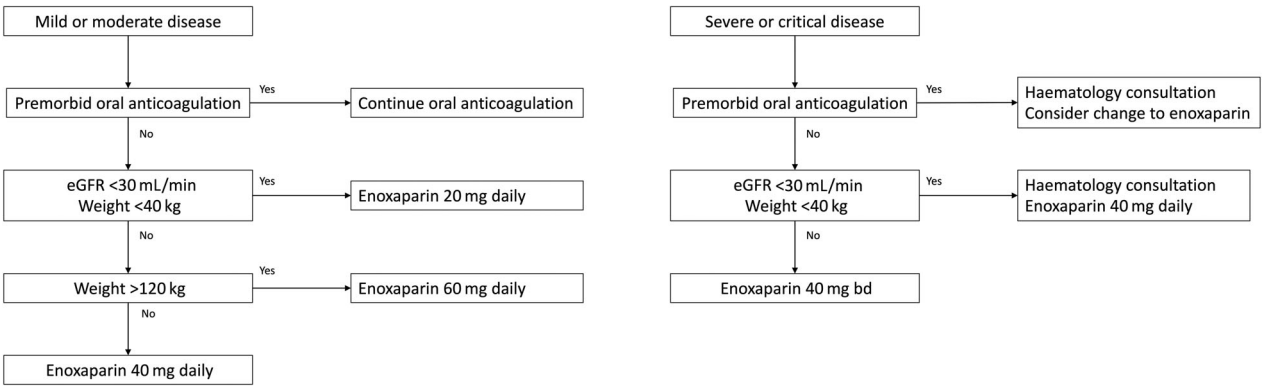

Figure 1 Institutional risk-adapted thromboprophylaxis guideline in hospitalised COVID-19 patients.

sputum sample. Disease severity was categorised as mild, moderate or severe/critical based on national consensus recommendations, combining clinical symptoms and signs, radiological findings, degree of hypoxia and respiratory support, and other features of organ failure.[9]

Thromboprophylaxis

Institutional management guidelines for COVID-19 patients were developed, which incorporated the routine use of anticoagulation as thromboprophylaxis (Fig. 1). Therapeutic anticoagulation was continued in patients with a pre-existing indication. All other patients without a contraindication received enoxaparin, with dose adjusted according to disease severity, weight and renal function. Dosage was not adjusted to D-dimer level.

Outcomes

The primary outcome was radiologically confirmed symptomatic DVT or PE during hospital admission. Routine lower limb screening ultrasounds were not performed. Secondary outcomes were adherence to local thromboprophylaxis guidelines and rates of bleeding complications.

Data collection

Electronic medical records were retrospectively reviewed from the day of admission until death or hospital discharge. Data were collected on patient demographics, disease severity, treatment, laboratory investigations including D-dimer level, anticoagulation use and clinical outcomes. Ethics was approved by the local Human Research Ethics Committee.

Results

A total of 86 patients was hospitalised with COVID-19 between March and August 2020. Median age was 77 years (range 25–97 years), including 48 (56%) females (Table 1). Eighty-three (97%) patients were admitted during the state's second wave in July and August 2020. Forty-one (48%) patients were from a residential aged care facility. Thirty of 41 (73%) patients had cognitive impairment due to dementia or acquired brain injury, with the majority (26/30; 87%) from high-level care facilities. Six (7%) patients had a history of VTE, two of whom were on anticoagulation at the time of admission. A further 14 patients were on anticoagulation for stroke prevention in atrial fibrillation. Twenty-nine (34%) patients had mild disease, 35 (41%) patients had moderate disease and 22 (25%) patients

Table 1 Patient characteristics

Characteristic	*n* (%), total = 86
Median age (range) (years)	77 (25–97)
Female	48 (56)
Living situation	
Residential aged care facility	41 (48)
Home	45 (52)
Weight (kg)	
<40	0 (0)
40–120	56 (65)
>120	4 (5)
No weight recorded	26 (30)
History of VTE	6 (7)
Premorbid anticoagulation	16 (19)
Apixaban	11
Dabigatran	2
Rivaroxaban	1
Warfarin	2

VTE, venous thromboembolism.

Table 2 Disease characteristics

Characteristic	Mild disease	Moderate disease	Severe/critical disease
Number of patients, *n* (%)	29 (34)	35 (41)	22 (25)
Median hospital length of stay, days (range)	18 (1–39)	17 (2–43)	12 (2–49)
Treatment, *n* (%)			
Hydroxychloroquine	0 (0)	0 (0)	1 (5)
Dexamethasone	3 (10)	18 (51)	8 (36)
Remdesivir	0 (0)	9 (26)	8 (36)
Elevated D-dimer, *n* (%)	16/28 (57)	24/33 (73)	21/21 (100)
Mortality, *n* (%)	2 (7)	4 (11)	15 (68)

had severe/critical disease (Table 2). Four patients required care in ICU. Median hospital length of stay was 17 days (range 1–49 days).

Twenty-one (24%) patients died in hospital. The median age of patients who died was 83 years (range 63–97 years). Fourteen (67%) deaths occurred in patients from residential aged care facilities. Only one patient died in the ICU; the remainder had advanced care directives for palliation in the event of severe clinical deterioration.

No in-hospital VTE was diagnosed. No lower limb ultrasounds were performed in any patient during their hospital admission. Six patients were investigated for PE with either computed tomography pulmonary angiogram or nuclear ventilation-perfusion scan.

Eighty-one (94%) patients received anticoagulation, either continuation of pre-existing therapeutic anticoagulation or thromboprophylaxis. In the five patients who did not receive anticoagulation, three patients were admitted for end-of-life care, one patient had a brief admission less than 24 h, and no reason was identified for the other patient. Seventy-three of 81 (90%) patients received anticoagulation as per institutional guidelines. Deviations from the guidelines were noted for eight (10%) patients. Among them, underdosing was noted in six patients for their weight (four patients) and disease severity (two patients). A higher dose than recommended for the disease severity was noted in two patients. Twenty-six (30%) patients had no recorded weight, of which 21 (81%) patients received anticoagulation (enoxaparin 40 mg daily in 19 patients and enoxaparin 20 mg daily in two patients with renal impairment).

Bleeding complications were uncommon, with four (5%) recorded events. One clinically relevant non-major bleeding event occurred in a patient on therapeutic anticoagulation for pre-existing VTE. The three cases of minor bleeding included one patient on pre-existing therapeutic anticoagulation for stroke prevention in atrial fibrillation, one patient on an intensified dose of enoxaparin for their critical illness and one patient on standard dose thromboprophylaxis.

D-Dimer was performed in 82 patients, with elevated levels in 61 (74%) of these patients. D-Dimer was elevated in 57% of patients with mild disease (median level 0.78 μg/mL), elevated in 73% of patients with moderate disease (median level 1.18 μg/mL), and elevated in 100% of patients with severe/critical disease (median level 2.27 μg/mL) (Table 2).

Discussion

Contrary to many other published reports, we observed a low rate of symptomatic VTE among our cohort of hospitalised COVID-19 patients; there were no cases of DVT or PE identified in 86 patients. A recent systematic review of COVID-19 patients reported an overall VTE prevalence of 14%.[1] However, included in this review were studies with low rates of thromboprophylaxis,[3,4,10] or where the use of thromboprophylaxis was not reported.[11–13] Similar to our study, Hill *et al*. reported lower rates of VTE compared with other groups.[5] Within their cohort of 2748 hospitalised patients, VTE was diagnosed in 3.1% of patients. In those not requiring mechanical ventilation, the rate of VTE was only 1.9%. Hanif *et al*. similarly reported VTE rates of 1.7% in 921 hospitalised COVID-19 patients,[6] suggesting that the prevalence of VTE complications in COVID-19 patients may not be as high as initially reported.

Routine use of thromboprophylaxis was high in our cohort, with 94% receiving anticoagulation, including 16 (19%) patients who continued pre-existing therapeutic anticoagulation. High (90%) adherence to institutional anticoagulation guideline was observed, which has likely contributed to the very low rates of VTE observed among our patients. Furthermore, our thromboprophylaxis protocol was intensified for patients with severe/critical illness and obesity, who are most at risk of developing VTE. Risk-adapted thromboprophylaxis was

tolerated well, with no major bleeeding and only one case of clinically relevant non-major bleeding.

The correlation between disease severity and risk of VTE is well established. In their systematic review, Nopp *et al.* report a 7.9% prevalence of VTE in non-ICU patients, compared with 22.7% in ICU patients.[1] Our cohort of inpatients appeared to have less severe disease compared to other published cohorts, likely contributing to our low rates of VTE. We noted that 75% of our hospitalised patients had asymptomatic/mild disease (19 patients; 34%) and moderate disease (35 patients; 41%). Only four patients were admitted to ICU, three of whom required mechanical ventilation.

Patients from residential aged care facilities accounted for 48% of the total hospital admissions, and 67% of mortality. Due to the advanced age of this cohort (median age 83 years; range 66–97 years), and the presence of multiple medical co-morbidities, these patients were commonly deemed unsuitable for treatment escalation, further investigations and ICU support. Therefore, it is possible that VTE was under-reported in this patient population.

Previous studies have shown an association between elevated D-dimer level and VTE, severe disease and mortality in COVID-19 patients.[14,15] Despite low rates of VTE, D-dimer was elevated in most of our patients, including patients with asymptomatic or mild disease. D-Dimer level appeared to correlate with disease severity.

We included consecutive patients and reported high adherence to local thromboprophylaxis protocols; however, we acknowledge that our study has several limitations. It is a single-centre retrospective study with a small sample size. Investigations to detect VTE were infrequently performed, which may underestimate the true prevalence of VTE. Main reasons for the low rate of VTE investigations include the need to avoid spreading the virus within the hospital setting, acute deterioration resulting in rapid death, and deteriorations managed palliatively in frail residential aged care residents. In addition, we reported only symptomatic VTE, which may cause reporting bias due to underreporting of symptoms as almost three quarters of patients from residential aged care facilities had significant cognitive impairment. We assessed patients only during their hospital admission, and therefore outpatient VTE rates following discharge were not reported. However, recent data suggests that post-discharge VTE risk can be as low as 0.6%.[16] Therefore, we felt that the lack of post-discharge data would not significantly alter the overall rate of VTE.

Conclusion

In summary, the present study provides retrospective and observational data on the use of risk-adapted thromboprophylaxis according to disease severity, bodyweight and renal function in hospitalised COVID-19 patients. To our knowledge, this is the only report describing such experience in an Australian setting. Given the small number of patients with severe disease in our cohort, further prospective research is required to better define VTE risk and optimal thromboprophylaxis strategy in these patients.

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