Introduction
Out of the total 29,812 COVID-19 patients in Singapore up to 21 May 2020, the majority have been admitted at Community Care Facilities (CCF) and general wards of Public Healthcare Institutions (PHI). Few patients have required admission to Intensive care Units (ICU). Coronavirus disease 2019 (COVID-19) can lead to coagulation activation and venous thromboembolism (VTE), which comprises macro-vascular thrombosis such as deep vein thrombosis (DVT) and pulmonary embolism (PE), and also micro-vascular thrombosis. Older, bedbound patients and those with underlying medical conditions such as sepsis, malignancy, recent surgery, patients requiring ICU admission and those with a previous history of VTE are at a higher risk.

Text
The incidence of VTE in COVID-19 patients is not definitely established, but recently published studies have reported an incidence rate of 25–27%. Klok et al. reported a higher incidence of VTE in COVID-19 patients admitted to ICU. Acute PE was detected on computed tomography (CT) pulmonary angiography in 23% patients with severe COVID-19. The increasing reports of VTE in ICU patients in recent studies may also be due to increased screening in these high-risk patients.

But there are not many studies reporting the incidence of DVT in non-ICU COVID-19 patients. A study reported that out of the total number of non-ICU COVID-19 patients who had signs of DVT, 50% of them were detected to be positive on Doppler compression ultrasound scan, with the thrombus most frequently detected in the iliac-femoral-popliteal veins. Two single-center studies have reported a 3% and 6% risk of VTE, respectively, in patients admitted to the ward. This risk is

An approach to a perceived risk of venous thromboembolism in non-ICU COVID-19 patients in Singapore

Sohil Pothiawala

Abstract
Coronavirus disease 2019 (COVID-19) can lead to coagulation activation and venous thromboembolism (VTE), with an incidence of around 25–27%. Patients admitted to the intensive care unit (ICU) are at highest risk. There are not many studies reporting its incidence in non-ICU patients. A large number of COVID-19 patients in Singapore, with symptoms ranging from mild to moderate, have been admitted to either Community Care Facilities (CCF) or in general wards of Public Healthcare Institutions (PHI). In case there is a surge of COVID-19 patients, there is a possibility that general wards in PHIs may need to admit an increasing numbers of acutely ill patients, with only the critical ones being admitted to ICU. The incidence of VTE in non-ICU patients is not exactly known and its detection in these patients is challenging. Thus, the healthcare staff managing these patients at the CCFs and general wards at the PHIs should be vigilant and monitor these patients for development of signs and symptoms of deep vein thrombosis, as well as trend D-dimer level. An algorithm for a potential approach to manage VTE in non-ICU COVID-19 patients is described. A prospective study is needed to establish the incidence of VTE in non-ICU patients in Singapore and the predictive value of D-dimer levels to detect this risk, as well as a therapeutic protocol to initiate appropriate pharmacological thromboprophylaxis in these patients.

Keywords
COVID-19, deep vein thrombosis, non-ICU

Corresponding author:
Dr. Sohil Pothiawala FAMS (EM), MRCSEd(A&E), MMed (EM), MBBS, Senior Consultant, Department of Emergency Medicine, Woodlands Health Campus, 2 Yishun Central 2, Singapore, 768024, Singapore. Email: drsohlpothiawala@yahoo.com
higher compared with non-COVID-19 patients who are hos-

pitalized in the wards.\textsuperscript{5,6}

Three CCF centers have been set up in Singapore, at

D’Resort, Singapore EXPO and Changi Exhibition Centre. A

fourth CCF is being set up at Tanjong Pagar Terminal. They

were initially designed to accommodate recovering COVID-

19 patients, but they subsequently started to take in COVID-

19-positive patients with relatively mild symptoms. Also, after

release of the circuit breaker, in case there is a surge of

COVID-19 patients, there is a possibility that general wards in

PHIs may need to admit increasing numbers of acutely ill

patients, with the critical ones being admitted to ICU. The

detection of PE and DVT may be challenging in non-ICU

COVID-19 patients. The exact incidence of VTE in this group

of patients is not known. Some of these patients already suf-

fer from shortness of breath due to COVID-19, occasionally

associated with borderline low oxygen saturation, thus sus-

pecting a diagnosis of PE may be more difficult. Moreover,

doctors are primarily focusing on the respiratory symptoms,

and hence systematic examination of the lower limbs for signs

of DVT is often overlooked. Therefore, healthcare staff man-

aging these patients at the CCFs and general wards at the

PHIs should be vigilant and monitor these patients for devel-

opment of signs and symptoms of VTE (e.g. DVT and PE).

The exact relationship between D-dimer level and

COVID-19, and the change in level during disease progres-

sion, is not fully studied. Cui et al. showed a D-dimer cut-off

value of > 1.5 µg/ml had a sensitivity of 85%, a specificity of

88.5%, and a negative predictive value of 94.7% to predict

VTE.\textsuperscript{1} Another study reported that a D-dimer cut-off

value of 1.57 µg/ml had a sensitivity of 95.7%, specificity of

29.3%, positive predictive value of 19% and negative predictive

value of 97.5% to rule out asymptomatic DVT. The prevalence of

DVT was 3.8%, 10.5% and 25.8%, when D-dimer was catego-

rized into the range of 1.0–1.8 µg/ml, 1.801–2.65 µg/ml and

>2.65 µg/ml, respectively.\textsuperscript{11}

Current international guidelines recommend thrombo-

prophylaxis with low-molecular-weight heparin (LMWH) or

unfractionated heparin for ICU patients with confirmed VTE,

or those who are at a higher risk of developing VTE.\textsuperscript{12} A

study by Klok et al. recommends pharmacological thrombo-

prophylaxis for all COVID-19 patients admitted to the ICU.\textsuperscript{2}

Some studies recommend administration of prophylactic
dose of LMWH in all hospitalized COVID-19 patients.\textsuperscript{13}
Due to patient surge during this pandemic, an increasing number of acutely ill patients may be admitted in the non-ICU setting. As these patients may at higher risk of developing VTE as compared with the low-risk patients, they may need to be initiated on prophylactic thromboprophylaxis, even in the absence of confirmed VTE at the time of admission. When to initiate anticoagulation remains controversial. For now, these decisions must be made on a case-by-case basis, considering the risk of VTE. Rather than treating all COVID-19 patients in non-ICU setting with prophylactic anticoagulation, these patients should maintain adequate hydration and they should also be encouraged to mobilize and perform static exercises. In patients without risk factors for hemorrhage, thromboprophylaxis may be reasonable for those with a baseline D-dimer level >1.5 µg/ml. Healthcare staff at CCFs and in general wards of the hospitals should regularly monitor patients for development of signs and symptoms of DVT, as well as D-dimer level trend. If there is a clinical suspicion of a patient developing VTE or a rising D-dimer level, the patient should be promptly referred to the hospital for Doppler ultrasound scan for DVT or CT pulmonary angiography for PE (Figure 1). This will aid early diagnosis, initiate anticoagulation and avoid complications.

Conclusion
Looking at the scarcity of data regarding the risk of VTE in non-ICU patients to date, and given that the majority of patients are currently being admitted in non-ICU setting in Singapore, a higher cut-off level for D-dimer might be necessary for the diagnosis of VTE in non-ICU COVID-19 patients. It is also reasonable to conclude that anticoagulation should not be initiated only based on the D-dimer level; but a high index of suspicion, combined with frequent examination for signs and symptoms of VTE and a rise in D-dimer level, may suggest the need to initiate thromboprophylaxis. A prospective study is needed to establish the incidence of VTE in non-ICU patients in Singapore and the predictive value of D-dimer levels to detect this risk, as well as a therapeutic protocol to initiate appropriate pharmacological thromboprophylaxis in these patients.

Acknowledgements
None.

Author contribution
SP conceived the idea for the manuscript and also contributed to the writing and editing of the review.

Availability of data
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Ethical approval
Not applicable.

Informed Consent
Not applicable.

Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Trial Registration (where applicable)
Not applicable.

Meeting
This manuscript has not been presented in abstract form at any meeting.

ORCID iD
Sohil Pothiawala https://orcid.org/0000-0002-4789-4326

References
1. Cui S, Chen S, Li X, et al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 1421–1424. doi:10.1111/jth.14830.
2. Klok FA, Kruip MJHA, Van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191: 145–147.
3. Grillot F, Behr J, Calame P, et al. Acute pulmonary embolism associated with COVID-19 pneumonia detected by pulmonary CT angiography. Radiology 2020 Apr 23. [Epub ahead of print]. doi:10.1148/radiol.2020201544.
4. Marone E and Rinaldi L. Upsurge of deep venous thrombosis in patients affected by COVID-19: Preliminary data and possible explanations. J Vasc Surg Venous Lymphat Disord 2020; 8: 694–695.
5. Middeldorp S, Coppers M, van Happs TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020 May 5; [Epub ahead of print]. doi:10.1111/jth.14888.
6. Lodigiani C, Lapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020; 191: 9–14.
7. Johnson ED, Schell JC and Rodgers GM. The D-dimer assay. Am J Hematol 2019; 94: 833–839.
8. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020; 395: 1054–1062.
9. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019-novel coronavirus-infected pneumonia in Wuhan, China: A retrospective cohort study. Eur Respir J 2020; 55: 200011. doi:10.1183/13993003.00111720.
10. Criel M, Falter M, Jaeken J, et al. Venous thromboembolism in SARS-CoV-2 patients: Only a problem in ventilated ICU patients, or is there more to it? Eur Respir J 2020; [Epub ahead of print]. doi:10.1183/13993003.01201-2020.
11. Rodríguez PD, Cervilla-Muñoz E, Ordieres-Ortega L, et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. Thromb Res 2020; 192: 23–26.
12. Spyropoulos AC, Levy JH, Agno W, et al. Scientific and Standardization committee communication: Clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020 May 27; [Epub ahead of print]. doi:10.1111/jth.15299.
13. Thachil J, Tang N, Gando S, et al. International Society on Thrombosis and Haemostasis (ISTH) interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020; 18: 1023–1026.