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LETTER TO THE EDITOR

Global haemostatic tests demonstrate the absence of parameters of hypercoagulability in non-hypoxic mild COVID-19 patients: a prospective matched study—Reply to comment from Muzaffar et al.

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To the editor,

We thank Muzaffar et al. [1] for providing feedback on our study [2]. The aim of our study was to evaluate the haemostatic profile of mildly ill and severely ill COVID-19 patients. We demonstrated the lack of hypercoagulability among mildly ill COVID-19 patients who did not require oxygen supplementation, an aspect not well evaluated in existing literature. On the other end of the clinical spectrum, our study reaffirmed that critically ill COVID-19 patients had a hypercoagulable state [3, 4] with no hyperfibrinolysis seen on thromboelastography (TEG) profiling and this also correlated well with parameters seen on clot waveform analysis as well as conventional haemostatic tests.

Public health measures in Singapore previously had a containment strategy till October 2021, where most SARS-CoV-2 positive patients were isolated in hospitals or community care facilities, where ambulant patients who had mild COVID-19 were not given pharmacological thromboprophylaxis. Our findings that mild COVID-19 patients lack hypercoagulability provided evidence supporting our national guidelines (National Centre for Infectious Diseases, Singapore) [5] which recommended standard thromboprophylatic dosing using low molecular weight heparin or unfractionated heparin only in severe COVID-19 inpatients or those who have a PADUA prediction score of ≥ 4. We note that full dose anticoagulation in critically ill patients with COVID-19 remains controversial with no increased in survival to hospital discharge or a greater number of days free of intensive care support [6].

With regards to methodology, TEG using the TEG 6s Hemostasis Analyzer was performed with whole blood in 3.2% trisodium citrate tubes within 1 h of venesection. As testing involves pipetting whole blood into the kaolin based multi-channel cartridge (NEW TEG® 6s Global Hemostasis) that provides four assays (Kaolin TEG, Kaolin TEG with Heparinase, Rapid TEG, TEG Functional Fibrinogen), full personal protective equipment (N95 mask, disposable gown and gloves) was worn as per institutional infection control guidelines.

While we described 2 patients in the mild COVID-19 category developing worsening illness (moderate COVID-19 illness), none of our patients enrolled as mild COVID-19 crossed over to the severe COVID-19 category. From practical standpoint, the complete exclusion of superimposed sepsis from secondary infections was not possible. However, none of the 20 patients had documented co-existing infections or positive microbiology tests (apart from SARS-CoV-2 PCR) during review of their clinical notes. Our patients were followed up closely by the medical/infectious disease team during the entire hospitalization. If any patient showed evidence of deterioration or concomitant infection, the patient would be transferred to intensive care unit for closer monitoring. Moreover, our center has criteria for consideration for transfer to the ICU should patients develop hypoxemia ($SaO_2 < 93\%$), elevated

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Table 1 Coagulation Index comparing mildly ill COVID-19 patients with severely ill COVID-19 patients

	Mildly Ill COVID-19 patients (n = 10) Median (IQR)	Severely Ill COVID-19 patients (n = 10) Median (IQR)	p-value
Coagulation Index[a]			
Baseline	2.3 (1.2, 3.7)	3.3 (3.1, 4.5)	0.04
Day 3	–	4.2 (3.4, 4.5)	–
Day 6	–	4.2 (3.8, 4.9)	–
Day 9	–	3.7 (3.6, 4.7)	–
Day 12	–	3.2 (2.3, 3.8)	–
Day 15	–	3.5 (1.9, 4.1)	–

[a]CI for celite-activated blood = 0.3258R − 0.1886K + 0.1224 MA + 0.0759α − 7.7922)

C-reactive protein (> 20 mg/L) or marked neutrophilia ($> 3 \times 10^9$/L) [5].

Viscoelastic hemostatic analyzers such as TEG and rotational thromboelastometry (ROTEM) have been adopted in investigating the global haemostatic profile of COVID-19 patients. Both TEG5000 and TEG6S are well correlated (r of 0.9) and have been validated in healthy volunteers [7]. We concur with the suggestion that validation studies in specific population such as the elderly and patients of Asian descent would be beneficial, with several such studies recently performed in China and India [8–10].

We acknowledge the use of coagulation index (CI) as a tool to globally evaluate coagulopathy, with the normal range between − 3 and 3. A value − 3 suggests a tendency towards hypocoagulability and values over 3 are suggestive of hypercoagulability. We found that our severely ill patients were hypercoagulable on recruitment with a median CI of 3.3 compared to mildly ill patients who had a normal coagulation state with a median CI of 2.3 (p = 0.04) (Table 1). For severely ill patients, the CI peaked at 4.2 (with higher interquartile range of 3.8–4.9) at Day 6 of evaluation, with waning hypercoagulability demonstrated even up to Day 15 of assessment.

The rapid increase in COVID-19 infection exacerbated by the highly infectious Omicron variant of SARS-CoV-2 and growing numbers of long COVID survivors are expected to cause an increased global healthcare and cardiovascular burden [11]. The evidence of persistent hypercoagulability and endothelial dysfunction in post-COVID-19 patients [12, 13], including post-COVID-19 thrombotic events [14–16], necessitate further well-designed studies on the role of post-discharge thromboprophylaxis.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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