



# COVID-19 associated coagulopathy in critically ill patients: A hypercoagulable state demonstrated by parameters of haemostasis and clot waveform analysis

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## Abstract

Patients with COVID-19 are known to be at risk of developing both venous, arterial and microvascular thrombosis, due to an excessive immuno-thrombogenic response to the SARS-CoV-2 infection. Overlapping syndromes of COVID-19 associated coagulopathy with consumptive coagulopathy and microangiopathy can be seen in critically ill patients as well. Blood was collected from 12 Intensive Care Unit (ICU) patients with severe COVID-19 who were on either mechanical ventilation or on high flow oxygen with a PaO<sub>2</sub>/FiO<sub>2</sub> ratio of <300 mmHg. Laboratory tests were performed for parameters of haemostasis, clot waveform analysis and anti-phospholipid antibodies. CWA parameters were raised with elevated aPTT median Min1 (clot velocity) 9.3%/s (IQR 7.1–9.9%/s), elevated PT median Min1 10.3%/s (IQR 7.1–11.1%/s), elevated aPTT median Min2 (clot acceleration) 1.5%/s<sup>2</sup> (IQR 1.0–1.6%/s<sup>2</sup>), elevated PT median Min2 5.2%/s<sup>2</sup> (3.6–5.7%/s<sup>2</sup>), elevated aPTT median Max2 (clot deceleration) 1.3%/s<sup>2</sup> (IQR 0.8–1.4%/s<sup>2</sup>) elevated PT median Max2 3.8%/s<sup>2</sup> (IQR 2.6–4.2%/s<sup>2</sup>), increased aPTT median Delta change (decreased light transmission due to increased clot formation) 87.8% (IQR 70.2–91.8%) and PT median Delta change 33.0%. This together with raised median Factor VIII levels of 262.5%, hyperfibrinogenemia (median fibrinogen levels 7.5 g/L), increased median von Willebrand factor antigen levels 320% and elevated median D-dimer levels 1.7 µg/dl support the diagnosis of COVID-19 associated coagulopathy. A lupus anticoagulant was present in 50% of patients. Our laboratory findings further support the view that severe SARS-CoV-2 infection is associated with a state of hypercoagulability.

**Keywords** Hypercoagulability · Coronavirus · Thrombosis · Sepsis · Thrombophilia

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## Highlights

- COVID-19 is associated with a hypercoagulable state in critically ill patients.
- Clot waveform analysis shows good correlation with increased levels of factor VIII, fibrinogen, vWFAg and D-dimer, reflecting hypercoagulability in COVID-19 patients.
- Major bleeding can occur in critically ill patients with severe COVID-19.
- Clinical trials including risk prediction models for venous thromboembolism and arterial thrombosis are required, these may incorporate parameters of haemostasis and global haemostatic tests to establish appropriate thromboprophylactic regimes.

## Introduction

The COVID-19 pandemic has to date claimed more than a million lives, with high mortality contributed in part by thromboembolic disease. Patients with COVID-19 are known to be at risk of developing venous, arterial and microvascular thrombosis, due to an excessive immunothrombogenic response to the SARS-CoV-2 infection [1, 2]. This is secondary to COVID-19 associated coagulopathy, which is a hypercoagulable state characterized by several guidelines [3–5] as having laboratory features of raised D-dimer, Factor VIII and hyperfibrinogenemia, with the potential contributory mechanisms including vasculitis [6], hyperinflammation (raised IL-1-Beta, IL-6 and TNF alpha), neutrophil extracellular traps and hyperviscosity, resulting in both systemic and local macro- and microthrombosis. Antiphospholipid antibodies can also be present transiently, although it is not yet proven if this translates to a clinical hypercoagulable state. Potential overlaps of COVID-19-associated coagulopathy with disseminated intravascular coagulopathy and microangiopathy can also be seen in critically ill patients.

Critically ill patients with COVID-19 have been evaluated with conventional haemostasis tests [7] as well as global haemostatic tests. Thromboelastography (TEG) in two case series [8, 9] and in another case series on rotational thromboelastometry (ROTEM) [10] confirmed a state of hypercoagulopathy with associated thrombosis. Tan et al. [11] described 3 critically ill COVID-19 patients with raised clot waveform parameters suggestive of a hypercoagulable state in COVID-19 infection with no thrombotic events described. We present a series of 12 critically ill COVID-19 patients who were not on

thromboprophylaxis or anticoagulation at the time of assessment, where standard haemostatic tests were performed and correlated with clot waveform analysis, a global haemostatic assay [12, 13].

## Methods

In this retrospective observational study, we evaluated 12 Intensive Care Unit (ICU) patients with severe SARS-CoV-2 infection at the National Centre for Infectious Diseases, Singapore, who were on either mechanical ventilation or high flow oxygen with a PaO<sub>2</sub>/FiO<sub>2</sub> ratio of <300 mmHg. A confirmed case of SARS-CoV-2 infection was defined with a positive result on real time reverse-transcriptase-polymerase-chain-reaction assay of nasopharyngeal swab specimens obtained. The majority of our COVID-19 patients, particularly ambulant and non-oxygen dependent are not routinely administered pharmacological thromboprophylaxis during their hospitalization due to the perceived lower incidence of venous thromboembolism (VTE) in our predominantly Asian population [14].

The 12 patients were assessed between Day 9 to Day 20 of their illness and were started on mechanical thromboprophylaxis as per ICU VTE protocols but were not on any pharmacological thromboprophylaxis at the time of evaluation. Ten patients were referred by the ICU team for advice on initiating pharmacological thromboprophylaxis given their prolonged activated partial thromboplastin time (aPTT) and/or prothrombin time (PT), and 2 were referred at clinical presentation of a suspected lower limb ischaemia. Approximately 10 mls of whole blood was obtained per patient for evaluation. The patients were then followed up for any thromboembolic or bleeding events.

**Tests of haemostasis** All coagulation tests including lupus anticoagulant were performed on <sup>STA</sup> R Max Series coagulation analyzer (Diagnostica Stago, France). PT was measured with <sup>STA</sup> Neoplastine CI Plus 10, aPTT with <sup>STA</sup> Cephascreen 10, fibrinogen (modified Clauss) with <sup>STA</sup> Liquid FIB, D-dimer with <sup>STA</sup> Liatest D-Di and thrombin clotting time with <sup>STA</sup> Thrombin 10. Clotting factor levels (Factors II, V, VII, VIII, IX, X, XI) were measured with <sup>STA</sup> Deficient II, V, VII, VIII, IX, X, and XI respectively. Von Willebrand factor (vWF) antigen was assayed with immunoturbidimetric method using <sup>STA</sup> Liatest vWF: Ag kit. Both assays for protein C and anti-thrombin III are functional chromogenic assays using <sup>STA</sup> Stachrom protein C and <sup>STA</sup> Stachrom ATIII kits respectively. Protein S assay is a functional clotting assay using a <sup>STA</sup> Staclot protein S kit. Lupus anticoagulant was performed using <sup>STA</sup> Staclot DRVV Screen, <sup>STA</sup> Staclot DRVV Confirm and PTT-LA. Anti-cardiolipin IgM and IgG were quantified using Inova test kits, and

anti-B2-glycoprotein-1, Euroimmun test kit, both were performed on the Inova Quanta-lyser 3000 analyzer.

**Clot waveform analysis** CWA was performed with Sysmex CN-6000 automated coagulation analyser (Sysmex Corporation, Kobe, Japan) with Dade Actin FSL (Siemens Healthcare, Marburg, Germany) for aPTT CWA and Innovin (Siemens Healthcare, Marburg, Germany) for PT CWA, as per International Society of Haemostasis and Thrombosis (ISTH) Scientific and Standardization Committee recommendation [15]. Four quantitative parameters were recorded—“Min1” (maximum velocity), “Min2” (maximum acceleration), “Max2” (maximum deceleration), and “Delta change” (difference between initial maximum and final maximum values of light transmittance).

### Statistical analysis

Haemostatic evaluation of the patients included tests of haemostasis, CWA, and anti-phospholipid antibodies. We analyzed the aPTT and PT CWA parameters in ICU patients and healthy subjects using mean and standard deviation, with analysis of their differences using the Wilcoxon rank-sum test. Statistical analysis was performed with STATA 16.1. A waiver of informed consent was provided by the Ministry of Health (Singapore) for this study, under the provisions of the Infectious Diseases Act.

### Results

The haemostatic profiles of 12 ICU patients with severe COVID-19 pneumonia were assessed between Day 9 to Day 20 of their illness. Majority were male (11 out of 12), with a median age of 52 years old, with a multiethnic background (Chinese, Indian, Malay and Bangladeshi). The median BMI was raised at 25.7 with patients having comorbidities of hypertension (50%), diabetes (41.7%) and hyperlipidemia (33.3%). The median onset of symptoms to ICU admission was 8.5 days (Interquartile range (IQR) 8–12 days) with a median SOFA score of 4 (IQR 2–6 points) on ICU admission. The median PaO<sub>2</sub>/FiO<sub>2</sub> ratio on admission to ICU was 168 (IQR 122–203) with 9 patients (75%) requiring mechanical ventilation. The median haemoglobin concentration was 11.9 g/dl (IQR 10.5–13.3 g/dl), with a normal median white blood cell count of  $9.4 \times 10^9$ /L (IQR 8.2–13.6 g/dl), lymphopenia of  $0.9 \times 10^9$ /L (0.6– $1.1 \times 10^9$ /L) and a raised median lactate dehydrogenase of 754 U/L (IQR 714–1098 U/L). The median Padua prediction score for risk of VTE was 5. The median length of ICU stay was 11.5 days (IQR 4.5–24.5 days) and median length of hospital stay 25 days (IQR 21–34.5 days). Table 1 summarizes the demographic and clinical characteristics of these 12 Covid-19 patients in

ICU. Table 2 highlights the multiple quantitative parameters that were recorded.

After risk assessment, all 12 patients were started on pharmacological thromboprophylaxis given their high risk of VTE and evidence for hypercoagulability from haemostatic tests and CWA. For the 2 patients with acute ischaemic limb (Fig. 1a and Case report by Fan et al. [16]), anticoagulation with unfractionated heparin was commenced immediately after blood draw and surgical thrombectomy was successfully performed without bleeding complications. Two older patients suffered from major bleeding— one had recurrent gastrointestinal tract bleeding requiring packed red cell transfusion during the first bleeding episode on day 11 of thromboprophylaxis and later dying from multiorgan failure on Day 38 of illness, and the other succumbing to intracranial haemorrhage on Day 4 of IV unfractionated heparin started for extracorporeal membrane oxygenation (ECMO). During initial assessment of their hemostatic profiles (Fig. 1b, c), these 2 patients were found to have concurrent bacterial infection where 1 had bacterial pneumonia with a raised procalcitonin of 10.4ug/L, and the second had *Stenotrophomonas maltophilia* bacteraemia with ventilator-associated pneumonia. Both had bleeding complications which may have been caused by consumption of clotting factors and platelets caused by micro and macrovascular pulmonary thrombosis (pulmonary intravascular coagulopathy [17]) reflected by the markedly raised D-dimer levels >20 mg/dl (these 2 patients were too unwell to undergo CT pulmonary angiography) and possibly exacerbated by consumption from the associated bacterial sepsis. None of the remaining 10 patients had VTE while on thromboprophylaxis during their hospitalization.

**Tests of haemostasis** PT and aPTT were either slightly prolonged or normal, with median values of 14.6 s (IQR 14.3–15.8 s) and 38.4 (IQR 34.5–43.6 s) respectively. For additional parameters used to assess DIC by ISTH criteria, median platelet count was normal at  $275.5 \times 10^9$  (IQR  $188$ – $357 \times 10^9$ ) and median fibrinogen was markedly elevated at 7.5 g/L (IQR 5.2–8.5 g/L). The value of D-dimer was markedly increased at >20 µg/ml for 2 of the patients (16.7%). Assuming that the D-dimer values for these 2 patients are at 20 µg/ml, it suggests that the mean values of the D-dimer was at least 5.7 (7.2) µg/ml (median, IQR: 2.1, 1.4–7.8 µg/ml) in the study population. None of the patients fulfilled ISTH criteria for DIC.

For quantification of clotting factors, the significant findings were that all 12 patients had elevated Factor VIII levels (median of 262.5%), approximately half (45.5%) had elevated factor IX levels, and 1 in 3 patients (33.3%) had an elevated factor II level. All 12 patients also had a markedly elevated vWF antigen level, with median value of 320% (IQR 259–371%). Anti-thrombin III levels were

**Table 1** Demographic and Clinical Characteristics of 12 ICU Patients with COVID-19

	Total number of patients (N = 12)			
	No.	%	Median	IQR
Age (years)			52	41, 61
Gender				
Male	11	91.7		
Female	1	8.3		
Ethnic group				
Chinese	4	33.3		
Malays	2	16.7		
Indians	4	33.3		
Others	2	16.7		
Body mass index; BMI (kg/m <sup>2</sup> )			25.7	23, 29.3
Comorbidities				
Hypertension	6	50.0		
Diabetes	5	41.7		
COPD	1	8.3		
Hyperlipidaemia	4	33.3		
IHD	0	0.0		
Renal impairment	2	16.7		
Onset of symptoms to hospital admission (days)				
Symptoms presented prior admission			3.5	3, 4
Symptoms presented post admission			11.5	0, 23
Onset of symptoms to ICU admission (days)				
Symptoms presented prior admission			8.5	8, 12
Symptoms presented post admission			–	–
Day of illness at point of haemostatic assessment			13.5	11.5, 18.5
SOFA score on ICU admission			4	2, 6
Padua (VTE) score on ICU admission			5	5, 6
PaO <sub>2</sub> /FiO <sub>2</sub> on ICU admission			168	122, 203
Mechanical ventilation				
No	3	25.0		
Yes	9	75.0		
Length of ICU stay (days)			11.5	4.5, 24.5
Length of hospital stay (days)			25	21, 34.5
ICU mortality				
No	10	83.3		
Yes	2	16.7		
Hospital mortality				
No	10	83.3		
Yes	2	16.7		

Out of the 2 deaths, 1 was due to bleeding complications

mostly normal with a median of 89.5% (IQR 78–96.5%). Protein C and S were either decreased or at normal levels in most patients (Table 2).

**Clot waveform analysis** Plasma from the 12 patients were evaluated by CWA on a single occasion. For CWA performed on aPTT, we found a markedly elevated median Min1 of 9.3%/s (reference range 2.85–6.65%/s); elevated median Min2 of 1.5%/s (reference range 0.46–1.08%/s)

and elevated median Max2 of 1.3%/s (reference range 0.37–0.91%/s). There was a significant decrease in light transmission, represented by a high median delta change of 87.8% (reference range 10.0–41.1%). CWA performed on PT also showed similar marked elevated median Min1 of 10.3%/s (reference range 1.96–5.51%/s); elevated median min2 of 5.2%/s (reference range 0.98–2.84%/s), elevated median Max2 of 3.8%/s (reference range 0.74–2.28%/s), and elevated median delta change of 33.0 (reference range

**Table 2** Haemostatic, Biochemical and Immunological Profile of the 12 ICU Patients with COVID-19

Biomarkers	Reference Ranges	n	No.	%	Median	IQR	Mean	SD
Lactate dehydrogenase, LDH (U/L)	270–550	11			754	714, 1098	876.5	242.8
Thrombin clotting time, TCT (sec)	15.0–18.0	11			16.4	16.2, 17.3	16.8	1.2
White blood cell, WBC (x 10 <sup>9</sup> /L)	4.0–9.6	12			9.4	8.2, 13.6	11.0	4.8
Lymphocyte count (x 10 <sup>9</sup> /L)	1.1–3.1	12			0.9	0.6, 1.1	0.9	0.4
Haemoglobin, Hb (g/dL)		12						
Below reference range			9	75.0				
Normal	Males: 13.6–16.6		3	25.0				
Above reference range	Females: 11.8–14.6		0	0.0				
Haemoglobin, Hb (g/dL)					11.9	10.5, 13.3	11.8	2.1
Platelets (x 10 <sup>9</sup> /L)	150–360	12						
Below reference range			3	25.0				
Normal			7	58.3				
Above reference range			2	16.7				
Platelets (x 10 <sup>9</sup> /L)					275.5	188, 357	293.6	153.9
Prothrombin time, PT (sec)	11.7–14.0	12						
Below reference range			0	0.0				
Normal			1	8.3				
Above reference range			11	91.7				
Prothrombin time, PT (sec)					14.6	14.3, 15.8	15.0	1.4
Activated partial thromboplastin time, aPTT (sec)	27.0–37.0	12						
Below reference range			0	0.0				
Normal			5	41.7				
Above reference range			7	58.3				
Activated partial thromboplastin time (sec)					38.4	34.5, 43.6	40.0	6.8
Fibrinogen (g/L)	1.8–4.5	12						
Below reference range			0	0.0				
Normal			2	16.7				
Above reference range			10	83.3				
Fibrinogen(g/L)					7.5	5.2, 8.5	6.8	1.9
D-dimer (µg/ml)	<0.50	12						
Below reference range			0	0.0				
Normal			1	8.3				
Above reference range			11	91.7				
D-dimer (µg/ml)								
≤20			10	83.3	1.7	1.4, 2.6	2.8	2.9
>20			2	16.7	–	–	–	–
Factor II (%)	70–120	12						
Below reference range			3	25.0				
Normal			5	41.7				
Above reference range			4	33.3				
Factor II (%)					107.5	74, 126	100.8	31.2
Factor V (%)	70–120	11						
Below reference range			2	18.2				
Normal			7	63.6				
Above reference range			2	18.2				
Factor V (%)					117	93, 145	123.1	44.9

**Table 2** (continued)

Biomarkers	Reference Ranges	n	No.	%	Median	IQR	Mean	SD
Factor VII (%)	55–170	10						
Below reference range			0	0.0				
Normal			9	90.0				
Above reference range			1	10.0				
Factor VII (%)					98.5	92, 150	119.6	39.2
Factor VIII (%)	60–150	12						
Below reference range			0	0.0				
Normal			0	0.0				
Above reference range			12	100.0				
Factor VIII (%)					262.5	196, 335.5	284.5	102.9
Factor IX (%):	60–150	11						
Below reference range			0	0.0				
Normal			6	54.5				
Above reference range			5	45.5				
Factor IX (%)					150	114, 186	155.2	50.6
Factor X (%)	70–120	12						
Below reference range			2	12.7				
Normal			9	75.0				
Above reference range			1	8.3				
Factor X (%)					111.5	91.5, 121	107.6	27.9
Factor XI (%)	60–150	10						
Below reference range			2	20.0				
Normal			6	60.0				
Above reference range			2	20.0				
Factor XI (%)					105.5	67, 145	110.5	53.7
von Willebrand factor, vWF (%)	56–160	12						
Below reference range			0	0.0				
Normal			0	0.0				
Above reference range			12	100.0				
von Willebrand factor, vWF (%)					320	259, 371	308.6	71.9
Anti-thrombin III (%)	80–130	12						
Below reference range			3	25.0				
Normal			9	75.0				
Above reference range			0	0.0				
Antithrombin III (%)					89.5	78, 96.5	84.4	15.1
Protein C (%)	70–150	12						
Below reference range			5	41.7				
Normal			7	58.3				
Above reference range			0	0.0				
Protein C (%)					78.5	46, 109.5	77.5	37.5
Protein S (%)	55–130	12						
Below reference range			3	25.0				
Normal			8	66.7				
Above reference range			1	8.3				
Protein S (%)					68	47.5, 83.5	65.2	26.4
Lupus anticoagulant		12						
Absent			6	50.0				
Present			6	50.0				

**Table 2** (continued)

Biomarkers	Reference Ranges	n	No.	%	Median	IQR	Mean	SD
Anticardiolipin IgG (GPL units)	0–20	4						
<20			3	75.0				
≥20			1	25.0				
Anticardiolipin IgM (MPL units)	0–20	4						
<20			2	50.0				
≥20			2	50.0				
Anti β2 glycoprotein-1 (RU/ml)	0–20	4						
<2			2	50.0				
≥2			2	50.0				
aPTT clot waveform (Min1, %/s)	2.86–6.78				9.3	7.1, 9.9	8.3	2.1
aPTT clot waveform (APTT, Min2, %/s <sup>2</sup> )	0.46–1.10				1.5	1.0, 1.6	1.3	0.4
aPTT clot waveform (APTT, Max2, %/s <sup>2</sup> )	0.37–0.93				1.3	0.8, 1.4	1.1	0.4
aPTT clot waveform (APTT, delta change %)	25.21–63.09				87.8	70.2, 91.8	82.8	11.5
Clot waveform (PT, Min1, %/s)	1.95–5.67				10.3	7.1, 11.1	9.2	2.8
Clot waveform (PT, Min2, %/s <sup>2</sup> )	0.97–2.93				5.2	3.6, 5.7	4.6	1.5
Clot waveform (PT, Max2, %/s <sup>2</sup> )	0.75–2.35				3.8	2.6, 4.2	3.4	1.1
Clot waveform (PT, delta change %)	6.52–17.28				33.0	23.9, 37.2	30.7	8.9

Reference intervals for clot waveform parameters were established locally based on 124 healthy controls in accordance with the Clinical and Laboratory Standards Institute guidelines

6.6–16.9%). Comparison of COVID-19 patients with healthy controls showed COVID-19 patients had CWA parameters which were above the upper limit of the respective reference intervals, with statistical significance ( $p < 0.001$ ) (Tables 3 and 4). There was no biphasic waveform pattern on light transmission curves of the COVID-19 patients that could suggest an underlying DIC [18, 19].

**Antiphospholipid antibodies** Lupus anticoagulant was present in 6 out of 12 patients (50%) which is also prevalent in other series [20, 21], with 2 out of 4 patients having mildly raised anticardiolipin antibodies.

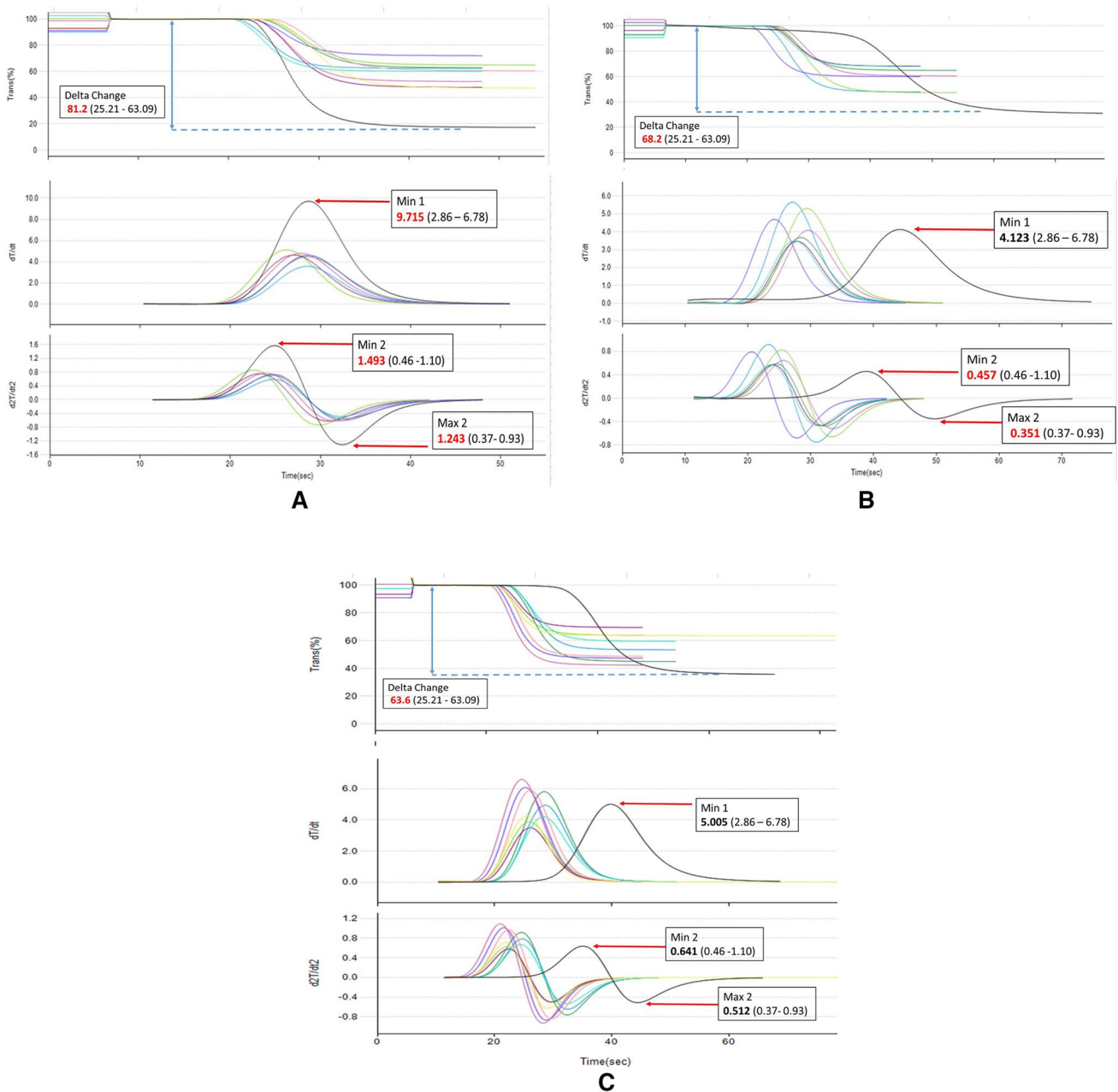
## Discussion

Our study further supports the available evidence that severe SARS-CoV-2 infection is associated with hypercoagulability [7, 21]. Clot waveform analysis (CWA) has not been well described as a tool to evaluate a hypercoagulable state, although emerging literature shows promising evidence that this may be useful in predicting for VTE [22] and also in several procoagulable states [23, 24]. CWA showed a hypercoagulable state with increased parameters of clot maximum velocity (min1), clot maximum acceleration (min2), clot maximum deceleration (max2) and delta change (decreased light transmission reflective of increased clot thickness)

characterizing a hypercoagulable state in 10 patients (with corresponding raised Factor VIII, vWF antigen, D-dimer and fibrinogen levels), with no evidence of concurrent bacterial infection at the time of assessment.

Two patients did not demonstrate a hypercoagulable state on their CWA. These 2 patients had probable pulmonary intravascular coagulopathy (PIC) with bacterial sepsis induced coagulopathy (SIC), and COVID-19-associated coagulopathy with depressed Factor II, X, XI levels and moderate thrombocytopenia. Patients with severe COVID-19 who develop SIC would have secondary hyperfibrinolysis with a reduction in fibrinogen levels and platelet counts [25]. Compared with the other 10 patients with a primary hypercoagulable state, they had relatively lower but still elevated levels of fibrinogen, factor VIII and vWF antigen, reflective of the underlying pro-inflammatory state and endothelial activation and dysfunction (resulting in raised vWF antigen levels) from severe COVID-19. Although their CWA showed a mildly increased delta change, the other CWA parameters were either normal or slightly depressed, likely due to the lower levels of clotting factors and fibrinogen due to consumption from both bacterial SIC and PIC when compared to raised CWA parameters (min1, min2, max2 and increased delta change) in the other 10 patients (see Fig. 1b, c). Collectively, in critically ill COVID-19 patients without a concurrent PIC or SIC, the CWA for both aPTT and PT demonstrate a state of hypercoagulability.

Major bleeding occurred in 2 of our patients, one had recurrent gastrointestinal bleeding while on



thromboprophylaxis and the other sustained a fatal intracranial haemorrhage on Day 4 of ECMO while on therapeutic unfractionated heparin. Major bleeding in the critically ill with COVID-19, though rare, is significant clinically given the high morbidity and mortality associated with it. A bleeding diathesis could have resulted from coexisting sepsis induced coagulopathy or pulmonary intravascular coagulopathy; precipitated by refractory hypoxaemia, or alternatively caused by local factors such as endothelial damage. Yang et al. [26] described a 4% incidence (2 out of 25 patients) of gastrointestinal bleeding in critically ill patients while Xiao et al. [27] reported a 13.7% incidence (10 out of 73 patients) but did not discuss severity. Xiao

et al. showed epithelial damage by the SARS-CoV-2 virus as an additional factor. They demonstrated fecal-oral transmission of the SARS-CoV-2 virus as a route of transmission, by means of entry into gastrointestinal epithelial cells by the angiotensin converting enzyme 2 (ACE2) protein. Mucosal damage to the esophagus was demonstrated with SARS-CoV-2 positive staining in tissues obtained from the esophagus, stomach, duodenum, and rectum. This may possibly explain why in critically ill patients with COVID-19 infection, gastrointestinal mucosal damage from SARS-CoV-2 infection combined with stress or uremic gastritis, cell necrosis from tissue hypoxia may cause



**Fig. 1 a** Hypercoagulable aPTT Clot Waveform tracing and parameters of a 35-year-old male with severe COVID-19 infection complicated by acute right ischaemic limb secondary to extensive thromboembolic disease in the abdominal aorta, right external iliac and right popliteal arteries. \*Patient's clot waveform tracing in black, healthy controls in multicolour (for reference). Patient's haemostatic and clot waveform parameters: PT 14.2 s (11.7–14.0 s), aPTT 38.7 s (27.0–37.0 s), fibrinogen 5.0 g/L (1.8–4.5 g/L), D-Dimer 2.26 µg/ml (<0.50 µg/ml), Platelets  $337 \times 10^9/L$  ( $150\text{--}360 \times 10^9/L$ ). Factor II 122% (70–120%), Factor VIII 196% (60–150%), Factor X 106% (70–120%), vWF 200% (56–160%), anti-thrombin III 74% (80–130%), Protein C 61% (70–150%), Protein S 79% (55–130%). Absent lupus anticoagulant and antiphospholipid antibodies. CWA: Min1 9.715%/s (2.86–6.78%/s), Min2 1.493%/s<sup>2</sup> (0.46–1.10%/s<sup>2</sup>), Max2 1.243%/s<sup>2</sup> (0.37–0.93%/s<sup>2</sup>), Delta change 81.2% (25.21–63.09%). **b** aPTT Clot Waveform tracing of a 40-year-old male on mechanical ventilation for severe COVID-19 pneumonia, Day 18 of illness (Day 2 ECMO), with probable pulmonary intravascular coagulopathy with concurrent bacterial pneumonia and sepsis induced coagulopathy, not initiated on anticoagulation yet. Clots were seen in the ECMO oxygenator as well as the dialysis circuit. \*Patient's clot waveform tracing in black, healthy controls in multicolour (for reference). Patient's haemostatic and clot waveform parameters. PT 18.2 s (11.7–14.0 s), aPTT 53.2 s (27.0–37.0 s), fibrinogen 3.8 g/L (1.8–4.5 g/L), D-Dimer >20 µg/ml (<0.5 µg/ml), Platelets  $115 \times 10^9/L$  ( $150\text{--}360 \times 10^9/L$ ). Factor II 46% (70–120%), Factor V 68% (70–120%), Factor VIII 196% (60–150%), Factor IX 115% (60–150%), Factor X 68% (70–120%), vWF 387% (56–160%), anti-thrombin III 54% (80–130%), Protein C 28% (70–130%), Protein S 19% (55–130%). Lupus anticoagulant moderately present and anti cardiolipin IgG <20 (0–20 GPL units), anti cardiolipin IgM 23 (0–20 MPL units), anti B2 glycoprotein-1 < 2 RU/ml (0–20 RU/ml). CWA: Min1 4.123%/s (2.86–6.78%/s), Min2 0.457%/s<sup>2</sup> (0.46–1.10%/s<sup>2</sup>), Max2 0.351%/s<sup>2</sup> (0.37–0.93%), Delta change 68.2% (25.21–63.09%). **c** aPTT Clot Waveform tracing of a 73-year-old male on Day 13 of illness with severe COVID-19 pneumonia with probable pulmonary intravascular coagulopathy and concurrent sepsis induced coagulopathy from *Stenotrophomonas maltophilia* bacteraemia and ventilator associated pneumonia. \*Patient's clot waveform tracing in black, healthy controls in multicolour (for reference). Patient's haemostatic and clot waveform parameters. PT 15.3 s (11.7–14.0 s), aPTT 41.3 s (27.0–37.0 s), fibrinogen 4.0 g/L (1.8–4.5 g/L), D-Dimer >20 µg/ml (<0.5 µg/ml), Platelets  $120 \times 10^9/L$ . Factor II 56% (70–120%), Factor V 93% (70–120%), Factor VIII 195% (60–150%), Factor IX 105% (60–150%), Factor X 68% (70–120%), Factor XI 47% (60–150%), vWF 200% (56–160%), anti-thrombin III 74% (80–130%), Protein C 61% (70–150%), Protein S 79% (55–130%). Lupus anticoagulant and antiphospholipid antibodies absent. CWA: Min1 5.005%/s (2.86–6.78%/s), Min2 0.641%/s<sup>2</sup> (0.46–1.10%/s<sup>2</sup>), Max2 0.512%/s<sup>2</sup> (0.37–0.93%/s<sup>2</sup>), Delta change 63.6% (25.21–63.09%)

gastrointestinal mucosal cellular injury, resulting in major gastrointestinal tract bleeding.

While ICH is a known complication of patients on ECMO, our patient who had catastrophic ICH had close monitoring of anti Xa levels which were within the therapeutic range (aPTT results were not used for titration of unfractionated heparin given the presence of a lupus anticoagulant) with mild thrombocytopenia while on therapeutic anticoagulation. Early reports of brain imaging findings in COVID-19 patients showed ischaemic and haemorrhagic features [28, 29], and more recently acute haemorrhagic necrotizing

encephalopathy [30], demyelinating lesions, diffuse leukoencephalopathy and microhaemorrhages [31]. These diffuse leukoencephalopathies and microhaemorrhages have been postulated to be late hypoxia related complications of critically ill patients with COVID-19 who were not in DIC, and we postulate could possibly result in catastrophic ICH while on anticoagulation.

Lupus anticoagulant was detected in 6 out of 12 (50%) of our patients, with lower number of patients who were positive for anti-cardiolipin and anti-β<sub>2</sub> glycoprotein antibodies (2 out of 4 patients who were tested). The increased incidence of a lupus anticoagulant in critically ill patients with COVID-19 was also seen in ICU studies by other centres [20, 32] with a higher prevalence of 87.7–88%. The presence of anti-phospholipid antibodies is likely caused by an immune dysregulation and cytokine storm. Given the prolongation of aPTT due to the lupus anticoagulant, monitoring with anti-Xa levels is recommended while patients are on therapeutic anticoagulation although the significance of these antibodies predisposing to development of thrombosis in COVID-19 is unclear and requires further evaluation.

The main limitations of our study are firstly, the small patient number which results in the inability to generalize findings. Secondly, as this study is from an ICU cohort, the threshold for ICU admission may also be a confounder as countries with a lower threshold for early ICU admission (ie. Singapore) for patients early in their illness may see a higher proportion of patients who have a hypercoagulable state whereas countries who admit patients later in their illness (ie. United States, United Kingdom, Italy, Brazil) may see patients admitted to ICU with severe COVID-19 complicated with SIC or PIC, which may result in higher bleeding manifestations [33, 34] due to consumptive coagulopathy.

Lastly, the variable time of assessment since onset of illness ranging between 9 and 20 days is a significant confounder, as the hypercoagulable state in COVID-19 is observed early during SARS-CoV-2 infection, while in patients who are not on thromboprophylaxis or already on long term anticoagulation, this may then progress on to pulmonary intravascular coagulopathy (PIC), a consumptive coagulopathy, with excessive activation of the coagulation system resulting in consumption of both clotting factors and platelets, shifting the hypercoagulable state into a hypocoagulable state [35]. Hence the different timing of assessment may result in discordant findings in both haemostatic parameters and clot waveform analysis. Our 12 patients were not on thromboprophylaxis at time of assessment, and those who had their haemostatic parameters and CWA assessed in the later part of their hospitalization could have developed PIC. Pathologic evidence from autopsy series demonstrating macroscopic findings of lung edema and patchy haemorrhages, microscopic findings of pulmonary endotheliitis [36], extensive fibrin thrombi in distended small vessels and capillaries [37, 38], increased numbers of megakaryocytes in

**Table 3** Comparison of aPTT Clot Waveform Parameters between ICU Patients and Healthy Controls

Clot Waveform Parameters	Patients (N = 12)			Controls (N = 124)			P-value
	No. (%)	Median (IQR)	Mean (SD)	No. (%)	Median (IQR)	Mean (SD)	
Min 1, %/s		9.3 (7.1, 9.9)	8.3 (2.1)		4.7 (4.1, 5.4)	4.8 (0.9)	<0.001
Min 2, %/s <sup>2</sup>		1.5 (1.0, 1.6)	1.3 (0.4)		0.8 (0.6, 0.9)	0.8 (0.2)	<0.001
Max 2, %/s <sup>2</sup>		1.3 (0.8, 1.4)	1.1 (0.4)		0.6 (0.5, 0.7)	0.6 (0.1)	0.0001
Delta change, %		87.8 (70.2, 91.8)	82.8 (11.5)		43.0 (37.8, 49.5)	44.2 (9.5)	<0.001
<b>CWA &gt; ULRR</b>							
Min 1 > 6.78	10 (83.3)			5 (4.0)			<0.001
Min 2 > 1.10	9 (75.0)			3 (2.4)			<0.001
Max 2 > 0.93	8 (66.7)			3 (2.4)			<0.001
Delta change > 63.09	12 (100.0)			7 (5.7)			<0.001

ULRR: Upper limit of reference interval. P < 0.05 was considered statistically significant

**Table 4** Comparison of PT Clot Waveform Parameters between ICU Patients and Healthy Controls

Clot Waveform Parameters	Patients (N = 12)			Controls (N = 124)			P-value
	No. (%)	Median (IQR)	Mean (SD)	No. (%)	Median (IQR)	Mean (SD)	
Min 1, %/s		10.3 (7.1, 11.1)	9.2 (2.8)		3.6 (3.2, 4.1)	3.8 (0.9)	<0.001
Min 2, %/s <sup>2</sup>		5.2 (3.6, 5.7)	4.6 (1.5)		1.9 (1.6, 2.1)	1.9 (0.5)	<0.001
Max 2, %/s <sup>2</sup>		3.8 (2.6, 4.2)	3.4 (1.1)		1.5 (1.3, 1.7)	1.5 (0.4)	<0.001
Delta change, %		33.0 (23.9, 37.2)	30.7 (8.9)		11.4 (10.1, 12.8)	11.9 (2.7)	<0.001
<b>CWA &gt; ULRR</b>							
Min 1 > 5.67	10 (83.3)			7 (5.7)			<0.001
Min 2 > 2.93	10 (83.3)			7 (5.7)			<0.001
Max 2 > 2.35	10 (83.3)			7 (5.7)			<0.001
Delta change > 17.28	11 (91.7)			7 (5.7)			<0.001

ULRR: Upper limit of reference interval. P < 0.05 was considered statistically significant. Reference intervals for Clot Waveform parameters were established locally based on 124 healthy controls in accordance with the Clinical and Laboratory Standards Institute guidelines

the pulmonary tissue support the lungs as the immunothrombotic epicentre in COVID-19. The result cumulates in end organ complications of thrombosis as seen in cases of lower limb ischaemia and deep venous thrombosis, acute myocardial infarctions and cerebrovascular accidents. Therefore, the treatment strategy on presentation of COVID-19 could be thromboprophylaxis with the blockade of hypercoagulation and thrombin generation with low molecular weight heparin or unfractionated heparin [39, 40]. Further prospective randomized control trials are awaited to determine if intermediate or full dose anticoagulation strategy will provide a decreased incidence of thrombotic events and survival benefit in critically ill patients.

## Conclusions

In summary, the use of haemostatic parameters and CWA further substantiate the evidence for a hypercoagulability state in severe COVID-19. Our analysis showed that elevated

CWA parameters together with elevated D-dimer, Factor VIII, vWF antigen and fibrinogen levels, support the presence of COVID-19-associated coagulopathy. CWA seems to reflect a hypercoagulable state in critically ill patients with COVID-19 as shown by elevated clot waveform parameters (min1, min2, max2 and delta change) with good correlation with elevated factor VIII, vWF antigen, D-dimer and fibrinogen levels. CWA parameters may hence offer a novel approach for assessment of COVID-19-associated hypercoagulability apart from viscoelastic tests. It is easily performed on automated analyzers with optical detection systems using standard PT and aPTT reagents and is not associated with additional costs. Patients with concurrent PIC or SIC with COVID-19-associated coagulopathy are more likely to show less elevated or low-normal CWA parameters. Major bleeding associated with a consumptive coagulopathy from SIC, PIC or local factors from endothelial damage from SARS-CoV virus infection can occur in critically ill patients with severe COVID-19, causing significant morbidity and mortality. Further randomized studies which include both ICU

and non ICU patients and risk prediction models for venous thromboembolism and arterial thrombosis are needed to establish the utility of standard haemostatic tests and global haemostatic tests such as viscoelastic tests, CWA and thrombin generation in patients with COVID-19 infection that may help to establish appropriate thromboprophylactic regimes, and to manage prothrombotic and bleeding risks.

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**Author contribution** BE Fan, J Ng and YW Chia conceived the study. BE Fan collated the data and wrote the manuscript. CLL Sum, HT Tan and MK Ang performed the coagulation tests. GH Lim performed the statistical analysis. All authors contributed substantially in analysing the data and editing the manuscript.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest. No funding for this study was obtained.

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