

# A review of COVID-19-related thrombosis and anticoagulation strategies specific to the Asian population

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## Abstract

The coronavirus disease 2019 (COVID-19) pandemic has placed an immense burden on healthcare systems worldwide. There is intensive research targeted at better understanding of the virus pathogenicity, development of effective treatment strategies and vaccines against COVID-19. It is increasingly being recognised that the pathogenicity of COVID-19 extends beyond the respiratory system. In severe cases, there can be widespread activation of the immune system, vascular injury and a resultant pro-thrombotic state. Severe COVID-19 is widely regarded as a risk factor for venous thromboembolism. Interim European and American guidelines have been created to guide anticoagulation strategies in COVID-19 patients. However, it is unclear if these guidelines can be extrapolated directly to Asians, in whom there are differences in the baseline risk of thrombosis and bleeding. Our review article aimed to summarise the current understanding of arteriovenous thromboembolic complications in COVID-19 and discuss management strategies for prevention and treatment of thrombotic events in Asian COVID-19 patients.

**Keywords:** Anticoagulation, COVID-19, pulmonary embolism, venous thrombosis, venous thrombotic events

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has spread globally at an alarmingly rapid rate. Within a span of seven months, there were more than 12 million cases of infection and 550,000 deaths worldwide as of July 2020.<sup>[1]</sup> Prolonged lockdown periods aimed at curtailing COVID-19 infection rates have challenged social norms and disrupted the lifestyles of many. The burden placed on healthcare systems and medical professionals worldwide has also been immense.<sup>[2-4]</sup>

COVID-19 primarily infects the respiratory system, resulting in a spectrum of disease ranging from mild upper respiratory tract infections to life-threatening acute respiratory distress syndrome (ARDS). The systemic complications of severe COVID-19 disease include widespread activation of the immune system and generation of a prothrombotic state.<sup>[5]</sup> Studies evaluating thromboembolic events in COVID-19 have reported findings of an increased incidence of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism (PE).<sup>[6-19]</sup> The development of

VTE is significantly associated with severe disease and higher mortality rate in COVID-19. The association of COVID-19 with arterial thrombotic events such as coronary and cerebrovascular events is, however, less clear.<sup>[6,8-10,13,16,20]</sup> In addition, findings of widespread pulmonary microthrombi formation are increasingly reported in postmortem studies.<sup>[21-27]</sup> The aetiology of pulmonary microvascular thrombosis has been attributed to a pulmonary intravascular coagulopathy process specific to COVID-19.<sup>[28]</sup>

In recognition of COVID-19 infection as a significant risk factor for the development of VTE, multiple interim European and American guidelines<sup>[29-36]</sup> on management of thrombotic

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risk in COVID-19 have been developed. It is unclear if these guidelines can be extrapolated directly to the Asian population, which has a significantly lower incidence of VTE and higher bleeding risk from anticoagulation use.<sup>[37-45]</sup> The role of anticoagulation in management of arterial and microvascular thrombosis in COVID-19 is also not well established. Thus, there is a need to ascertain the population incidence rate of arteriovenous thromboembolic events and microvascular thrombosis in COVID-19 to guide management.

This review article summarises the current understanding of arteriovenous thromboembolic complications and pulmonary microvascular thrombosis in COVID-19. We also propose a management strategy for prevention and treatment of thrombotic events in Asian COVID-19 patients based on current evidence in the literature and existing management guidelines.

## METHODS

The main clinical question addressed in this article is whether COVID-19 increases the risk of arteriovenous thromboembolic events. A better understanding of the thrombotic risks associated with COVID-19 would help physicians to improve clinical management of this patient group. Our review also aimed to discuss how clinical management in Asian COVID-19 patients might differ from those in Caucasian guidelines due to Asian predilections for reduced thrombotic tendencies and increased bleeding risk. We reviewed and summarised information from medical journals and major clinical guidelines reporting on pathophysiology, incidence and management of VTE, cerebrovascular and acute coronary vascular events in COVID-19.

Comprehensive searches of major medical databases were carried out, including MEDLINE via PubMed, Ovid, Embase and Cochrane Library. Search terms and keywords used were 'COVID-19', 'thrombosis', 'deep vein thrombosis', 'pulmonary embolism', 'anticoagulation', 'coagulopathy', 'myocardial infarction', 'stroke', 'cerebrovascular events' and 'coronary events'. Our search did not yield any meta-analysis or randomised controlled trials on the topic of interest. The evidence that we obtained was from retrospective cohort studies and case series. As the COVID-19 cohorts that were studied were highly heterogenous due to selection bias, we decided against performing pooled analysis of the laboratory coagulation parameters and incidence of thrombotic events. Instead, we summarised the literature in a descriptive manner, stating the range of incidences of VTE, cerebrovascular and acute coronary vascular events across the different cohorts of COVID-19 patients.

## COVID-19-RELATED ARTERIOVENOUS THROMBOEMBOLISM

### Coagulation parameters

We identified 18 cohort studies that described coagulation parameters of patients with COVID-19 [Table 1]. The patient

population, methodology and description of laboratory results were highly heterogenous between these studies.

Median D-dimer values ranged from 0.16 mg/L to 0.66 mg/L in non-critically ill COVID-19 patients<sup>[6,10,14,16,18,24,46-56]</sup> but were consistently higher in critically ill COVID-19 patients, ranging from 0.39 mg/L to 2.4 mg/L across the studies. Elevated D-dimer levels were also found to be associated with increased risk of thrombosis and mortality. Median activated partial thromboplastin time (APTT) values were abnormal in a single study by Tang *et al.*<sup>[52]</sup> with six other studies reporting normal median values. The incidence of disseminated intravascular coagulopathy (DIC) was reported by two studies; Al-Samkari *et al.*<sup>[6]</sup> and Tang *et al.*<sup>[52]</sup> reported the incidence of DIC to be 0.75% (3/400) and 8%, respectively.

The clinical significance of lupus anticoagulant and its possible association with thrombotic complications in COVID-19 is yet unclear. Studies that evaluated levels of lupus anticoagulant have found increased incidence of positive lupus anticoagulant in COVID-19 patients. Harzallah *et al.*<sup>[57]</sup> found that 25 (45%) out of 56 patients in a COVID-19 cohort tested positive for lupus anticoagulant, while Helms *et al.*<sup>[10]</sup> found that 50 (87.7%) out of 57 critically ill patients with clinical suspicion for coagulopathy tested positive for lupus anticoagulant. Bowles *et al.*<sup>[58]</sup> performed lupus anticoagulant assays in a subset of 34 patients with abnormal APTT results and found that 31 (90%) of them tested positive for it.

The diagnostic criteria for antiphospholipid syndrome involve positive titres of immunoglobulin G and immunoglobulin M isotypes of anticardiolipin and anti-B2 glycoproteins antibodies. The published case series performed limited evaluation of these antiphospholipid antibodies.<sup>[10,57,58]</sup> This limits their utility in the evaluation of antiphospholipid syndrome as a plausible mechanism of thrombosis in COVID-19.

### Venous thromboembolism

We included 14 observational cohort studies that had reported on the incidence of VTE in COVID-19 patients [Table 2]. The majority of patients in the cohort studies were critically ill Caucasian COVID-19 patients. Four studies<sup>[6,14,17-19]</sup> included non-critically ill COVID-19 patients and two studies<sup>[6,17]</sup> included Asian critically ill COVID-19 patients.

The baseline characteristics of the COVID-19 cohorts studied, criteria for admission to the intensive care unit (ICU) and definition of severe COVID-19 infection differed between studies. The threshold to perform diagnostic imaging, such as computed tomography pulmonary angiography and venous ultrasonography of the extremities, was also not standardised across studies.

The incidence of VTE in non-critically ill COVID-19 cohorts ranged from 0% to 4.8% across five studies,<sup>[6,13,17-19]</sup> while incidence rates in the critically ill COVID-19 cohort was markedly higher, ranging from 7.6% to 60% across 13

**Table 1. Laboratory coagulation parameters in COVID-19 patients.**

Study	Critically ill/ severe disease (No./total [%])	D-dimer (median [IQR])			Patients who died (mg/L)	Patients with VTE (mg/L)	D-dimer prognostic value	Median (IQR)		Others
		Non-critically ill (mg/L)	Critically ill (mg/L)	APTT (s)				PT (s)		
Wang et al <sup>(53)</sup> (n=138)	36/138 (26%)	0.17 (0.10-0.29)	0.414 (0.191-1.324)	NR	NR	NR	NR	31.4 (29.4-33.5)	13.0 (12.3-13.7)	NA
Guan et al <sup>(47)</sup> (n=1,099)	173/1,099 (16%)	43.2% >0.5 mg/L	59.6% >0.5 mg/L	NR	NR	NR	NR	NR	NR	NA
Han et al <sup>(48)</sup> (n=94)	10/94 (11%)	10.36±25.3	20.04±32.39	NR	NR	NR	NR	29.01±2.93	12.43±1.00	NA
Tang et al <sup>(52)</sup> (n=183)	NR	0.66 (0.38-1.50)	NR	2.1 (0.8-5.3)	NR	NR	NR	41.6 (36.9-44.5)	13.7 (13.1-14.6)	8% had DIC
Zhou et al <sup>(56)</sup> (n=191)	50/191 (26%)	68% >0.5 mg/L	NR	5.2 (1.5-21.1)	NR	OR for in-hospital death 20.04 when D-dimer >1 mg/L	NR	NR	6% had PT >16 s	NA
Wu et al <sup>(54)</sup> (n=201)	53/201 (26%)	0.61 (0.35-1.28)	NR	4.0 (1.0-11.0)	NR	NR	NR	28.7 (23.3-33.7)	11.1 (10.2-11.9)	NA
Guo et al <sup>(48)</sup> (n=187)	NR	0.43 (0.19-2.66)	NR	NR	NR	NR	NR	32.0 (30.1-35.0)	12.8 (12.0-14.0)	NA
Mao et al <sup>(50)</sup> (n=214)	88/214 (41%)	0.40 (0.2-8.7)	0.9 (0.1-20.0)	NR	NR	NR	NR	NR	NR	NA
Helms et al <sup>(10)</sup> (n=150)	150	NA	2.27 (1.16-20.00)	NR	NR	NR	NR	NR	NR	87.7% positive for lupus AC 14.7% met SIC criteria
Fraissé et al <sup>(8)</sup> (n=92)	92	NA	2.4 (1.7-7.9)	NR	4.4	NR	NR	NR	NR	NA
Middelorp et al <sup>(14)</sup> (n=198)	75/198 (38%)	1.1	2.0 (0.8-8.1)	NR	2.6 (1.1-18)	Sub-distribution hazard ratio 1.6 to develop VTE	NR	NR	NR	NA
Fogarty et al <sup>(46)</sup> (n=83)	83	NA	0.73 (0.55-1.58)	NR	NR	NR	NR	31.0 (29.3-33.1)	12.9 (12.0-14.5)	NA
Al-Samkari et al <sup>(6)</sup> (n=400)	144/400 (36%)	NR	NR	NR	1.53 (0.95- 3.28)	OR 6.79 (2.3-19.3) for thrombosis when D-dimer >2.5 mg/L	NR	NR	NR	3/400 had DIC
Zhang et al <sup>(55)</sup> (n=343)	NR	0.54 (0.2-1.41)	NR	NR	NR	HR 51.5 for in patient death (92.0% sensitivity, 83.3% specificity) when D-dimer >2.0 mg/L	NR	29.5±4.5	11.7 (11.2-12.3)	NA
Thomas et al <sup>(16)</sup> (n=63)	63	NA	0.39 (0.12-3.62)	NR	NR	NR	NR	NR	NR	NA
Tang et al <sup>(51)</sup> (n=449)	449	NA	1.94 (0.90-9.44)	4.70 (1.42- 21.00)	NR	OR 1.058 (1.028- 1.090) with 28-day mortality	NR	NR	15.2±5.0	NA
Xu et al <sup>(17)</sup> (n=138)	15/138 (11%)	0.39 (0.28-0.83)	0.74 (0.44-1.35)	NR	NR	NR	NR	NR	NR	NA
Moll et al <sup>(18)</sup> (n=210)	102/210 (48%)	0.103 (0.050-0.243)	0.396 (0.250-0.400)	NR	NR	NR	NR	34.3 (31.1-38.8)	13.85 (13.17-14.90)	NA

APTT: activated partial thromboplastin time; COVID-19: coronavirus disease 2019; NA: not applicable; NR: not reported; OR: odds ratio; PT: prothrombin time; VTE: venous thromboembolism

**Table 2. Incidence of venous thromboembolism (VTE) in COVID-19 patients.**

Study	n	No./total (%)							
		VTE imaging	VTE event	DVT alone	PE	PE±DVT	Anticoagulation	Bleeding risk	Mortality
<b>Asian studies</b>									
Cui et al <sup>(7)</sup>	81 (all critically ill)	NR	20/81 (25%)	20/81 (25%)	NR	NR	None	NR	8/81 (10%)
Xu et al <sup>(17)</sup>	138 (15 critically ill)	NR	NR	4/138 3/15 in ICU patients (20%)	NR	NR	21.5% of non-critically ill received VTE prophylaxis 100% of critically ill received VTE prophylaxis	NR	NR
<b>Caucasian studies</b>									
Lodigiani et al <sup>(13)</sup>	362 (48 critically ill)	16/44 (36%)	16/362 (4.4%) 12/314 (3.8%) in non-ICU patients 4/48 (8.3%) in ICU patients	6/362 (1.6%) 4/314 (1.2%) in non-ICU patients 2/48 (4.2%) in ICU patients	NA	10/362 (2.8%) 8/314 (2.4%) 2/48 (4.2%) in ICU	75%-100% (41% on VTE prophylaxis, 21% intermediate, 23% therapeutic)	NR	NR
Klok et al <sup>(11)</sup>	184 (all critically ill)	NR	68/184 (36.9%)	1/184 (0.5%)	65/184 (35%)	46/184 (25%)	100% (Nadroparin, varying dose)	NR	41/184 (22%) Thrombotic complications associated with hazard ratio of 5.4 with mortality
Helms et al <sup>(10)</sup>	150 (all critically ill)	25/99 (25%)	NR	3/150 (2%) vs. 3/233 (1.3%) in non-COVID-19 ARDS	25/150 (16.7%) vs. 3/233 (1.3%) in non-COVID-19 ARDS	NA	NR	4/150 (2.7%) had major bleeding events	13/150 (8.7%)
Fraissé et al <sup>(8)</sup>	92 (all critically ill)		39/92 (42%)	6/92 (6.5%)	19/92 (20.6%)	6/92 (6.5%)	43/92 (47%) on prophylactic VTE doses 49/92 (53%) on therapeutic doses	16 bleeding events in patients on therapeutic anticoagulation	41%
Middeldorp et al <sup>(14)</sup>	198 (75 critically ill)	Screening US DVT lower limb done in 55/198 patients	39/198 (20%) 35/75 (47%) in critically ill Hazard ratio of critically ill compared to non-critically ill = 7.9	26/198 (13.0%) 2/123 (1.6%) in critically ill 24/75 (32%) ICU	13/198 (6.6%) 2/123 (1.6%) in critically ill 11/75 (15%) ICU	NA	84% on prophylactic VTE doses 16% on therapeutic doses	NR	38/198 (30%)

Contd...

Table 2. Contd...

Study	n	No./total (%)							
		VTE imaging	VTE event	DVT alone	PE	PE±DVT	Anticoagulation	Bleeding risk	Mortality
Poissy et al <sup>(15)</sup>	107 (all critically ill)	36/107 CT pulmonary angiogram (33.6%)	24/107 (25.3%)	5/107 (4.7%)	22/107 (20.6%) As compared to 6.1% in case-control of ICU patients	NR	91% (20/22) on VTE prophylaxis	NR	15/107 (14%)
Al-Samkari et al <sup>(6)</sup>	400 (144 critically ill)	19 (4.8%) VTE were radiologically confirmed	22/400 (5.5%)	9/400 (2.2%)	10/400 (2.5%)	3/400 (0.7%)	100% prophylaxis	4.8% (2.9-7.3) had bleeding events* 2.3% (1.0-4.2) were major bleeding events*	NR
Litijos et al <sup>(12)</sup>	26 (all critically ill)	NA	NR	14/26 (54%)	NA	6/26 (23%)	NR	NR	3/26 (12%)
Thomas et al <sup>(16)</sup>	63 (all critically ill)	5/11 CTPA positive	NR	NR	5/63 (7.9%)	NR	Prophylaxis with dalteparin	NR	10/63 (16%)
Goyal et al <sup>(6)</sup>	393	NR	13/393 (3.3%) 3/263 (1.1%) in non-mechanically ventilated patient 10/130 (7.7%) in mechanically ventilated	NR	NR	NR	NR	NR	40/393 (10.2%)
Bilaloglu et al <sup>(19)</sup>	3,334 (829 patients critically ill)	NR	235/3,334 (7.0%) 108/2,505 (4.2%) in non-ICU patients 130/829 (15.6%) in ICU patients	129/3,334 (3.8%) 51/2,505 (2.0%) in non-ICU patients 78/829 (9.4%) in ICU patients	106/3,334 (3.2%) 54/2,505 (2.2%) in non-ICU patients 52/829 (6.2%) in ICU patients	NR	NR	NR	817/3,334 (24.5%)
Moll et al <sup>(18)</sup>	210 (102 patients critically ill)	NR	11/210 (5%) 0/108 (0%) in non-ICU patients 11/102 (11%) in ICU patients	7/210 (3%) 0/108 (0%) in non-ICU patients 7/102 (7%) in ICU patients	4/210 (2%) 0/108 (0%) in non-ICU patients 4/102 (4%) in ICU patients	NR	90% on prophylactic anticoagulation	2/210 (1%) had major bleeding events	35/219 (16.7%)

\*Data presented as median (interquartile range). ARDS: acute respiratory distress syndrome; COVID-19: coronavirus disease 2019; CTPA: computed tomography pulmonary angiogram; ICU: intensive care unit; NA: not applicable; NR: not reported; VTE: venous thromboembolism



studies. Notably, the majority of the patients in these studies received at least prophylactic doses of anticoagulation. A cohort study<sup>[4]</sup> in Asians in which patients did not receive chemical thromboprophylaxis reported a VTE incidence rate of 25%.

Two studies<sup>[10,15]</sup> compared the incidence rates of VTE in COVID-19 patients to matched cohorts of non-COVID-19 patients. Helms *et al*<sup>[10]</sup> compared 150 COVID-19 ARDS cases with a matched cohort of non-COVID-19 ARDS patients. VTE complications and PE incidence were 2.6 times and 6.2 times more likely in patients with COVID-19, respectively, despite 70% of cases receiving prophylactic anticoagulation and 30% receiving therapeutic doses of heparin. Poissy *et al*<sup>[15]</sup> compared VTE incidence in a COVID-19 cohort to historic matched controls from the same intensive care unit and to matched controls with severe influenza infection. The VTE incidence in COVID-19 was 3.3 times higher compared to matched ICU controls and 2.74 times greater compared to patients with severe influenza infection.

The results from these cohort studies suggest that COVID-19 is an independent risk factor for VTE. However, more studies in an Asian population are needed to further determine VTE risk in Asian COVID-19 patients.

### Arterial thrombosis

The incidence of arterial thrombosis in COVID-19 is much lower than that of VTE. Acute coronary syndrome [Table 3] and strokes [Table 4] in COVID-19 patient cohorts ranged from 0% to 3.6%<sup>[6,8-10,13,16]</sup> and 0.9% to 2.7%, respectively.<sup>[8,10,11,13,20,59]</sup>

**Table 3. Incidence of acute coronary syndrome in patients with coronavirus disease 2019.**

Study	n	ACS/MI cases (No. [%])
Lodigiani <i>et al</i> <sup>[13]</sup>	362	4 (1.1)
Helms <i>et al</i> <sup>[10]</sup>	150	0 (0)
Fraisse <i>et al</i> <sup>[6]</sup>	92	1 (1.0)
Samkari <i>et al</i> <sup>[6]</sup>	400	NSTEMI: 9 (2.3)
Thomas <i>et al</i> <sup>[16]</sup>	63	MI: 2 (3.0)
Goyal <i>et al</i> <sup>[9]</sup>	393	MI: 14 (3.6)

ACS: acute coronary syndrome; MI: myocardial infarction; NSTEMI: non-ST elevation MI

**Table 4. Incidence of stroke in patients with coronavirus disease 2019.**

Study	n	Stroke cases (No. [%])
Yaghi <i>et al</i> <sup>[20]</sup>	3,556	32 (0.9)
Lodigiani <i>et al</i> <sup>[13]</sup>	388	9 (2.5)
Klok <i>et al</i> <sup>[11]</sup>	184	5 (2.7)
Helms <i>et al</i> <sup>[10]</sup>	150	2 (1.3)
Fraisse <i>et al</i> <sup>[6]</sup>	92	2 (2.2)
Merkler <i>et al</i> <sup>[59]</sup>	1,916	31 (1.6)

None of the studies compared the incidence of acute coronary syndrome and myocardial infarction between COVID-19 and non-COVID-19 controls. A study done in two academic teaching hospitals in New York,<sup>[59]</sup> comprising 1,916 COVID-19 patients, reported that the incidence of ischaemic stroke in COVID-19 was greater than that of patients admitted to the same centre with influenza (odds ratio 7.6, 95% confidence interval [CI] 2.3–25.2). However, the COVID-19 cohort was not matched with the influenza cohort in terms of disease severity, with 25% of the COVID-19 being critically ill as compared to 6% in the influenza cohort. Multivariate analysis of stroke risk did not take into account critical illness status, thus limiting any strong conclusion regarding direct risk of ischaemic stroke in COVID-19.

Another large cohort study reviewing the characteristics of stroke patients with COVID-19 was performed by Yaghi *et al*<sup>[20]</sup> on 3,556 patients admitted to the Langone health system in New York. The authors compared the clinical characteristics of COVID-19 patients with stroke to those of concurrent stroke without COVID-19 (contemporary control) and historical cohort of stroke patients admitted to the same health system (historical control). The overall incidence of stroke was very low, with only 0.9% of COVID-19 patients experiencing an ischaemic stroke. As compared to contemporary stroke controls, COVID-19 patients had higher mortality, higher median peak D-dimer levels and were more likely to have a cryptogenic stroke subtype (65.6% vs. 30.4%,  $p = 0.003$ ). Cryptogenic stroke was defined by the authors as a ischaemic stroke that is not caused by atherosclerotic disease or cardioembolic phenomenon, the two commonest subtype of ischaemic stroke. The finding of reduced primary atherosclerotic disease as a cause of ischaemic stroke in COVID-19 cohorts was also observed in the cohort study by Merkler *et al*.<sup>[59]</sup>

These findings suggest that atherosclerotic disease and arterial thrombosis are not the predominant cause of ischaemic strokes in COVID-19 cohorts. Instead, mechanisms related to severe illness or sepsis might account for the increase in incidence of cryptogenic strokes in COVID-19. They include: (a) hypotension and inadequate cerebral perfusion; (b) relative hypertension leading to posterior reversible encephalopathy syndrome; (c) septic embolisation; (d) stress cardiomyopathy; and (e) paroxysmal atrial fibrillation. Another large study on 700 COVID-19 patients similarly concluded that the risk of cardiac arrests and arrhythmias was related to critical illness status rather than COVID-19 disease state.<sup>[60]</sup>

### Autopsy findings of pulmonary embolism and pulmonary microvascular thrombosis

Histopathologic findings in postmortem COVID-19 cohorts [Table 5] frequently demonstrate histopathological features similar to that in ARDS, namely diffuse alveolar damage, Type 2 pneumocyte hyperplasia, hyaline membrane

**Table 5. Autopsy findings in lungs of patients with COVID-19.**

Study	n	Findings	Distinctive features
Ackermann et al <sup>(21)</sup>	7	All specimens showed diffuse alveolar damage, linear intra-alveolar fibrin deposition and Type 2 pneumocyte hyperplasia. 4 out of 7 specimens had pulmonary artery thrombi (similar to matched influenza cohort). 7 out of 7 specimens showed alveolar capillary microthrombi (9 times more prevalent in COVID-19 as compared to influenza cohort: 159 vs. 16 thrombi/cm <sup>2</sup> of vascular lumen).	Severe endothelial damage with disruption of cell membranes Widespread vascular thrombosis with microangiopathy and alveolar capillaries occlusion Increased angiogenesis of pulmonary vessels
Wichmann et al <sup>(27)</sup>	12	8 (67%) out of 12 autopsies revealed diffuse alveolar damage, hyaline membranes thickening, pneumocytes hyperplasia, lymphocytic infiltration of alveolar with inflammatory exudates. 7 (58%) out of 12 cases had DVT. 4 (33%) out of 12 cases had PE.	High incidence of DVT and PE, which were also the cause of death
Menter et al <sup>(25)</sup>	21	Histology showed severe capillary congestion with hyaline membranes, reactive pneumocyte changes, diffuse alveolar damage. 4 (19%) out of 21 cases had PE. 5 (45%) out of 11 cases had alveolar capillary microthrombi.	Morphological changes in lung not as severe as SARS or MERS virus Authors postulated that COVID-19 may predispose to pulmonary microangiopathy through additional mechanism on top of direct alveolar endothelial injury
Carsana et al <sup>(23)</sup>	38	There was evidence of diffuse alveolar disease, capillary congestion and Type 2 pneumocytes hyperplasia in all cases. Majority also had hyaline membranes, interstitial inflammatory infiltrates and oedema. 33 (86.8%) out of 38 cases had platelet-fibrin thrombi in small arterial vessels.	Diffuse thrombosis of small pulmonary vessels is frequently present in autopsy findings of COVID-19 cases.
Magro et al <sup>(24)</sup>	5	Lung and skin biopsies showed generalised thrombotic microvascular injury.	Extensive deposition of complement components within lung septal microvasculature, suggesting complement pathways as a mechanism of thrombosis
Dolhnikoff et al <sup>(22)</sup>	10	8 (80%) out of 10 cases had fibrinous microthrombi in small pulmonary arterioles.	Frequency of pulmonary micro-thrombosis is high in autopsy findings of COVID-19.
Schaller et al <sup>(26)</sup>	12	All cases had evidence of diffuse alveolar damage, hyaline membrane formation, intra-alveolar oedema and thickened alveolar septa with perivascular lymphocyte-plasmocytic infiltration.	

COVID-19: coronavirus disease 2019; DVT: deep venous thrombosis; PE: pulmonary embolism; SARS: severe acute respiratory syndrome; MERS: Middle East respiratory syndrome

thickening with fibrin deposition and infiltration of alveolar spaces with inflammatory exudate. In addition, a high frequency (46%–100%) of PE and microthrombi formation within pulmonary arterioles and alveolar capillaries were noted in the postmortem studies.<sup>[19,25]</sup>

### Anticoagulation use in COVID-19

Two recently published retrospective cohort studies have described an association between anticoagulation use and reduced mortality rates among patients with severe COVID-19 disease.

Tang et al<sup>[52]</sup> reported that the use of prophylactic doses of heparin, the majority being low-molecular-weight heparin (LMWH) at 40–60 mg/day, was associated with a significant reduction in 28-day mortality for a subset of patients with severe COVID-19 disease. Further analysis on the same cohort showed that in patients with severe COVID-19 with an International Society on Thrombosis and Haemostasis (ISTH) sepsis-induced coagulopathy (SIC) score of  $\geq 4$ , the use of heparin was associated with significantly reduced 28-day mortality (40.0% vs. 64.2%,  $P = 0.029$ ) as compared to patients without anticoagulation therapy. The components of the ISTH SIC score include platelet count  $< 100 \times 10^9$  platelet cells/L,

prothrombin time/international normalised ratio  $> 1.4$  and sequential organ failure assessment score  $> 2$ . Tang et al. also stratified the mortality risk of patients based on D-dimer results and demonstrated that the use of heparin in severe COVID-19 was associated with a 20% reduction in 28-day mortality (32.8% vs. 52.4%,  $P = 0.017$ ).

Another large cohort study evaluating anticoagulation therapy in COVID-19 was performed on COVID-19 patients admitted to the Mount Sinai Health System in New York City, United States. The study reported that the use of treatment doses of anticoagulation was associated with a significant reduction in hospital mortality rates (29.1% vs. 62.7%) and a longer median survival (21 days vs. nine days) among COVID-19 patients who required mechanical ventilation. In the study, the use of treatment doses of anticoagulation in critically ill COVID-19 patients was associated with a low overall incidence of major bleeding events ( $< 3\%$ ).<sup>[61]</sup>

### Pathological processes behind thrombotic complications

The progression of acute disease in COVID-19 can be divided into three phases: an early phase that comprises viral infiltration and replication resulting in lymphocytopenia, a second phase comprising of respiratory compromise and abnormal chest

imaging, and a third phase consisting of an exaggerated inflammatory response driven by host immunity with elevated inflammatory biomarkers and secondary organ damage.<sup>[62]</sup>

Severe COVID-19 can cause a prothrombotic state that rarely progresses to overt DIC.<sup>[62]</sup> The processes leading to thrombotic complications in severe COVID-19 can be postulated to arise from mechanisms that stem from Virchow's triad: endothelial injury, stasis and hypercoagulability.

### Direct and indirect endothelial injury in severe COVID-19 infection

Direct endothelial cell injury can occur due to invasion of endothelial cells by the COVID-19 virus or central venous and vascular catheters in severely ill COVID-19 patients. Direct vascular injury causes a release of prothrombotic factors, including von Willebrand factor (vWF) and activation of the clotting cascade.

The systemic release of inflammatory cytokines from severe COVID-19 infections can cause dysfunction of endothelial cells lining the pulmonary vasculature, allowing increased macrophage and neutrophil migration and presentation of activated tissue factor. The pulmonary microvasculature is particularly susceptible to injury by COVID-19 due to its close anatomical juxtaposition with Type II pneumocytes. Proximal airway epithelial cells and Type II pneumocytes ubiquitously express angiotensin-converting enzyme (ACE-2) receptor, a receptor that the Coronavirus family shows great tropism for.<sup>[28]</sup> However, smaller airway epithelium does not express ACE-2 well and is less susceptible to coronaviruses.<sup>[63]</sup> The inflammatory cytokines responsible for vascular injury in severe COVID-19 infections include interleukin-6 (IL-6), tumour necrosis factor-alpha and interferon gamma.<sup>[36]</sup> Notably, non-survivors of severe COVID-19 infections have consistently exhibited higher levels of inflammatory markers, including IL-6, ferritin and C-reactive protein.<sup>[64]</sup>

### Stasis potentiating prothrombotic state in severe COVID-19 infections

Long-term immobilisation of severe COVID-19 infection patients from protracted illness and hospitalisation may increase the risk of VTE. Intentional fluid restriction as part of a lung-protective ventilation strategy in severe COVID-19 ARDS can cause inadvertent haemoconcentration and predispose patients to venous stasis. In addition, patients with severe hypoxaemia from ARDS also develop hypoxic vasoconstriction of pulmonary capillaries with further reduction of pulmonary blood flow. The combination of aforementioned factors may lead to the formation of pulmonary microvascular thrombi. Of note, pulmonary vasculature microthrombi and vascular endothelial dysfunction may be the primary cause of hypoxaemia in COVID-19 rather than parenchymal lung disease.<sup>[28]</sup> This is supported by observations that the marked hypoxaemia associated with severe COVID-19

disease was often not characterised by dense consolidation and low lung compliance seen in severe ARDS.<sup>[65]</sup>

### Hypercoagulability in severe COVID-19 infections

The widespread activation of the immune system and ensuing cytokine storm drive an inflammatory cascade and resultant hypercoagulable state. This results in widespread damage and activation of vascular endothelial cells, an increased activity of antigen-presenting cells and activation of platelets and coagulation pathways.<sup>[62,66]</sup> Patients with severe COVID-19 respiratory illness were found to have increased levels of serum fibrinogen, vWF, factor VIII, fibrin-degradation products such as D-dimer, and lupus anticoagulant.<sup>[66]</sup> Pulmonary vascular endothelial injury, release of prothrombotic factors, activation of clotting cascade, and migration of macrophages and neutrophils leads to microvascular thrombosis. This thrombotic tendency of the pulmonary microvascular has been described as pulmonary intravascular coagulopathy.<sup>[58]</sup>

### Thrombosis in severe COVID-19 infections a different entity from disseminated intravascular coagulopathy

Overt DIC is rare in COVID-19 patients, and platelets and fibrinogen levels are often not markedly reduced. Mild thrombocytopenia (platelets  $<150 \times 10^9$  platelet cells/L), mildly prolonged prothrombin time and fibrinogen levels at the upper limits of normal can be occasionally seen in severe COVID-19 infections.<sup>[66]</sup> The coagulation derangements that are occasionally seen in severe COVID-19 more closely represent SIC or a DIC subtype with suppressed fibrinolysis activity.<sup>[62,66]</sup>

## DISCUSSION

### Current guidelines for management of thrombotic complications in COVID-19

Interim guidelines<sup>[29-36]</sup> on anticoagulation use in COVID-19 have been proposed by major medical societies and hospitals from North America and Europe. These guidelines recognise COVID-19 as an independent risk factor for the development of VTE. The CHEST guidelines from America<sup>[31]</sup> consider all hospitalised patients with COVID-19 to be at increased risk of VTE. This is because the incidence of VTE in non-critically ill patients with COVID-19 is above 1% despite the use of VTE thromboprophylaxis. As such, current VTE guidelines for COVID-19 are consistent in their recommendation of starting standard prophylactic anticoagulation for all hospitalised COVID-19 patients.

However, there is no consensus regarding the role of therapeutic anticoagulation in management of thrombotic complications associated with COVID-19. Guidelines from the European Society of Cardiology and Mount Sinai Health System recommend the use of therapeutic anticoagulation for patients with severe COVID-19 infection who are mechanically ventilated and/or demonstrate markedly elevated biomarkers for venous thrombosis.<sup>[30]</sup>



### VTE, cerebrovascular, coronary vascular disease incidence and bleeding risk in Asian population

The VTE incidence in Asians may be up to 80% lower when compared to Caucasian counterparts, based on data from population studies.<sup>[37,41]</sup> A large cohort study by Nicole Tran *et al*<sup>[67]</sup> evaluated the incidence of VTE among different Asian ethnic groups and Caucasian. This study reported a hazard ratio of 0.4–0.6 for VTE in Chinese, Japanese and Filipino as compared to Caucasians, with the risk of South Asians developing VTE being similar to that in Caucasians.

The lower incidence of VTE in the Asian population has been attributed predominantly to a lower prevalence of genetic mutations that predispose patients to a prothrombotic state, including Factor V Leiden and Prothrombin G20210A mutation. Decreased awareness of VTE risk among physicians in Asian hospitals and a lower tendency for performing imaging tests have also been proposed as an explanation for the lower reported incidence of VTE in studies performed on Asians.<sup>[39]</sup> The genetic pool of South Asians may be closer to Middle Easterners and Europeans, thus accounting for the increased risk for VTE as compared to other Asian ethnicities.

The reduced risk of VTE in Asians is also apparent in ICU cohorts, wherein critical illness is a recognised acquired risk factor for the development of VTE. The incidence of VTE in Caucasian population in intensive care unit settings is as high as 31% without the use of thromboprophylaxis. VTE thromboprophylaxis significantly reduces the incidence of asymptomatic VTE to as low as 11%.<sup>[68]</sup> The reported incidence of radiologically diagnosed VTE in Asian ICU patients without the use of VTE prophylaxis was lower at 19%,<sup>[69]</sup> with a further reduction to 9.5% following routine use of VTE thromboprophylaxis.<sup>[45]</sup>

VTE incidence rates in many Asian countries are increasing and approaching rates that are reported in developed Caucasian countries. This is attributed to improved clinician awareness and screening for VTE as well as an overall increase in risk factors for VTE. Significant risk factors for VTE in many Asian countries include longer life expectancies and higher incidences of malignancy.<sup>[37]</sup> It is crucial for clinicians managing Asian patients to actively screen for risk factors for VTE in spite of the reduced ethnic risk for VTE among Asians.

The incidence of ischaemic stroke differs significantly between ethnicities. In a large population study, the age- and gender-adjusted ischaemic stroke incidence was 43% lower in Chinese and 63% lower in South Asians as compared to Caucasian patients.<sup>[70]</sup> The proportions of ischaemic stroke subtypes also differ greatly between Asians and Caucasians, suggesting a racial predisposition to different pathophysiological processes. While the commonest cause of stroke among Caucasians is cardioembolic in nature (up to 30%), primary atherosclerosis in small vessels causing lacunar strokes is the most common (up to 50%) reason for stroke among Asians.<sup>[71-73]</sup>

Coronary vascular disease, of which the predominant pathophysiology process is atherosclerosis, is highest among South Asians as compared to Caucasians (hazard ratio 1.35, 95% CI 1.3–1.4)<sup>[74]</sup> and Chinese.<sup>[75,76]</sup> Significant differences in the incidence of coronary artery disease also exists among different Asian ethnic groups.<sup>[77]</sup>

A large study evaluating the risk of intracranial haemorrhage (ICH) in patients on warfarin reported a hazard ratio of 4.06 in the Asian group as compared to Caucasians.<sup>[42-44]</sup> Asian patients on novel oral anticoagulants (NOACs) had a significantly increased risk of developing ICH (2.11% vs. 0.97%,  $P < 0.001$ ) as compared to Caucasian patients.<sup>[78]</sup> Several authors have reported NOACs to be associated with a lower bleeding risk when compared to Vitamin K antagonists among Asian cohorts, suggesting that NOACs should be the oral anticoagulation of choice in the Asian population.<sup>[79-81]</sup>

### Venous thromboembolism prophylaxis in Asian COVID-19 patients

The Asian venous thromboembolism guidelines,<sup>[39]</sup> recently updated in 2017, emphasise the assessment of risk factors for VTE to guide the use of VTE prophylaxis in Asians. The major risk factors for development of VTE remain consistent across all ethnicities. Significant VTE risk factors include advanced age, obesity, pregnancy, malignancy, major abdominal surgery, critical illness, prolonged immobility, stroke and trauma.<sup>[38,39,45]</sup>

Asians are considered less prothrombotic and have an increased risk of bleeding from anticoagulation. However, there is growing evidence that COVID-19 itself is a strong independent risk factor for thrombosis. Furthermore, as clot formation is facilitated in COVID-19, the risk of bleeding is concurrently reduced. This leads to an inherent risk of thrombosis and a lower risk of bleeding in COVID-19, independent of ethnicity. Thrombotic risk in COVID-19 is proportional to the severity of the disease.

Criteria for hospitalisation vary between countries; some choose to admit all patients diagnosed with COVID-19, while others only admit those who are at high risk of deterioration. Asian COVID-19 patients who require hospital admission due to risk of further deterioration should be considered for VTE prophylaxis. Patients who are well enough to be managed in the community are at lower risk for developing thrombosis. These patients likely do not require VTE prophylaxis in the absence of other known VTE risk factors.

Patients categorised as having severe COVID-19 or critically ill (requiring ICU admission) should be prescribed at least a prophylactic anticoagulation dosage of LMWH or unfractionated heparin. Predictors of progression to severe COVID-19 may include the need for oxygen supplementation (suggesting early respiratory failure), high risk scores for VTE such as the Padua score,<sup>[82]</sup> and elevated serum biochemical markers for thrombosis such as D-dimer

levels.<sup>[52,55,56]</sup> The Padua score and D-dimer levels have been demonstrated in studies to correlate with increased mortality, critical illness status and poor prognosis in COVID-19.

### **Venous thromboembolism treatment in Asian COVID-19 patients**

As the bleeding risk from anticoagulation use is higher in Asians, it is ideal to establish a definitive diagnosis of VTE with imaging tests before starting a patient on therapeutic anticoagulation. In patients with COVID-19, clinicians should be aware of the increased risk of thrombotic complications and reduce their threshold to perform relevant imaging tests for the diagnosis of arteriovenous thromboembolic events. All diagnostic imaging tests should be carried out safely with appropriate infection control measures in place. VTE that is confirmed on imaging should then be managed with standard treatment doses of anticoagulation.

A subgroup of critically ill and severely hypoxaemic patients may not be able to undergo diagnostic imaging tests for PE due to their unstable clinical condition or kidney failure limiting the use of radiocontrast agents. Point-of-care ultrasonography in this group of patients may help to further determine the likelihood of PE.

A multidisciplinary team, comprising a minimum of an intensivist and a haematologist, should weigh the risk of clinical deterioration from untreated VTE against the bleeding risk from empirical therapeutic anticoagulation. Global haemostatic tests, such as thromboelastography and rotational thromboelastometry, may be performed to define bleeding risks and guide risk stratification in patients who are being considered for empirical therapeutic anticoagulation.

### **Arterial thromboembolic events, ischaemic strokes and myocardial infarctions in COVID-19**

Our review of the literature shows that the overall incidence of arterial thromboembolic events is low in COVID-19. The majority of the ischaemic strokes in COVID-19 cohorts were due to cardioembolic or cryptogenic causes, both of which are uncommon subtypes of ischaemic strokes in Asians. The risk of ischaemic stroke and myocardial infarction in Asians with COVID-19 may not be specifically elevated beyond baseline atherosclerotic risk factors and critical illness status. There is insufficient evidence to recommend antiplatelets or anticoagulation therapy for the prevention of arterial-thromboembolic events in Asian COVID-19 patients.

### **Pulmonary microvascular thrombus and COVID-19**

Our literature review did not provide sufficient data to clearly define the underlying incidence and risk factors of pulmonary microvascular thrombus formation in COVID-19.

Pulmonary microthrombi may be suspected in patients with severe hypoxaemia, disproportionately low degree of radiological infiltrates within the lung parenchyma and a normal to low-normal lung compliance. A major differential

is PE, for which therapeutic anticoagulation is proven to be effective in reducing morbidity and mortality. No studies to date have evaluated the role of anticoagulation in the prevention or treatment of pulmonary microvascular thrombosis. There should be a reduced threshold to perform diagnostic imaging when PE or pulmonary microthrombi is suspected. Computed tomography pulmonary angiography can confirm the diagnosis of a pulmonary embolus, allowing clinicians to distinguish between PE and pulmonary microthrombi as the predominant cause of respiratory failure. This is clinically important as the role of therapeutic anticoagulation in the latter is not well established.

## **AREAS FOR FURTHER RESEARCH**

### **Further definition of the indication and role of anticoagulation in COVID-19**

At least 27 clinical trials focused on the role of anticoagulation in the management of arteriovenous thromboembolic events in COVID-19 have been registered on the ClinicalTrials.gov database. As of date, 12 randomised controlled trials evaluating the role of anticoagulation in COVID-19 have started recruiting patients. The results of these trials will provide more guidance on the clinical indications for therapeutic anticoagulation in COVID-19.

### **Utility of D-dimer as a risk stratification tool in COVID-19**

Elevated D-dimer levels were found to positively correlate with the likelihood of critical illness, increase in VTE and mortality in COVID-19 [Table 1]. COVID-19 patients with raised D-dimer levels may potentially benefit from closer monitoring in high dependency units or ICUs. There should be a heightened clinical suspicion for arteriovenous thromboembolic complications and lowered threshold to perform diagnostic imaging scans in patients with raised D-dimer levels.

Further studies are needed to determine if D-dimer levels can be utilised clinically as a risk stratification tool for VTE and to predict likelihood of progression from mild to severe COVID-19.

### **Specific arteriovenous thromboembolic risk within the Asian population**

The incidence and risk of coronary artery disease, ischaemic strokes and VTE in different population and ethnicity groups with COVID-19 need to be established. Knowledge of this data would aid clinicians in improving management of thromboembolic complications in COVID-19 patients.

## **CONCLUSION**

COVID-19 is a significant risk factor for the development of VTE. Despite the lower incidence of VTE and higher bleeding risk from anticoagulation use in Asians, VTE prophylaxis should be considered for all hospitalised Asian

COVID-19 patients. Asian COVID-19 patients who are at high risk of clinical deterioration or critically ill should be managed with at least prophylactic anticoagulation in the absence of contraindications. There should be increased awareness of VTE and a reduced threshold to perform diagnostic imaging for VTE in Asian COVID-19 patients. Adequate infection control measures should be maintained throughout. Confirmation of a diagnosis of VTE before starting therapeutic anticoagulation is recommended due to the higher bleeding risk from anticoagulation use in Asians.

The overall incidence of myocardial infarction and ischaemic strokes in COVID-19 is low. The risk of these arterial thrombotic events in COVID-19 is likely related to severe illness and systemic sepsis, rather than COVID-19-specific mechanisms.

The results of ongoing randomised control trials will further elucidate the role of anticoagulation in the management of arteriovenous thromboembolic complications in COVID-19.

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### Conflicts of interest

There are no conflicts of interest.

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