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REVIEW

Systemic inflammation in COVID-19 patients may induce various types of venous and arterial thrombosis: A systematic review

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Abstract

COVID-19 is a global pandemic with a daily increasing number of affected individuals. Thrombosis is a severe complication of COVID-19 that leads to a worse clinical course with higher rates of mortality. Multiple lines of evidence suggest that hyperinflammation plays a crucial role in disease progression. This review compiles clinical data of COVID-19 patients who developed thrombotic complications to investigate the possible role of hyperinflammation in inducing hypercoagulation. A systematic literature search was performed using PubMed, Embase, Medline and Scopus to identify relevant clinical studies that investigated thrombotic manifestations and reported inflammatory and coagulation biomarkers in COVID-19 patients. Only 54 studies met our inclusion criteria, the majority of which demonstrated significantly elevated inflammatory markers. In the cohort studies with control, D-dimer was significantly higher in COVID-19 patients with thrombosis as compared to the control. Pulmonary embolism, deep vein thrombosis and strokes were frequently reported which could be attributed to the hyperinflammatory response associated with COVID-19 and/or to the direct viral activation of platelets and endothelial cells, two mechanisms that are discussed in this review. It is recommended that all admitted COVID-19 patients should be assessed for hypercoagulation. Furthermore, several studies have suggested that anticoagulation may be beneficial, especially in hospitalized non-ICU patients. Although vaccines against SARS-CoV-2 have been approved and distributed in several countries, research should continue in the field of prevention and treatment of COVID-19 and its severe complications including thrombosis due to the emergence of new variants against which the efficacy of the vaccines is not yet clear.

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1 | INTRODUCTION

Since the outbreak in December 2019, coronavirus disease 2019 (COVID-19) has wreaked havoc across the globe and caused great morbidity and mortality in its wake. What started off as a local illness in Wuhan, China, has since escalated into a global emergency of pandemic scale with over 93 million confirmed cases around the world and 2.6 million deaths as of March 2021.[1] Due to the enormous burden that the virus has caused, it has since been the subject of extensive research in order to better understand its transmission, prevent its spread and reduce its negative impact on health and well-being. The pandemic has been confirmed to originate from a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is transmitted mainly through respiratory droplets from close contacts, although infection from contaminated surfaces and zoonotic transmission has been described. The virus can produce a wide range of symptoms in its host ranging from mild constitutional symptoms to severe and life-threatening respiratory illness.[2]

Despite mainly targeting the respiratory system, COVID-19 is a systemic disease that affects multiple regions in the body including the hematopoietic system causing blood hypercoagulability.[3] The increased risk of thrombosis in infected patients lead to an increase in the risk of disseminated intravascular coagulation (DIC) and venous thromboembolism (VTE).[4] It has been found that deaths caused by novel coronavirus pneumonia have elevated D-dimer and fibrin degradation products.[5] Due to hypercoagulation associated with COVID-19, it has been found that anticoagulation therapy resulted in better prognosis in severe COVID-19 patients.[4] The degree of hypercoagulation is associated with the severity of the disease which results in thromboinflammation.[6] In this study, we have compiled data to understand the pathophysiology of the immune system in the increased risk of thrombosis seen in COVID-19 patients.

2 | METHODS

PubMed, Embase, Medline and Scopus were searched using combinations of the following keywords: severe acute respiratory syndrome coronavirus, severe-acute-respiratory-syndrome-coronavirus-2, 2019-ncov, 2019ncov, covid-19, covid19, covid2019 ncov2019, ncov-2019, hcov19, sars-cov-2, coronavirus, coronaviruses, corona-virus, corona-viruses, covid, hcov, coronavirus [MeSH Terms], "Thrombosis"[Mesh], Thrombosis, anticoagulation, blood clot, anticoagulants. English, peer-reviewed and published article from January to July 2020 were included during the initial phase of screening, regardless of the study design. No restrictions were made about country, age or gender. Any duplicated articles were removed and reviews or any articles that did not include primary data were excluded from the study. During the full-text screening, only studies that included inflammation marker blood tests for COVID-19 patients with any thrombotic events were selected including case reports and case series. Cohort studies with control groups were also selected only if they reported the blood inflammation marker results in two separate groups of COVID-19 patients with and without thrombotic events. Studies reporting mixed populations of COVID-19 patients with or without thrombosis and split them based on disease severity were excluded as no conclusion could be driven for the purpose of our review. Articles devoid of original patient data, or those written in any language other than English were excluded from the study. Title and abstract as well as full-text screening were conducted by two different reviewers for each study using Covidence (Covidence Systematic Review Software, Melbourne, Australia). Disagreements were resolved by consensus. Demographic and clinical data of patients reported in each study (whenever data were available) were extracted independently by two different reviewers using Covidence and disagreements were resolved by consensus. Extracted data included age, sex, comorbidities, treatment/interventions, clinical progress, thrombotic events, and inflammatory and cardiac blood test results. Categorical variables were expressed as percentages, while continuous variables were expressed as mean standard deviation or range of results. Data were extracted from each study by two different reviewers.

3 | RESULTS

3.1 | Studies selection and specifications

Figure 1 shows the flow diagram which summarizes the protocol and results of database search and screening. A total of 1177 studies were obtained after removing duplicates. Title and abstract screening resulted in the selection of 199 studies out of which 54 studies met our inclusion criteria and were accordingly included in the review. A total of 144 studies were excluded due to various reasons. In summary, 65 studies did not report enough data, 45 studies had the wrong setting or wrong outcome (such as pseudothrombocytopenia), 28 were irrelevant, four were duplicates, one text was not in English, one article with no primary data, and one was an ongoing study.

The 54 included studies were seven cohort studies with control and 48 case series/reports as one study has

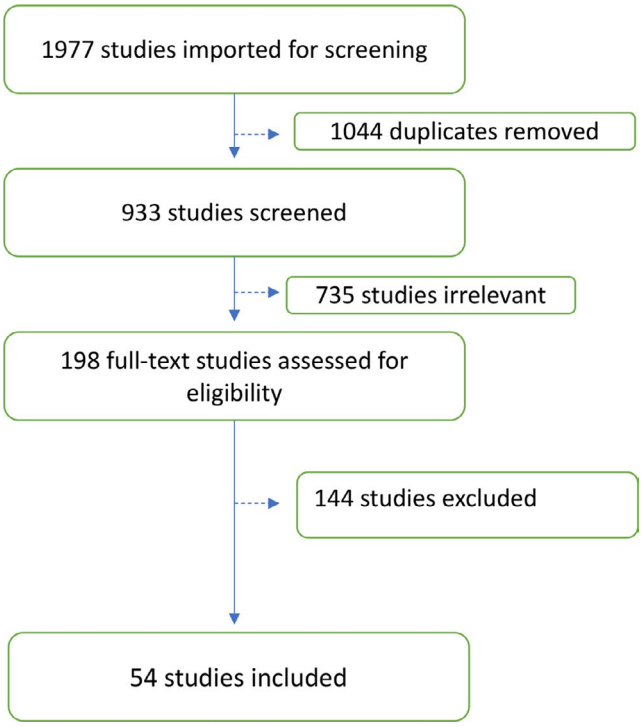

FIGURE 1 Flow diagram illustrating the study selection protocol

two parts: a cohort study with control and a case series. The studies were conducted in different countries including the United States, the UK, China, Spain, Turkey, Iran, Italy, Switzerland, Netherlands, Canada, Norway and France.

3.2 | Cohort studies with control groups

3.2.1 | Demographic information

Table S1 includes the demographic data and the clinical outcome for COVID-19 patients with no thrombotic event (NT) or with thrombotic events (T) in each of the seven selected cohort studies. The cohort studies included 839 COVID-19 patients in total, of which 186 developed different types of thrombotic events during the course of infection.[7-13]

The NT group included patients with an average/median age range of 52 to 69 years, while the T group included patients with an average/median age range of 50 to 75.7 years. Comorbidities did not differ significantly between the NT and the T groups in five of the cohort studies. Only Li et al[12] and Stoneham et al[13] reported significantly higher proportions of COVID-19 patients with thrombosis who had comorbid diabetes, cardiovascular diseases (CVD) and hypertension (HTN) (P =.001, 0.044 and 0.001 respectively).

3.2.2 | Clinical data

Table S2 summarizes the clinical features of COVID-19 patients in the T and NT groups including clinical progression, outcomes, treatments, laboratory markers for inflammation including C-reactive protein (CRP), procalcitonin (PCT), ferritin and coagulation parameters including D-Dimer, platelets, fibrinogen and prothrombin time (PT) in the cohort studies. Out of the different coagulation markers reported in the cohort studies with control, only D-dimer was consistently significantly higher in the T group as compared with the NT group in all of the included seven studies. Conversely, platelet count, fibrinogen level and PT showed varied patterns across the seven studies between the T and the NT groups. In two out of the seven control studies,[7,12] the platelet count was significantly lower in the T group as compared with the NT group (P =.037, 0.035). Similarly, Koleilat et al[10] reported a significantly higher fibrinogen level in the T group as compared to the NT group (P =.002). In the study conducted by Zhang et al,[9] PT was significantly higher in the T group than the NT group. The inflammation markers did not show a consistent pattern across the studies between the T and NT groups. Only three studies reported significantly higher inflammation markers in the T group compared with the NT group. For example, Chen et al[7] reported that PCT was significantly higher in the T group than the NT group (P <.01). Furthermore, both CRP (P =.012) and PCT (P <.01) levels were significantly higher in the T group than the NT group.[9] Li et al[12] reported significantly higher CRP (P =.025) levels in the T group as compared with the NT group. Figure 2 summarizes the levels of inflammation and coagulation markers in the T and NT groups.

Table 1 summarizes the types of thrombosis reported by the seven studies which included deep vein thrombosis (DVT),[7-12] pulmonary embolism (PE),[10,11,13] thrombosis in the aortic arch[11] and cerebral thrombosis.[12]

All patients included in the study conducted by Chen et al[7] received prophylactic low-molecular-weight heparin (LMWH) including those who developed deep vein thrombosis (DVT). Similarly, different proportions of the T and NT groups received prophylactic anticoagulants including LMWH as reported by Zhang et al,[9] Koleilat et al[10] and Larsen et al[11] Only Larsen et al[11] reported that a significantly higher proportion of the NT group received prophylactic LMWH (P =.002).

3.3 | Case reports/series

3.3.1 | Demographic information

Table S3 summarizes the demographics, clinical features, inflammatory markers and coagulation parameters of

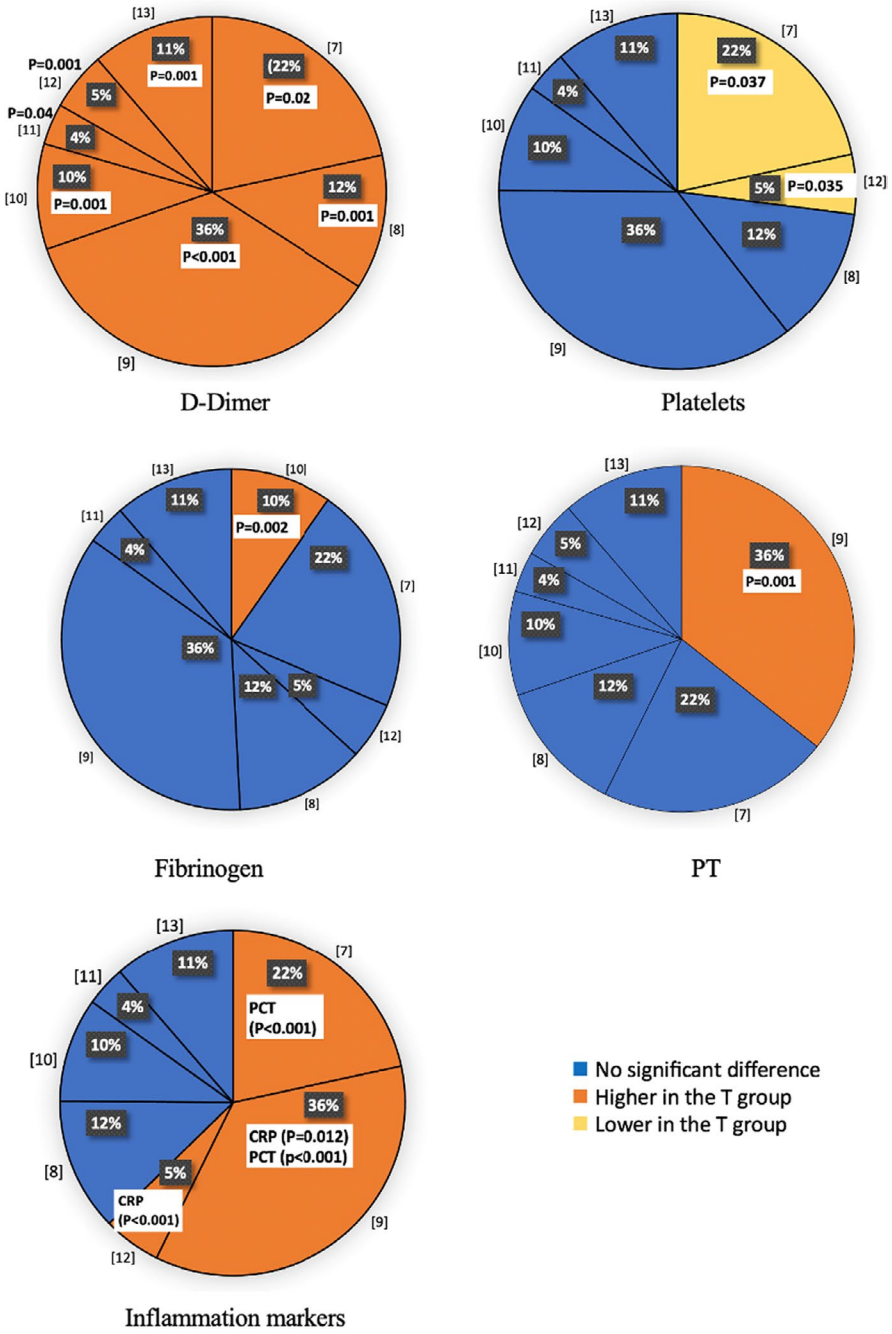

FIGURE 2 Summary of the blood markers/coagulation factors in the seven included cohort studies with control. Each pie chart illustrates the number of studies that reported no sginificant difference, significantly higher or significantly lower blood marker/coagulation factors in the T group as compared to the NT group. Each section of the pie charts shows the percentage of patients in each study out of the 185 patients of the T group in the 7 cohort studies, and the reference number is added next to each section. D-Dimer was the only coagulation factor that was consistently significantly higher in the T group as compared to the NT group.[7-13] Significantly lower platelet count was reported in two studies,[7,12] while only one study reported significantly higher fibrinogen level in the T group as compared to the NT group.[10] Similarly, significantly longer prothrombin time (PT) in the T group was reported by one study.[9] Unlike the D-Dimer, inflammation marker results did not show a consistent pattern as only three studies reported significantly higher levels of inflammation markers in the T group as compared to the NT group.[7,9,12] However, the number of patients in the 3 studies represents 63% of the total number of patients that developed thrombosis in the cohort studies

the COVID-19 patients with thrombotic complications that were described in the 48 case studies included in this report.[13-60] The case studies included a total of 163 patients whose ages ranged from 29 to 83.1 and 46.5% of which were males.

3.3.2 | Clinical data

D-dimer values above 1 μg/mL were reported in 35 studies out of the 40 case studies, while 30 studies reported values above 1.5 μg/mL. Out of 23 studies that reported the platelet counts, four studies reported elevated platelet counts[21,29,40,41] and four studies reported low platelet counts.[26,30,31,59] Only 13 studies reported the fibrinogen levels, out of which 11 studies reported elevated levels. Finally, out of 14 studies reported PT, six reported prolonged prothrombin times. Figure 3 summarizes the levels of coagulation markers of the COVID-19 patients who developed thrombosis as reported by the case reports/series. CRP level was found to be >100 mg/L in 29 studies, which included 62% of patients in the studies that reported CRP. Furthermore, 21 studies reported CRP levels >150 mg/L, which included 30% of patients. Only 12 studies reported

TABLE 1 Types of COVID-19-associated thrombosis reported in the seven included cohort studies with control

Type of thrombosis	Number of Studies	References
DVT	6	[7-11, 13]
PE	3	[10, 11, 13]
Aortic arch thrombosis	1	[11]
Cerebral thrombosis	1	[12]

Abbreviations: DVT, Deep Vein Thrombosis; PE, Pulmonary Embolism.

IL-6, out of which 8 reported levels >80 pg/mL (including 73% of patients). Only 28% of COVID-19 patients with thrombosis in the 20 studies that reported ferritin had levels >1500 ng/mL and 32% had levels >1000ng/mL. Figure 4 summarizes the levels of CRP, IL-6 and ferritin of the COVID-19 patients who developed thrombosis as reported by the case reports/series.

Table S4 includes the reference ranges for the blood markers/coagulation factor reported in this review.

Table 2 summarizes the types of thrombosis reported in the 48 studies. COVID-19 associated PE was reported by 21 studies.[13,15,17,23-25,27,28,30,32,33,35-37,40,45,46,48,50,53,56] Furthermore, patients in 10 studies were reported to have suffered from strokes.[19,20,27,35,46,51,55,57,58] Different other types of venous and arterial cerebral thrombosis were reported by 10 studies including intracerebral haemorrhage, thrombosis/occlusion of the middle cerebral artery (MCA), cerebral infraction of the right MCA, occlusive strokes in the brachial and cephalic veins, cerebral venous sinus thrombosis and other types of cerebral thrombosis.[22,23,25,36,39,43,47,50,52,59] Thrombotic events with cardiac implications in COVID-19 patients were reported in five studies such as acute coronary syndrome, acute right ventricular (RV) failure, acute myocardial infraction, intraventricular hematoma and intramural RV thrombus.[27,30,38,47,56] DVT was also reported to be associated with COVID-19 in nine studies.[13,27,28,31,32,35,45,48,60] Lastly, different types of venous and arterial thrombosis were reported in COVID-19 patients (Table 2).

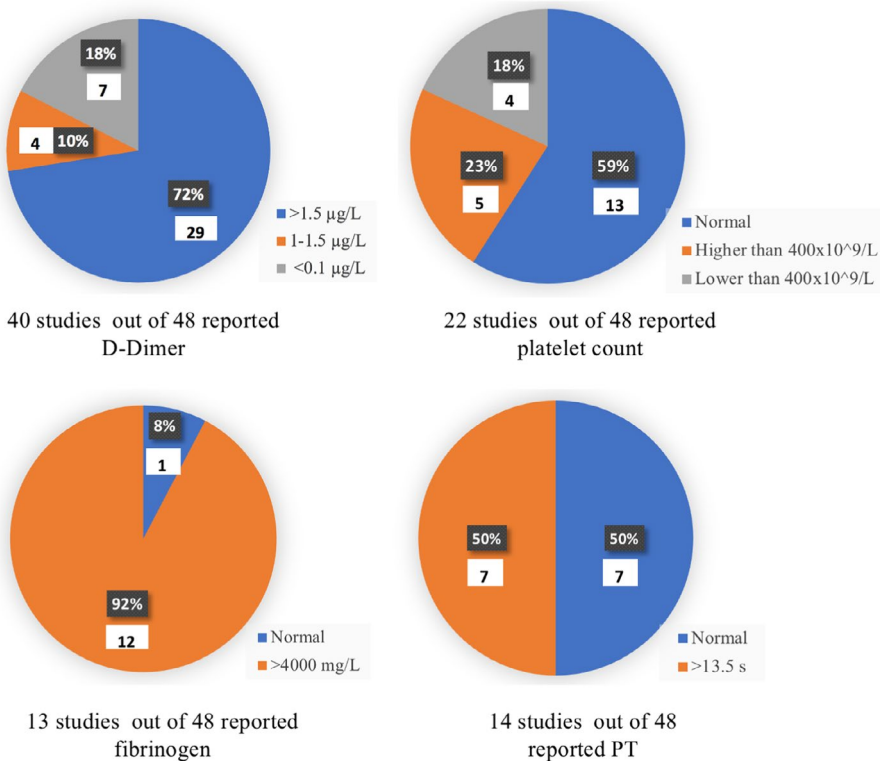

FIGURE 3 Summary of the blood markers/coagulation factors in the 48 included case studies. Each pie chart illustrates the number of studies that reported normal, elevated or low levels of blood marker/coagulation factors in COVID-19 patients with thrombosis and the percentage of patients out of the total number of patients in all studies that reported each blood marker/coagulation factor. Out of the studies that reported the D-Dimer, 35 and 30 reported levels >1 mg/L or >1.5 mg/L respectively. These studies included 88% and 83% of the total number of patients in the 40 studies respectively. Platelet count, fibrinogen and prothrombin time (PT) were not reported in many studies and did not show consistent patterns across the studies that reported them. For example, 15 studies (73% of patients) reported normal platelet count while 8 studies (4 each) reported high (9% of patients) or low (18% of patients) counts. Only 13 studies reported fibrinogen levels out of which 11 reported levels >4000 mg/L (76% of patients). Out of 14 studies that reported PT, 8 studies reported normal PT (53% of patients). In case series where multiple patients were reported, the mean/median values of each marker were used for this graph

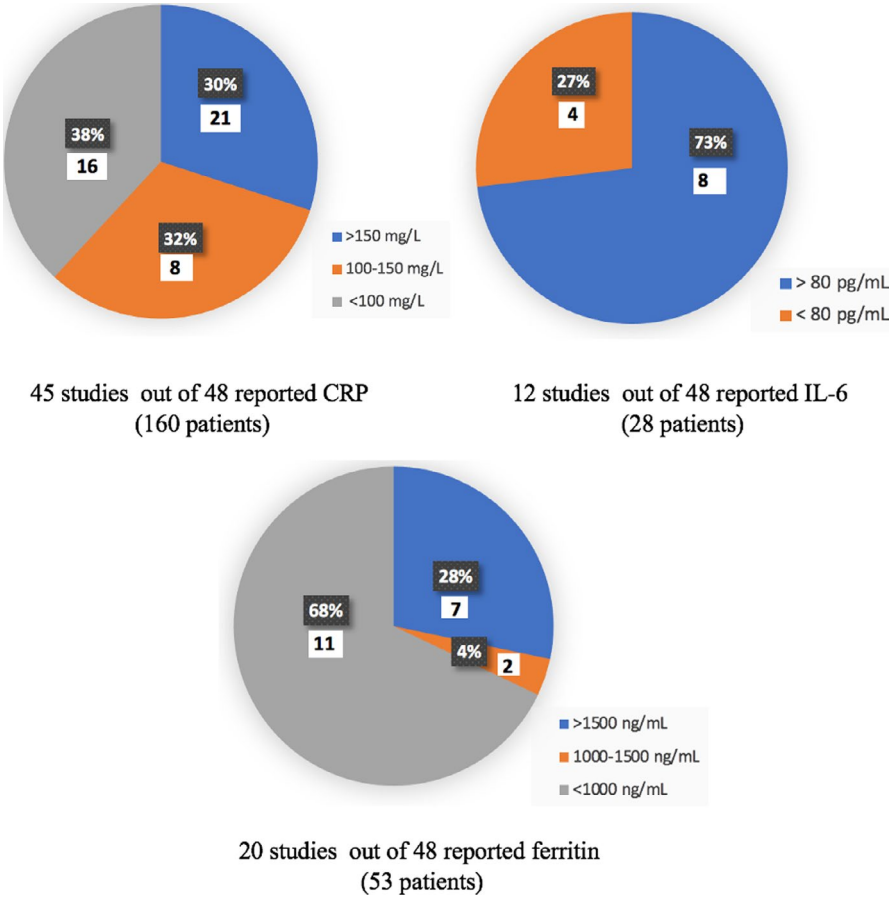

FIGURE 4 Summary of the inflammation markers in the 48 included case studies. Each pie chart illustrates the number of studies that reported certain levels of CRP, IL-6 or ferritin in COVID-19 patients with thrombosis and the percentage of patients out of the total number of patients in all studies that reported each inflammation marker. CRP level was found to be >100 mg/L or >150 mg/L in 29 and 21 of the studies respectively (including 62% and 30% of patients respectively). Only 12 studies reported IL-6 levels, out of which 8 reported levels >80 pg/mL (including 73% of patients). Only 28% of COVID-19 patients with thrombosis in the 20 studies that reported ferritin, had levels >1500 ng/mL and 32% had levels >1000ng/mL. In case series where multiple patients were reported, the mean/median values of each marker were used for this graph. IL-6 and ferritin levels were reported for only 9 out of 32 patients and 2 out of 4 patients, respectively, in 2 different studies.[20,57] Therefore, only those patients were considered for the total patients count in these 2 studies

Treatment by hydroxychloroquine (HCQ) was reported by 20 studies. The use of anticoagulants, antibiotics, antivirals, anti-inflammatory, ventilation and intensive care unit (ICU) admission was reported by the different studies.

4 | DISCUSSION

COVID-19 was found to cause a pro-inflammatory state leading to cytokine release syndrome, an intense inflammatory response leading to acute respiratory distress syndrome (ARDS) and multi-organ dysfunction.[61] It has been well established that coagulation disorders including coagulopathy and hypercoagulation are among the severe complications of COVID-19 that may lead to poor prognosis and mortality. This study investigated the interplay between inflammation and the coagulation cascades in COVID-19 patients by comparing the inflammation and coagulation blood markers/factors in COVID-19 patients with and without thrombosis. Furthermore, data were collected from case studies without control including case reports and case series to gain a better insight into individuals or small groups of COVID-19 patients who developed thrombosis during the course of infection.

4.1 | Coagulation markers in COVID-19 patients with and without thrombosis

Our study revealed that the D-dimer was the coagulation parameter that was most consistently elevated in COVID-19 patients with thrombosis. Several studies reported that COVID-19 associated coagulation disorders were characterized by an increase in D-dimer concentration with almost normal PT and platelet count.[62] This concurs with our observed inconsistent patterns of platelet

TABLE 2 Types of COVID-19-associated thrombosis reported in the 48 included case reports/series

Type of thrombosis	Number of Studies	References
DVT	9	[27, 28, 31, 32, 35, 45, 48, 13, 60]
PE	21	[15, 17, 23, 24, 25, 27, 28, 30, 32, 33, 35, 36, 37, 40, 45, 46, 48, 50, 13, 53, 56]
Strokes	10	[19, 20, 27, 29, 35, 46, 51, 55, 57, 58]
Cerebral thrombosis	10	[22, 23, 25, 36, 39, 43, 47, 50, 52, 59]
Cardiac thrombosis	5	[27, 30, 38, 47, 56]
Mesenteric thrombosis	1	[22]
PVT	1	[44]
CRAO	1	[14]
Aortic thrombosis	3	[34, 35, 54]
Other arterial thrombosis	6	[18, 21, 27, 41 42, 60]
Other venous thrombosis	4	[26, 28, 31, 59]

Abbreviations: CRAO, Central Retinal Artery Occlusion;DVT, Deep Vein Thrombosis; PE, Pulmonary Embolism; PVT, Portal Vein Thrombosis.

counts, fibrinogen levels and PT where several studies reported either normal levels of these coagulation parameters and/or no significant difference in their values between the T and NT groups. The D-dimer is the product of fibrin cleavage by plasmin during the breakdown of clots, and D-dimer has been reported in several studies as a biomarker for poor prognosis and mortality in COVID-19 patients. Choi et al[63] conducted a study to analyse the efficiency of D-dimer as a diagnostic tool of VTE. They classified the levels of D-dimer that stratified patients into low (<1 μg/mL), intermediate (1-7.5 μg/mL) and high (>7.5 μg/mL) levels and the probabilities of VTE were 3%, 18%, and 43%, respectively. This means that with a cut-off value as low as 1 μg/mL, there is still a 3% probability of having VTE. Demelo-Rodriguez et al reported 1.57 μg/mL as a new D-dimer cut-off value with a 95.7% sensitivity and 29.3% specificity.[8] The positive and negative predictive values of DVT were 19% and 97.5% respectively. This suggests that this D-dimer cut-off performs well in ruling out VTE but is associated with a high false positive rate and must be interpreted with caution. In our review, 83% of patients in the case studies that reported the D-dimer had levels higher than 1.5 μg/L.

4.2 | Inflammation markers in COVID-19 patients with and without thrombosis

Unlike D-dimer, only three studies out of the seven cohort studies with control reported significantly higher inflammation markers in the T group compared with the NT group. COVID-19 cytokine storm syndrome (CSS) usually refers to the excessive immune response, which is characterized by high levels of CRP, IL-6 and ferritin, as well as other features such as lymphopenia and multi-organ failure. Some clinical criteria such as COVID-19 pneumonia, the need of mechanical ventilation, fever, and CRP >100 mg/L and ferritin >1000 ng/mL were used to detect CSS for research purposes. IL-6 levels ≥80 pg/mL were reported to predict an increased risk of respiratory failure and death.[64] Furthermore, Reddy et al[65] and Manson et al[66] defined hyperinflammation in COVID-19 patients as CRP and ferritin serum levels higher than 150 mg/L and 1500 ng/mL respectively. In this review, CRP levels were found to be >100 mg/L in 62% of patients in the studies that reported CRP. Furthermore, 73% of patients included in the 12 studies that reported IL-6 had levels >80 pg/mL. Ferritin levels higher than 1000 ng/mL were detected in 32% of COVID-19 patients with thrombosis, which were reported only by 20 studies. A meta-analysis of recent studies showed that derangements in inflammatory and coagulation markers were proportionate to disease severity, and thus, these markers were reliable in prognostication of disease on admission. In particular, the analysis found the highest derangement to be in ferritin, driven by interleukin-8 (IL-8) expression. IL-6 levels and CRP were also elevated. However, PCT was conversely often within normal range despite high disease severity. In this review, serum PCT level was not consistently reported by many of the included studies. Unlike CRP, PCT serum levels, whenever reported, were either elevated or normal. However, it was reported as significantly higher in the T group than the NT group in two studies[7,9] PCT is a glycoprotein precursor to calcitonin and elevated serum PCT is a potential indicator of bacterial infection

or sepsis.[67,68] COVID-19 patients with high PCT may have concomitant bacterial infections.[67] Maximal plasma IL-6 was found in COVID-19 patients with high PCT levels compared to those with low PCT.[68] Unlike serum IL-6 and CRP that significantly correlate with COVID-19 severity and can be used as independent factors to predict disease risk, PCT needs further investigation.[67] These elevations in inflammatory markers were reported to be paralleled by derangements in PT, platelet count and most significantly, D-dimer levels. Therefore, endothelial injury caused by a pro-inflammatory state may contribute to a pro-coagulant state.[69]

The above results suggest a correlation between hyperinflammation and hypercoagulation in COVID-19 patients.

4.3 | COVID-19, the cytokine storm and hypercoagulation

Short half-lives restrict cytokine communication with other immune cells to lymphoid tissue and sites of local inflammation. However, at high-enough levels, cytokines can exert a systemic effect, which may lead to increased production and mobilization of neutrophils and monocytes, and an elevated T-cell response. Such a systemic effect can lead to collateral damage through a wide range of physiological processes such as inducing fever, cell death, and impairing vascular physiology and coagulation. Excessive cytokine production can overtake the immune regulatory mechanisms causing cytokine storm and hypercytokinemia.[70] The cytokine storm may lead to the activation of the endothelial cells leading to capillary leakage, hypotension and hypercoagulation.[71] Inflammation induces thrombosis via activation of the coagulation cascade and downregulation of anticoagulation factors.[72,73]

4.3.1 | COVID-19 and the cytokine storm

The severity of COVID-19 infection is associated with a dysregulated inflammatory immune response which inhibits protective immune mechanisms and hinders viral clearance. Unmodulated non-resolving inflammation can progress to a state of hyperinflammation which inhibits the adaptive immune response, causes tissue damage, organ failure and death which was observed in severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19.[74] This dysregulated immune response, rather than viraemia, was found to be the cause of mortality of some COVID-19 patients.[75] The main consequences of the cytokine storm are the progressive widespread systemic inflammation, loss of vascular tone, and progressive organ failure, especially the heart and kidneys. Uncontrolled overproduction of inflammatory cytokines, including IL-6, can increase the expression of CRP and lead to acute lung injury and ARDS.[71,76-78] Furthermore, IL-6 was reported to cause vascular leakage and the activation of complement and coagulation cascades.[71,79,80] Pre-existing conditions/comorbidities that affect the health of the vascular system may decrease body resilience and the ability to tolerate systemic cytokines. Diabetes, HTN and CVD are the main risk factors that underly COVID-19 pathogenesis.[70] The exaggerated inflammatory response characteristic to COVID-19 could be attributed to the impaired interferon type I (IFN-I) response due to the reduced and/or delayed production of IFN-I in addition to the aberrant pro-inflammatory cytokine secretion by alveolar macrophages.[75,81] COVID-19 patients in ICU were found to have significantly higher levels of IL-6, IL-10 and tumour necrosis factor alpha (TNF-α) compared with non-ICU patients.[75,82]

The cytokine storm may cause lymphopenia which impairs the capacity of the adaptive immune system to generate antibodies specific to the virus and reduce the production of interferon gamma (IFN-γ) by the CD4+ T cells.[74,75] Lymphopenia, which is prevalent in elderly people, plays a role in the progression of the cytokine storm due to the impaired clearance of the virus.[82] This may explain the role of age as one of the risk factors of COVID-19. T-cell numbers are negatively correlated with IL-6, IL-10 and TNF-α concentrations.[82] Furthermore, It is hypothesized that SARS-CoV-2 may infect dendritic cells leading to T-cell apoptosis.[76,82] T-cell exhaustion due to prolonged infection may also be a result of the immune inhibitory expression of programmed cell death protein 1 (PD-1) on the cell surface.[82,83] In fact, the percentage of PD-1+CD8+ T cells was found to be higher in the ICU COVID-19 patients than the Non-ICU patients.[82] This impaired capacity to provide an efficient adaptive immune response may lead to uncontrolled viral replication, which may cause the excessive release of the inflammatory mediators.

4.3.2 | SARS-CoV-2: Hyperinflammation and thrombosis

Inflammation may play a role in the primary and secondary haemostasis mechanisms including both the intrinsic and extrinsic pathways. Primary haemostasis is the formation of the primary platelet plug, which plugs off small injuries. Endothelial damage leads to the adhesion of platelets by exposing the underlying collagen to circulating platelets which bind directly to the collagen via specific surface receptors. The endothelial cells and the platelets release von Willebrand factor (vWF), which

further strengthen the adhesion. This interaction between the endothelial collagen and the platelets triggers a signalling cascade that results in activation of platelet integrins which mediates tight binding of platelets to the extracellular matrix. Platelet activation includes the release of certain mediators which activate more platelets and promote certain modifications that increase the platelets affinity to bind to fibrinogen. The coagulation cascade of secondary haemostasis include the intrinsic/contact activation pathway and the tissue factor (TF)/extrinsic pathway. Both pathways lead to the production of fibrin through a series of serine protease cleavage reactions to activate several zymogens, which are inactive coagulation factors. The main role of the extrinsic pathway is to generate thrombin. During the extrinsic pathway, TF is exposed and binds to the circulating VII, forming an activated complex called TF-VIIa, which activates IX and X to Xa. The intrinsic/contact activation pathway can also lead to the formation of Xa through the formation of a complex of high-molecular-weight kininogen (HMWK), prekallikrein and XII on collagen. This leads to the formation of kallikrein and XIIa which converts XI into XIa. This activates IX, which with its cofactor VIIIa form the tenase complex, which activates X to Xa. This part of the coagulation cascade is common between the intrinsic and extrinsic pathways where both Xa and its cofactor Va subsequently activate prothrombin to thrombin which converts fibrinogen to fibrin. Furthermore, it activates XIII to XIIIa, which crosslinks the fibrin polymers produced from activated monomers. Additionally, thrombin can activate other components of the coagulation cascade such as VIII and V.[84]

Under physiologic conditions, the coagulation system is maintained through a series of checks and balances so that it rests in a neutral position between procoagulant and anticoagulant tendencies. Certain pathological environments, particularly those with high inflammatory burdens, can tip the balance towards a procoagulant state and promote the formation of thrombi. This is believed to be due to the extensive crosstalk between inflammation and coagulation, which exaggerates both the primary and secondary haemostasis response in the absence of thrombogenic stimuli resulting in pathologic clots. Additionally, proinflammatory cytokines have been shown to downregulate the physiologic antithrombotic mechanisms that would seek to prevent inappropriate coagulations.

Role of IL-6 and TNF-α in inducing coagulation

The main mediators of inflammation-induced activation of the coagulation system are IL-6, IL-1 and TNF-α.[85,86] As such, COVID-19 has been associated with the high burden of hypercoagulation due to the exaggerated cytokine response that it incites in its host. The main mechanism by which inflammation induces the coagulation cascade is through the upregulation of TF in leukocytes, particularly the monocytes.[87-90] IL-6 was found to be secreted when SARS-CoV-2 infects monocytes, macrophages, and dendritic cells. IL-6, IL-1 and TNF-α were found to induce TF expression on monocytes, endothelial cells and smooth muscle cells and are important mediators in the crosstalk between inflammation and coagulation. When the endothelium is disrupted, TF comes into direct contact with blood in the lumen and can activate the coagulation cascade by forming a complex with factor VII to form TF-VIIa leading to the downstream production of thrombin, which subsequently converts fibrinogen into fibrin.[85] It also activates platelets and contributes to the formation of platelet plugs. Finally, activated thrombin also activates coagulations factors V, VIII, XI and XIII which in turn activate more thrombin that can convert fibrinogen into fibrin downstream of the coagulations cascade.[85] Furthermore, the expression of P-selectin on the membrane of the activated platelets will promote the binding of platelets to endothelial cells and leukocytes such as neutrophils leading to the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which subsequently enhances the expression of TF.[86] In vivo experiments showed that inhibition of IL-6 can completely abrogate the TF dependent coagulation in endotoxemia.[86,88] Moreover, IL-6 was reported to induce megakaryopoiesis that may increase the platelet count[91,92] and to induce the synthesis of other coagulation factors such as fibrinogen and factor VIII.[91,93,94]

IL-6 may bind to its specific cell surface interleukin-6 receptor (IL-6R), which is exclusively expressed by the immune cells and form a complex with glycoprotein 130 (gp130) to activate the Janus kinase/signal transducer and activator of transcription proteins (JAK/STAT) pathway. The activation of this signalling pathway may lead to multiple effects on both adaptive and innate immune systems, which can contribute to the cytokine storm. IL-6 may also bind to the soluble IL-6R and form a complex with gp130 which is expressed by all types of cells. This may lead to the activation of the JAK/STAT pathway in cells that do not express IL-6R including the endothelial cells. This will result in a systemic cytokine storm and the secretion of vascular endothelial growth factor (VEGF) and more IL-6 production in addition to reducing the expression of E-cadherin on endothelial cells. This together with VEGF leads to the increased vascular permeability and hypotension.[76,79] A recent study examined the sera of patients with COVID-19 found that elevated levels of IL-6 correlated with an elevation in complement levels. Additionally, various coagulation factors were dysregulated, including increased levels of antifibrinolytic enzymes such as serine protease inhibitors (SERPINs).[95]This can be explained by

the capacity of IL-6 to induce the synthesis of acute-phase mediators such as complement proteins. The complement system is known to be prothrombotic through tissue factor activation. In fact, C3-deficient mice have prolonged bleeding times and lower levels of fibrin within vessel walls.[96] Thus, IL-6 with its association with elevated complement levels and anti-thrombolytic enzymes is likely an important factor in thromboembolic events in COVID-19 patients. Elucidating the mechanisms behind such association is crucial to developing effective therapeutic targets. Furthermore, identifying IL-6 as a potential drug target has brought about the consideration of the anti-IL-6 drug tocilizumab for COVID-19 therapy, which is discussed in section 4.6.2.2.

Role of CRP in inducing coagulation

IL-6 induces the production of acute-phase proteins such as CRP, which is known to be a sensitive biomarker of inflammation.[6779] Grimnes et al[97] revealed that high levels of CRP may trigger VTE. They conducted a case-crossover study of 707 patients from the general population with VTE. Their results revealed that the level of CRP was 58% (95% CI 39%-77%) higher in the hazard period than in the control periods. CRP is hypothesized to activate the vascular cells through multiple mechanisms. It may inhibit nitric oxide (NO) synthase expression and consequently reduce NO production, which has an anticoagulation effect. CRP was found to trigger thrombosis by inducing the adhesion of platelets to the endothelial cells.[98,99] It may upregulate the expression of interleukin-8 (IL-8), intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, which can induce coagulation[100,101] CRP may exist in a monomeric or a pentameric form. Unlike the pentameric form of CRP, monomeric CRP binds to the Fc fragment of immunoglobulin G (IgG), low affinity IIIa, receptor (FcγRIII) expressed on the platelets, which enhances the interaction between the platelets and neutrophils.[102] When the platelets are activated, they convert pentameric CRP to the monomeric CRP.[103,104] Therefore, this mutual activation process between the CRP and the platelets may explain why platelet activation may result in the activation of neutrophils and monocytes and invasion into the vascular wall.[105]

Role of ferritin in inducing coagulation

Ferritin is another inflammatory marker in COVID-19 patients and its serum elevation together with IL-6 was found to be correlated with higher mortality.[76] Ferritin is an intracellular iron storage protein, which plays a key role in inflammation. Hyperferritinemia indicates that high circulating ferritin may play a critical role in inflammation during which cellular death is a major source of serum ferritin. When ferritin is released into the serum, it loses part of the inner iron content which results in increased circulating free iron, noted in severe inflammatory states.[72] High level of iron was found to enhance the production of reactive oxygen species and systemic markers of oxidative stress.[106] Furthermore, high iron concentrations help induce a pro-coagulation state leading to the formation of blood clots and stroke.[72,107]

Role of neutrophils and complement in inducing coagulation

Neutrophil extracellular traps (NETs) are extracellular webs formed of DNA, histones, microbicidal proteins and oxidant enzymes that are released by neutrophils to combat infections. Uncontrolled release of NETs may initiate inflammation and thrombosis.[108-110] NETs together with the complement system were found to produce the immunothrombotic response to invading pathogens. The N (nucleocapsid) protein of SARS-CoV-2 can provoke the production of the anaphylatoxin C5a, which subsequently activates neutrophils, leading to the amplification loop of complement and neutrophil activation and further production of C5a.[111,112] In a study conducted by Busch et al,[112] they analysed a large cohort of COVID-19 patients and used enzyme-linked immunosorbent assays (ELISA) to measure activated coagulation factors and their natural inhibitors. Their study revealed that hypercoagulability and thrombotic events are driven by NETosis, contact activation and complement. Furthermore, they found that the levels of C5a was elevated especially in the sever cases. Another study compared COVID-19 patients with and without thrombosis. The thrombosis group had higher levels of D-dimer, CRP, ferritin and platelets. They found a strong association between markers of neutrophils hyperactivity such as calprotectin and cell-free DNA and D-dimer. This led to the conclusion that levels of neutrophil activation and NET formation in the hospitalized COVID-19 patients are associated with higher risk of thrombotic complications.[110] It was also reported that complement inhibition improved the outcomes in SARS-CoV and MERS-CoV murine models. It was therefore suggested that complement inhibition can be used as a treatment option for COVID-19-related systemic thrombosis.[42,113,114]

Role of inflammation in inhibiting the regulatory mechanisms of coagulation

The coagulation cascade is regulated by multiple factors including antithrombin, which is the main inhibitor of thrombin, Xa and IXa. Increased activation of the coagulation cascade during inflammation results in increased consumption of antithrombin. Inflammatory responses are rich in neutrophils, which can cause increased degradation of antithrombin through proteolytic

cleavage enzymes such as elastases that are abundant during inflammation. There is also decreased synthesis of antithrombin during inflammation,[85] which further contributes to a deficiency in antithrombin to counteract activated thrombin, Xa and IXa. Protein C (PC) is another regulatory mediator which together with its cofactor protein S cleaves activated Va and VIIIa. It was found that the PC regulatory pathway is not functional in patients with severe inflammation where the plasma zymogen PC levels were low due to impaired synthesis and degradation by the neutrophilic elastases. Furthermore, thrombomodulin, which is required for the activation of PC, is downregulated due to the pro-inflammatory cytokines. Another factor that may impair the activity of the PC regulatory pathway is the low levels of the cofactor protein S during inflammation due to binding to the complement regulatory protein C4b binding protein, which is overexpressed due to acute-phase inflammatory reactions.[115]

Role of ACE2 in inducing coagulation

SARS-CoV-2 uses its spike protein to invade the cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed by Type 2 alveolar cells of the lungs, myocardial cells, kidney proximal tubule cells, bladder urothelial cells and other tissues. SARS-Cov-2 binds to the ACE2 protein with much higher affinity than SARS-CoV binding.[74] ACE2 is part of the renin-angiotensin-aldosterone system (RAAS), which comprises several proteins that play multiple roles in regulating blood pressure.[116] Angiotensin-converting enzyme (ACE) is an enzyme expressed by different types of tissues and can convert angiotensin I (ATI) to angiotensin II (ATII), which is known to induce inflammation.[117] ACE2 cleaves the inflammatory ATII to the anti-inflammatory ATI. Severe SARS-CoV-2 infection depletes ACE2 and consequently increases the level of ATII. This leads to RAAS dysfunction and induces several inflammatory responses including Toll-like receptor 4 (TLR4) activation, which triggers innate immune response and enhanced inflammation.[74,118] As ACE2 is also expressed in the endothelial cells of the blood vessels, and its downregulation due to SARS-CoV-2 infection may lead to a proinflammatory response and impair the integrity of the vascular endothelium. This will consequently increase vascular permeability and activate coagulation.[119]

4.4 | Thrombosis due to direct viral attack

SARS-CoV-2 infects host cells by binding ACE2 receptor,[120,121] which is expressed with high density in the lungs, heart, veins and arteries.[122] This has a great implication as a possible mechanism of endothelial cell injury and consequent thrombosis due to viral entry of the endothelial cells through ACE2 binding. Endothelial cell injury may lead to the activation of the primary and secondary pathways of haemostasis due to the exposure of subendothelial matrix and exposure of TF leading to platelet activation. Furthermore, endothelial damage induced by viral entry may upregulate the expression of TF and suppress the anticoagulant activity and thus disrupt the balance between pro- and anticoagulant states and promote thrombus formation.[123] Another potential mechanism by which SARS-CoV2 may activate the coagulation system is its genomic structure. Cell-free circulating RNA (cf-RNA) has been shown to promote coagulation by serving as a cofactor for the auto-activation of factor VII-activating protease.[120,124] Furthermore, it was reported that human and mouse platelets express ACE2 to which SARS-CoV-2 can bind and enhance thrombosis in COVID-19 patients. Through this binding, SARS-CoV-2 directly activates the ACE2/mitogen-activated protein kinase pathway to potentiate platelet activation and aggregation. Using recombinant human ACE2 and an anti-spike monoclonal antibody was found to reveres this process by suppressing SARS-CoV-2-induced platelet activation.[125]

4.5 | Thrombosis in SARS, MERS and COVID-19

Hypercoagulation was found to be a common feature in many of the coronaviruses. There seems to be a predisposition to a prothrombotic state in all of these infections including the two previous pandemics SARS (2002) and MERS (2012). A hypercoagulable state and subsequent occurrence of thrombotic events has been described in relation to both pandemics as well as the recent COVID-19 pandemic.[126] Similar to the reported thrombotic events in this review, several case reports of thrombi were described in patients infected with SARS-CoV, including PE, DVT, multiple organ thrombosis including cardiac and cerebral thrombosis, ischaemic strokes and VTE.[126-132] Interestingly, thrombi within placental circulation also contributed to foetal complications (oligohydramnios, intrauterine growth delay, and small foetal size) in SARS-CoV-infected patients.[133] Furthermore, prolonged PT, prolonged activated partial PT, elevated D-dimer, worsening thrombocytopenia,[131] reactive thrombocytosis[132] and increased thrombopoietin levels[134] were reported. Interestingly, one study found that these haematological parameters were not associated with ICU admission or mortality rates.[135] Similarly, MERS was also associated with thrombotic complications such as DIC that was

found to be a major cause of mortality,[5,136] in addition to thrombocytopenia.[137,138]

4.6 | Treatments

4.6.1 | Anticoagulants

The association between hypercoagulation and COVID-19 poses a need for screening and guidelines on management to increase patient survival. Recent studies have laid out recommendation in effort to target COVID-19-associated hypercoagulation, beginning with screening. All admitted patients with SARS-CoV-2 should have their D-dimer, PT, fibrinogen and platelet counts assessed to screen for evidence of hypercoagulation.[6] However, our collected data in this review indicates that D-dimer elevation is more consistently elevated in COVID-19 patients with thrombosis as compared to the other coagulation blood markers. Thrombotic events seem to correlate with disease severity, and thus, management follows an escalating pattern based on patient status. Heparin is anticoagulant that induces conformational changes in the antithrombin which substantially enhances its anticoagulation activity.[115,139] COVID-19 patients admitted on the ward are recommended to receive standard-dose prophylaxis, with either LMWH (such as enoxaparin) or unfractionated heparin.[6,140] Patients with severe illness due to COVID-19, marked by ICU status or ARDS, are recommended to receive escalated-dose of VTE prophylaxis.[6,141] Therapeutic anticoagulation is recommended for COVID-19 patients with confirmed VTE, presumed PE, atrial fibrillation, mechanical heart valves, or provided as long-term prevention of a secondary VTE. Recent preliminary unpublished data from ongoing randomized controlled clinical trials suggest that therapeutic anticoagulation reduced the need for mechanical ventilation or other organ supportive interventions compared with prophylactic anticoagulation in hospitalized moderately ill (non-ICU) COVID-19 patients. This benefit was not seen in severely ill ICU patients.[142] Lastly, outpatients with morbid obesity, immobility or prior history of VTE should be considered to receive a standard-dose VTE prophylaxis on a case-by-case basis.[6] Many COVID-19 patients required thrombectomy as reported by some of the included studies such as Andrea et al,[18] Baccelleiri et al,[21] Giacomelli et al,[34] Kaur et al[42] and Yaghi et al[57] Furthermore, many COVID-19 patients in the included studies required thrombolysis (Akel et al,[15] Andrea et al,[18] Bruggmann et al,[25] Co et al,[29] Creel-Bulos et al,[30] and Harari et al[38]). Cena et al[28] reported the early placement of an inferior vena cava filter, which was to the therapeutic anticoagulation to prevent a massive pulmonary embolism.

4.6.2 | Anti-inflammatories

This review highlighted the possible role of inflammation in promoting hypercoagulation. Therefore, targeting the hyperinflammatory state in COVID-19 poses another avenue for disease management, as anti-inflammation would help slow down the propagation of inflammatory state responsible for the hypercoagulation and multi-organ failure.[143,144]

Glucocorticoids (Dexamethasone)

Numerous anti-inflammatory drugs are available to target the hyperinflammatory state and cytokine storm frequently seen with SARS-CoV-2, including glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), chloroquine/HCQ, immunosuppressants and inflammatory cytokine antagonists.[144] Corticosteroids in particular hold potent anti-inflammatory and antifibrotic properties, but the use of low-dose glucocorticoids, especially dexamethasone, has been hotly contested.[145] Earlier reports documented that the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC) and Surviving Sepsis Campaign COVID-19 all recommended against the use of systemic corticosteroids to treat invasive mechanically ventilated (IMV) adults infected with coronavirus.[145] However, on 16 June 2020, the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial announced preliminary findings that low doses of dexamethasone improved survival in COVID-19. A dosage of 6 mg dexamethasone once daily for up to 10 days has been shown to reduce deaths by one-third in ventilated patients, and one-fifth in patients only receiving oxygen as compared to patients who received standard care. When assessing the impact of dexamethasone intervention, treating 8 ventilated patients or 25 patients requiring oxygen will prevent 1 death. However, dexamethasone demonstrated no benefit in patients with milder disease not requiring respiratory support.[145-147] Although systemic glucocorticoid treatment in COVID-19 has become standard of care in moderately to severely ill patients, it still requires further exploration of optimal dosage, timing of administration and duration of treatment.[147]

IL-6 Inhibitors (Tocilizumab)

Identifying IL-6 as one of the main inducers of inflammation has made it a potential anti-inflammatory drug target. The anti-IL-6 drugs may either block the cytokine or its receptor. Tocilizumab is an immunosuppressive drug which competes with IL-6 for its receptor and block its signalling pathways.[148] The use of tocilizumab has been reported as a therapeutic agent for COVID-19. Preliminary results of the RECOVERY trial revealed that using tocilizumab in addition to corticosteroids has improved the survival and

other clinical outcomes in COVID-19 patients who suffered from hypoxia and systemic inflammation.[149]

4.7 | Some COVID-19 vaccines have been approved but research should continue

Developing vaccines for SARS-CoV-2 utilize the S (spike) glycoprotein as a target antigen, due to its crucial role in eliciting the immune response during infection.[150,151] As of 4 March 2021, CDC has reported Pfizer-BioNTech, Moderna and Johnson&Johnson/Janssen as approved and recommended COVID-19 vaccines. As of 27 February 2021, CDC has reported that AstraZeneca and Novavax COVID-19 vaccines are in phase 3 clinical trial. However, AstraZeneca vaccine has been approved for emergency use in some countries, including the United Kingdom and European Union.[152] On December 14, WHO was notified of a new SARS-CoV-2 variant that was circulating in the United Kingdom (UK). It was identified through viral genomics sequencing in the UK and is believed to be phylogenetically unrelated to the SARS-CoV-2 virus that was originally circulating in the UK at the time of detection. As such, the new variant is being referred to as SARS-CoV-2 VOC 202012/01 or B.1.1.7.[153,154] The new variant contains 23 mutations on the spike proteins. The most significant mutation is N501Y which alters an amino acid within the receptor binding domain and may confer increased transmissibility in the new variant by allowing for tighter binding with ACE2R.[155] The new variant has an estimated increase of around 70% in transmissibility of the virus, possibly conferred by mutations in the spike protein, specifically the RBD.[156157] Preliminary data suggest that although transmissibility may be increased, there seems to be no change in severity or clinical outcomes from the new variant. However, it has been noted to infect predominantly younger individuals aged less than 60 years old. Another variant of SARS-CoV-2 emerged in South Africa independently of B.1.1.7 (known as 20H/501Y.V2 or B.1.351). This variant shares some mutations with B.1.1.7. COVID-19 patients infected with this variant were detected in countries other than South Africa including the United States. Furthermore, P.1 is another variant of SARS-CoV-2, which emerged in Brazil with 17 unique mutations, including three in the spike protein receptor binding domain.[154] As of 8 March 2021, CDC reported that the currently authorized COVID-19 vaccines may provide some protection against some of the SARS-CoV-2 variants including B.1.1.7, while reduced antibody neutralization and efficacy have been observed for the South African variant.[158] Therefore, research should continue in the field of prevention and treatment of COVID-19 and its severe complications including thrombosis.

4.8 | Recommendations

Many of the included studies had important recommendations for the early detection, prevention and treatment of the COVID-19-associated hypercoagulation. For example, Ashrafi et al,[19] Beccara et al,[22] Breakey et al,[24] Hughes et al[39] and Overstad et al,[48] recommended the use of prophylactic anticoagulants in COVID-19 patients, while Akel et al[15] and Gomez-Arbelaez et al[35] suggested the extended use of prophylaxis after the patients are discharged. Preliminary data from unpublished clinical trials suggest that therapeutic anticoagulation is superior to prophylactic in moderately ill hospitalized patients but not in critically ill patients.[142] However, risk of thrombosis should be balanced with the risk of haemorrhage when anticoagulants are used.[23] Lowering the threshold for computed tomography (CT) angiography scans and anticoagulation was suggested by Akel et al,[15] Benger et al,[23] Nicholson al.[47] and Sung et al[52]Bruggemann et al[25] stated that the commonly used diagnostic approaches could be insufficient to detect the COVID-19-triggered thrombotic complications and Griffin et al went on to recommend surveillance for development of DIC in COVID-19 patients with measurement of platelet counts, D-dimer and fibrinogen levels. Co et al[29] suggested the development of an acute stroke unit to manage COVID-19 patients and to establish a clinical pathway and guidelines for the management of these complications in COVID-19 patients. Finally, Ueki et al[56] recommended that the treatment of COVID-19 requires multidisciplinary expertise to address its various clinical manifestations. They also added that the interactions between oral and intravenous anticoagulants and the other drugs such as antivirals should be considered when treating the COVID-19 patients. Finally, inflammation can be therapeutically targeted using corticosteroids such as dexamethasone and the anti-IL-6 drugs such as tocilizumab.[145-149]

5 | CONCLUSIONS

A myriad of thrombotic events are frequent in COVID-19 patients, which includes PE, DVT, strokes and other types of venous and arterial thrombotic events. Such events could be attributed to the hyper-inflammatory response associated with COVID-19. It is recommended that all admitted patients with SARS-CoV-2 should have their D-dimer, PT, fibrinogen and platelet counts assessed to screen for evidence of hypercoagulation. Amongst these, our collected data in this review indicate that D-dimer elevation is more consistently elevated in COVID-19 patients with thrombosis as compared to the other coagulation parameters. Different treatment strategies have been used

including prophylactic and therapeutic anticoagulants in addition to thrombectomy and thrombolysis. The use of anti-inflammatory drugs is also crucial where corticosteroids have been widely and successfully used to control the hyperinflammatory response triggered by SARS-CoV-2. A high index of suspicious should be maintained to detect any thrombotic complications secondary to COVID-19. This may include the availability of multidisciplinary expertise to assess patients' conditions, to lower the threshold for the more specialized diagnostic approaches such as CT angiography scans, to balance the benefit and risk of using anticoagulants and to consider drug interactions. Some vaccines against SASR-CoV-2 have been now approved and distributed in several countries. However, research should continue in the field of prevention and treatment of COVID-19 and its severe complications including thrombosis due to the emergence of new variants against which the efficiency of the vaccines is not clear.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have contributed to different phases of the project including reviewing the literature, data extraction and writing/editing/reviewing the manuscript.

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