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A review of pathophysiological mechanism, diagnosis, and treatment of thrombosis risk associated with COVID-19 infection

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ABSTRACT

Severe coronavirus (COVID-19) infection has been reportedly associated with a high risk of thromboembolism. Developing macrovascular thrombotic complications, including myocardial injury/infarction, venous thrombo-embolism, and stroke have been observed in one-third of severe COVID-19 hospitalized patients, leading to an increase in mortality and morbidity. The diagnosis of COVID-19 associated coagulopathy may be challenging because there are close similarities between pulmonary embolism and severe COVID-19 disease. Therefore, a critical step in improving the clinical outcome of patients with hospitalized COVID-19 is the recognition of coagulation abnormalities and the identification of patients with poor prognoses, prophylactic guidance, or antithrombotic therapy. Prescribing anticoagulants in all patients hospitalized with COVID-19 and 2–6 weeks post-hospital discharge in the absence of contraindications is recommended by most consensus documents published on behalf of professional societies. However, a decision on some variable factors such as intensity and duration of anticoagulation may be made based on an individual case and needs future randomized trial studies. Regarding little information on this subject, this study aims to review how inflammation and thrombosis are related to COVID-19 patients, discuss the types of thrombosis in these patients, and summarize the diagnosis and treatment of thrombosis in COVID19 patients.

1. Introduction

The coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that can lead to the thromboinflammatory disease and plays a critical role in the path-ophysiology. This virus is a new ribonucleic acid (RNA) virus strain [1] which was declared a pandemic by the World Health Organization (WHO) in March 2020. The strains of this virus (sequence identity of 99.98%) were classified into two haplogroups (A and B), one of which is predominant worldwide, and the second is reported in America and Asia more than in Africa and Europe [2].

The spike-like protein (S protein) of SARS-CoV-2 can enter cells through angiotensin-converting enzyme 2 (ACE-2). This enzyme plays a vital role in viral proliferation and is mainly found on the alveolar epithelium and endothelium [3]. The expression of ACE2 in different organs is related to the panoply of clinical systemic symptoms of COVID-19, such as respiratory, hepatic, renal, gastrointestinal, and cardiac damage [4]. The down- and upregulation of ACE2 can play a critical role in hypertension, heart failure, overall cardiovascular disease (CVD), and myocardial infarction [5].

There are clinical spectra of COVID-19 ranging from mild to critically ill cases. Patients who have chronic respiratory disease, old age, and coexisting with medical conditions can be the principal target of the virus [6,7]. Moreover, other factors such as infection and bedridden can increase the risk of venous thromboembolism (VTE) [8,9]. Deep vein thrombosis (DVT) or fatal pulmonary thromboembolism (PTE) in COVID-19 patients causes the treatment to be challenging and patients with VTE may have a worse clinical outcome. Therefore, understanding the mechanism taking part in the severity of COVID-19 and mortality is important to identify and treat patients with the highest thromboem-bolic risk and mortality. This study aims to investigate and explain the relationship between inflammation and thrombosis and summarize the prophylaxis, diagnosis, and treatment of thromboembolism in patients affected by COVID-19.

2. Research method

This study involved articles and relevant data investigating the thrombosis and blooding in patients affected by COVID-19 and the prophylaxis, diagnosis, and treatment of thromboembolism in these

patients. Information that was published until March 1, 2022, was collected by searching in PubMed/MEDLINE, Google Scholar, Scopus, Clinical trials. gov website, Cochrane Library, and valid encyclopedias. The keywords including "deep vein thrombosis", OR "Coagulopathy", "Disseminated intravascular coagulation," "venous thromboembolism", and "hemostasis" were combined with the keywords including "SARS-CoV-2" OR "COVID-19" to be used as search terms. All kinds of the research project,comments, editorials, reviews, letters, and eBooks that have been published were included. In addition, preprint databases (Preprints.org, biorxiv.org) were also searched for papers accepted but not yet published. Google Chrome's built-in translation tool was used to review from other languages to English language studies.

3. Results

3.1. Thrombosis and inflammation

3.1.1. How does thrombosis occur?

The vascular injury that causes clotting has several steps, including activation of the coagulation cascade and formation of a platelet plug. Components such as polymorphonuclear cells, endothelial cells, microparticles, and complement systems are involved in this complex process [10]. The coagulation cascade is divided into two pathways which converge to form fibrin as the final common pathway product. To form and expand the clot, the fibrin can entangle platelets and other cellular elements [10]. Several agonists play a role in platelet activation, including thrombin via protease-activated receptors (PAR) 1 and 4 and collagen via glycoprotein (GP) VI receptors. The first coagulation cascade, the contact activation pathway, caused intrinsic activation of the coagulation cascade via initial activation of FXII, followed by sequential activation and amplification of FXI, followed by FIX activation [11]. Typically, trauma to tissue and endothelial cell activation can induce the extrinsic coagulation cascade, known as the tissue factor (TF) pathway [12]. The expression of TF in vascular cells is upregulated after pathologic conditions, such as endothelial cell damage or endothelial cell activation [13]. Both two coagulation cascade pathways converge to thrombin that can convert fibrinogen to stabilize the fibrin clot, which rapidly entangles platelets leading to clot propagation [14]. Activation of platelet is the most prominent mechanism [15], whereas activation of the coagulation cascade is predominate in the venous circulation [16].

3.1.2. Pathophysiology of thrombosis and inflammation in COVID19

After SARS-CoV-2 infection, viral-dependent mechanisms such as invasion of endothelial and alveolar epithelial cells and viral-independent mechanisms including immunological damage such as perivascular inflammation can lead to the breakdown of the endothelial–epithelial barrier [17]. Then, the monocytes and neutrophils are invasive and extravasation of a protein-rich exudate into the alveolar space, consistent with other forms of survivors of acute respiratory distress syndrome [18]. A previous study demonstrated that increasing levels of cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-2R were observed in severe COVID-19-associated systemic inflammation [19]. The outcomes of severe COVID-19 were associated with increased levels of IL-6 [20]. The virus infection can induce acute inflammation that is associated with prothrombotic changes in fibrin clot dynamics, including increased clot turbidity of fibrin and strand density [21]. Therefore, levels of markers such as fibrinogen and D-dimer may be elevated [22]. During inflammation, not only the promotion of leukocyte recruitment occurs but also coagulation and platelet activation, leading to increasing thrombin [23,24]. Severe inflammation can also increase prothrombotic tendency, leading to disseminated intravascular coagulation. These results can decrease detectable clotting factors as these are consumed rapidly, therefore reducing hemostatic function and increasing bleeding risk [25]. Inflammation impacting local hemodynamics, arterial circulation, and plaque stability can probably trigger thrombosis [26]. Inflammation in

the arterial circulation can drive atheromatous plaque progression, which can trigger thrombosis via impacting local hemodynamics, plaque stability, and plaque rupture or erosion events [27]. Also, inflammation can induce an adverse effect on the function of endothelial such as decreasing in the activity of the antithrombotic factors, tissue factor pathway inhibitor, and protein C, as well as increasing in the release of von Willebrand factor (vWF), which facilitates platelet-endothelium and platelet-platelet binding [27].

4. Thrombosis in COVID19 patients

4.1. Microvascular complications

Pathological occlusion of arterioles, capillaries, and venules (microvessels) by platelet- and/or fibrin-rich thrombi is known as microvascular thrombosis [28]. Diagnostically, the development of microvascular thrombosis is a challenge because the microthrombi have a small size (often $\leq 10 \mu m$) that is difficult to be visualized; there is no specific biomarker to detect microthrombi, and occurring microthrombi is only transiently [28]. Clinically, microvessel occlusion can occur in ischemia with the effects ranging from alterations in plasma coagulation markers to severe multiorgan failure [29].

Given the possible relationship between microvascular thrombosis and organ failure, it seems that microvascular thrombosis plays an important role in the course of COVID-19 [30]. Proximally, one-third of hospitalized severe COVID-19 patients develop macrovascular thrombotic complications, which are associated with an increased risk of hospital mortality [31]. In many severe COVID-19 patients, coagulation abnormalities that mimic thrombotic microangiopathy or DIC were observed; whereas coagulopathy associated-COVID-19 has distinct features [32]. The autopsy series of patients who died due to severe COVID-19 showed the presence of diffuse microthrombosis and hemorrhage along with abundant intravascular megakaryocytes in all major organs, including the heart, lungs, liver, and kidneys [33]. The lung and skin damage consistent with complement-mediated microvascular injury has also been reported [34].

Fig. 1 shows the COVID-19-associated coagulopathy mechanisms. SARS-CoV-2 enters the target cells via activation of ACE2 receptors on the surface of the lung, arterial, and venous epithelial cells [35]. The viral infection can induce prothrombotic gene expression injury and causes direct dysfunction and endothelial injury [36]. This viral infection has a direct effect on host innate immune responses, such as aggravation of endothelial injury, microvascular thrombosis, massive local release of proinflammatory cytokines, activation of monocytes and complements cascade, and aggravation of endothelial injury [37]. The neutrophils and tissue factor (TF) are major mediators of immunothrombosis. After activation of monocytes and monocyte-derived extracellular vesicles via TF, the process of thrombosis begins [38]. Then, the release of neutrophil extracellular traps (NETs) and neutrophil elastase can stabilize microthrombi, which immobilize inflammatory cells and promote intravascular fibrin formation via degradation of TF antagonist, a tissue factor pathway inhibitor [39]. The virus infection and NETs can directly activate platelet via toll-like receptors on platelets and other cells. Therefore, it integrates inflammation, pulmonary infection, and thrombosis [40,41]. Some evidence demonstrated that platelets and megakaryocytes may have viral receptors that could be infected by earlier SARS-CoV [42,43]; however, more accurate future studies are needed for more accurate conclusions.

4.2. Arterial thrombosis

In patients with COVID-19, increased thrombotic events such as stroke and acute myocardial infarction have been reported. It seems that 2.7 to 3.8% of COVID-19 patients have a stroke [44–46]. Acute infection of SARS-CoV-1 may induce a hypercoagulable state, which along with cardiac dysfunction and hypotension give rise to cerebral arterial
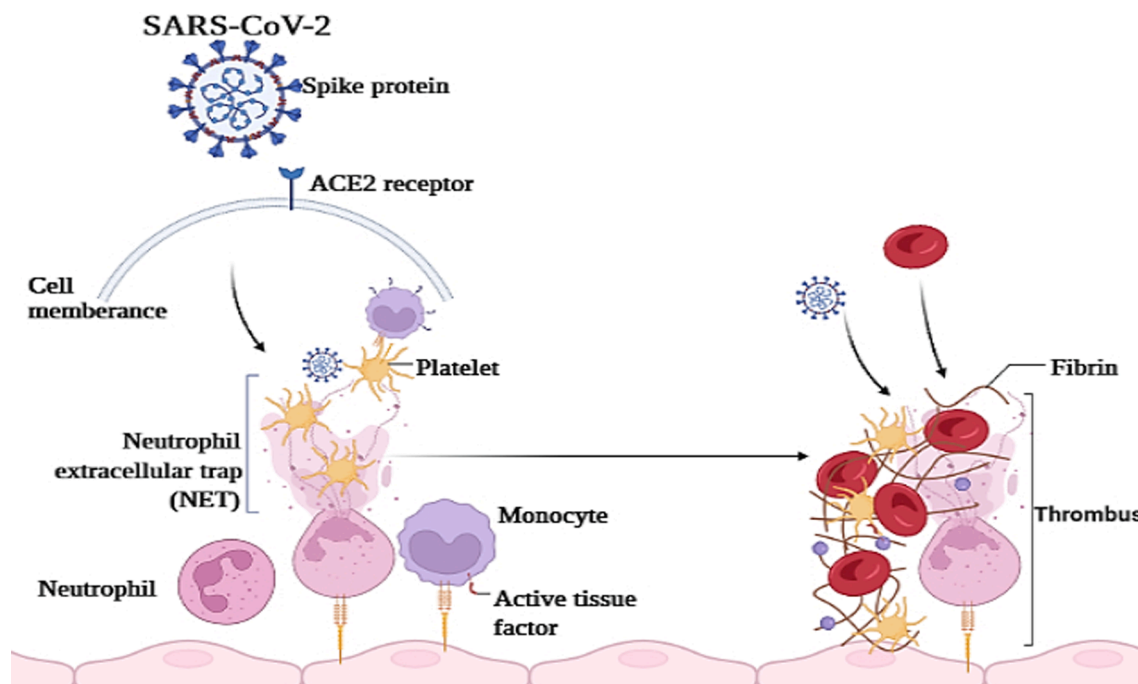
Fig. 1. View of the pathophysiological mechanism of coagulopathy in COVID-19 patients. First, the viral infections can injure host endothelial cells, then abnormal blood flow dynamics and uncontrolled platelet activation occurs.

thromboembolism [14]. After the ischemic and hemorrhagic stroke, the course of COVID-19 in patients can get more complicated [47]. Pre-existing cardiovascular risk in patients with COVID-19 is often associated with an acute stroke which is a risk factor and a negative prognostic factor [48,49]. The presence of a prothrombotic state or a vasculitis-like mechanism may explain how SARS-CoV-2 infection can trigger stroke in the host [47]. Myocardial damage associated with increased troponin levels may be observed in 7–17% of COVID-19 patients admitted to the general ward and in 22–31% of those admitted to the ICU [19,31,50]. Also, the COVID-19 patients with myocardial injury showed higher in-hospital mortality than patients with cardiovascular disease (CVD) but without myocardial injury. In addition, the mortality increased even if the myocardial injury was present in COVID-19 patients with pre-existing CVD [51]. It seems that some factors such as cytokine storm, viral myocarditis, stress-induced cardiomyopathy, classic myocardial infarction due to infection-induced atherosclerotic plaque instability, and microangiopathy can explain the relationship between myocardial injury and underlying CVD with COVID-19 [52,53]. Therefore, urgent reperfusion and frequent lack of standard procedures to perform reperfusion are essential to ensure the best care for COVID-19 patients with acute ischemic stroke and acute myocardial infarction.

4.3. Venous thromboembolism

Many risk factors for venous thromboembolism (VTE) such as older age, obesity, the level of ICU care, and immobility are existed for hospitalized patients with COVID-19. However, it is confirmed that severe SARS-CoV-2 infection is associated with an inherently increased risk of thromboembolic complications and coagulopathy [54]. The relative lack of consumptive coagulopathy in patients with COVID-19 may explain why these patients are more prothrombotic rather than disease evolution into a bleeding propensity due to hyperfibrinolysis [55]. Also, after SARS-CoV- 2 infections, a predilection for thrombotic micro-angiopathy to affect the lung vasculature rather than widespread systemic organ damage from microthrombosis was observed [33,56]. In COVID-19 patients, the elevation of D-dimer as a fibrin degradation product may one of the earlier manifestations of the perturbed

coagulation cascade [57]. The D-dimer is a marker of coagulation cascade activation in the microvascular beds and is elevated in 46% of SARS-CoV-2-infected patients and 56% of those with severe disease [58]. Increasing levels of D-dimer can be directly related to COVID-19 in-hospital mortality [31,59]. In addition, in the setting of COVID-19 infection, elevated D-dimer levels as the surrogate marker for the thrombotic burden were reported in nearly all cases of VTE [60–63]. Elevated D-dimer concentration and thrombotic microangiopathy in pulmonary vessels of patients with COVID-19 can raise the concern of pulmonary embolism (PE) as a reason for acute respiratory failure. Acute PE has the highest rate in severely COVID-19 patients admitted to the intensive care unit (ICU) [44,64]. However, regarding the high heterogeneity observed between the results of studies, further high-quality prospective research is necessary to obtain a more accurate conclusion.

5. Diagnosis of thrombosis in COVID19 patients

For the correct and timely diagnosis of thrombosis and thrombo-embolic complications in patients hospitalized with COVID-19, a combination of patient history, results of laboratory tests reflecting hemostasis, physical examination findings, and/or results of focused imaging investigations must be considered [65]. Imaging studies such as bilateral compression ultrasonography of the legs and/or bedside point of care cardiac ultrasonography can be used to detect proximal DVT, myocardial thrombus, clot-in-transit to the pulmonary trunk, or right ventricular dilatation in COVID-19 patients with high suspicion of thrombosis can use [66,67]. However, to fully exclude thrombosis, it is not enough to just trust the negative results of these tests [67]. A normal D-dimer test with high-sensitivity assays and a CTPA may be reasonable tools for the diagnosis of thrombosis in COVID-19 patients [65]. In patients with COVID-19 and critical patients with DIC and consumptive coagulopathy, the initial prothrombotic cascade is similar. However, the clear differences between COVID-19-associated coagulopathy and patients that have classical DIC are elevations in D-dimer and fibrin/ fibrinogen degradation product levels in COVID-19 patients while thrombocytopenia and prolongations of activated partial

thromboplastin time (aPTT) and/or prothrombin time (PT) are less common or usually mild [68].

6. Some methods of prevention and treatment of thrombosis in COVID19 patients

In hospitalized COVID-19 patients, early vigilant monitoring of coagulation abnormalities is a critical measure because it can help to identify patients at a high risk of poor prognosis, improve patients' clinical outcomes, and guide antithrombotic prophylaxis or treatment to prevent thromboembolic complications. The elevated D-dimer in COVID-19 patients is a prognostic value for the severe course of COVID-19 infection which can predict thrombotic events, acute kidney injury, and death [69]. Generally, in severe COVID-19 patients (ICU care), a worsening trend of coagulation parameters can indicate the development of cytokine storm, impending clinical deterioration, and progression to multiorgan failure [70]. In severe COVID-19 patients, standard laboratory and viscoelastic tests, increased platelet and fibrinogen contribution to CS, elevated D-dimer levels revealed increased clot strength (CS), and hyperfibrinogenemia can be a good procoagulant pattern [71].

Since cross-link between viral infection-induced inflammatory response and thrombosis, known as infection-induced thromboinflammation, levels of C-reactive protein (CRP), IL-6, factor VIII, vWF, and plasma viscosity are increased in COVID-19 patients, while antithrombin is modestly decreased [71,72].

To identify hospitalized COVID-19 patients at a high risk of poor in-hospital outcomes, or to triage patients that would require hospital admission and close monitoring, measuring of D-dimer levels, PT/aPTT, thrombocyte count, and fibrinogen levels (if assays are available) seem to be necessary [73,74]. In the absence of contraindications for controlling thrombosis, the use of prophylactic doses of anticoagulants in all patients hospitalized with COVID-19 is recommended by most of the guidelines and consensus documents published on behalf of professional societies, focusing on hemostasis and thrombosis advocates [73,75]. Also, in hospitalized COVID-19 patients especially.

those with no bleeding risk factors and with high VTE risk for 2 to 6 weeks post-hospital discharge, administration of thromboprophylaxis with low molecular weight heparin (LMWH) or a non-vitamin K antagonist oral anticoagulants is recommended [44,46,76]. Likewise, some available documents support that the use of intermediate-dose LMWH in selected severe COVID-19 patients may balance thrombotic and bleeding risk [77,78].

7. Conclusion and perspective

Recent studies have provided a growing understanding of the pattern of COVID-19 in immunology, epidemiology, and subsequent coagulopathy and coagulopathy treatment strategies. Severe COVID-19 patients can lead to thromboinflammatory disease and play a critical role in the pathophysiology and clinical deterioration of these patients [79]. Severe COVID-19 can lead to thromboinflammatory disease and play a critical role in the pathophysiology and clinical deterioration of these patients [80]. Most evidence is limited by small retrospective studies. Therefore, it is necessary to evaluate the true prevalence of thrombosis in COVID-19 in more studies. Given that, a consecutive increase in D-dimer may indicate the presence of thrombosis in patients with severe COVID-19. In addition, designation of the exact role of biomarkers such as.

D-dimer and/or scoring systems to stratify patients' risk, establishing the optimal thromboprophylaxis strategy and designing adequate and feasible diagnostic protocols for venous thrombosis (DVT)/pulmonary embolism (PE) can be added to standard reporting criteria in order to facilitate future research. There is a need for markers to identify the increased risk of thrombotic events at an early stage of COVID-19 and to prevent thrombotic events and organ damage as far as possible. In severe COVID-19 patients, it is better to use prophylactic anticoagulation with

LMWHs to prevent thrombotic events and counteract the pro-inflammatory influence of cytokines and other factors. The future randomized trial regarding the appropriate antithrombotic prophylaxis and treatment results may help to individualize the treatment of thrombotic in COVID-19 patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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