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REVIEW ARTICLE

Coagulopathy and thromboembolic events in patients with SARS-CoV-2 infection: pathogenesis and management strategies

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Abstract

In October 2019, a viral infectious disease appeared in the city of Wuhan in China. A new betacoronavirus, SARS-CoV-2, has been recognized as the responsible pathogen in this infection. Although coronavirus disease is principally expressed as a pulmonary infection, critical SARS-CoV-2 infection is frequently complicated with coagulopathy, and thromboembolic events are recognizable in several patients. Dehydration, acute inflammatory condition, protracted immobilization during disease, existence of multiple cardiovascular risk factors such as diabetes, obesity or hypertension, previous coronary artery disease, ischemic stroke, peripheral artery disease are frequent comorbidities in SARS-CoV-2 hospitalized subjects, which possibly augment thrombo-embolic risk. However, other causal factors can still be identified such as unrestricted angiotensin II action, the use of immunoglobulins, an increased production of adhesion molecules able to induce vascular inflammation and endothelial activation, complement stimulation, excessive production of neutrophil extracellular traps (NETs), and increased platelet count. Low-molecular-weight heparin should be chosen as early treatment because of its anti-inflammatory action and its ability to antagonize histones and so defend the endothelium. However, several therapeutic possibilities have also been proposed such as fibrinolytic treatment, drugs that target NETs, and complement inhibition. Nevertheless, although the violence of the pandemic may suggest the use of heroic treatments to reduce the frightening mortality that accompanies SARS-CoV-2 infection, we believe that experimental treatments should only be used within approved and controlled protocols, the only ones that can provide useful and specify information on the validity of the treatments.

Keywords SARS-Cov-2 · Coagulation · Disseminated intravascular coagulation · Neutrophil extracellular traps · Complement activation · Low-molecular-weight heparin

Introduction

Clinical pattern and laboratory findings of thromboembolic events in SARS-CoV-2 patients

In October 2019, a viral infectious disease appeared in the city of Wuhan in Hubei Province, China. A new betacoronavirus, SARS-CoV-2, able of human-to-human diffusion, has been recognized as the responsible pathogen in this infection [1, 2]. At the time of writing, the global pandemic is still present. Latest balance calculates > 8,000,000 people affected worldwide, with > 450,000 deaths.

Although it is well known that coronavirus disease 2019 (COVID-19) is principally expressed as a pulmonary infection, several findings suggest that it should be considered as a systemic pathology implicating several organs and systems comprising neurological, cardiovascular, gastrointestinal, hematopoietic, and immune system [3–5]. Furthermore, as reported by numerous research, grave SARS-CoV-2 infection is frequently complicated with coagulopathy, and thromboembolic events are recognizable in several patients [6, 7]. In a retrospective study, 260 out of 560 subjects (46.4%) with laboratory proved SARS-CoV-2 disease had an increase of D-dimer, and the augment was more prominent among grave patients (59.6% vs 43.2%). Authors argue that D-dimer

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alteration can indicate the gravity of the infection and an augmented concentration is correlated with a poorer prognosis [8].

These results were confirmed by other studies. A different retrospective analysis performed in China comprising 41 subjects demonstrated that prothrombin time (PT) and D-dimer concentrations were greater on admittance in infected subjects necessitating Intensive Care Unit (ICU) assistance (median PT 12.2 s for intensive care vs 10.7 s; median D-dimer 2.4 mg/L for intensive care assistance vs 0.5 mg/L for non-intensive care assistance), whereas augmented D-dimer concentrations were also connected with death in the multivariable analysis [9, 10].

In the analysis performed by Tang et al., including information from 183 subjects with SARS-CoV-2 disease, on admittance, patients who died had substantively greater fibrin degradation products (FDP) concentrations and augmented PT and activated partial thromboplastin time (aPTT) with respect to survivors, with a reduction of fibrinogen and antithrombin (AT III) levels [11]. Remarkably, 71.4% of patients who died vs 0.6% of patients who survived satisfied the criteria for disseminated intravascular coagulation (DIC). In a prospective research valuing D-dimer and FDP concentrations in SARS-CoV-2 patients and normal subjects, infected patients presented greater concentrations of these parameters, and patients with more serious disease presented greater values of FDP and D-dimer with respect to patients with minor symptoms [12]. The average time interval from admittance to DIC onset was 4 days.

Thus, DIC emerged in most of the deaths, and this is not unexpected as infection is one of the most frequent causes of DIC. It is well-known that DIC starts when endothelial cells and monocytes are stimulated to produce cytokines after a serious damage, with abnormal production of von Willebrand factor and Tissue Factor (TF). The subsequent circulation of uninhibited thrombin can stimulate platelets and activate fibrinolysis [13].

In a previous study, Gralinski et al. explored effects of SARS-coronavirus disease on coagulation.

Their results propose that modification of the urokinase pathway during infection causes a graver lung alteration and that plasminogen activator inhibitor-1 (PAI-1) has a defending action after the infection [14]. Moreover, Berri et al. confirmed that plasminogen aggravates the inflammation due to infection, while fibrinolysis may also be provoked by severe infection [15].

Nevertheless, although Tang et al. described findings congruent with a condition of DIC (high FDP and D-dimer, elongated PT and APTT, and reduced platelet counts) [11], only a part of these data (increased D-dimer) have been confirmed by other studies, while other alterations such as increased PT/APTT are not confirmed. Moreover, decreased fibrinogen clotting activity and low platelet counts, which are characteristic elements of DIC, are reported normal or even increased in other studies [16].

The causes for this incongruity are uncertain. It cannot be excluded that the two groups of patients, although both hospitalized to the ICU, were at diverse stages in the course of the infection.

An additional factor of doubt is the fact that it is difficult to differentiate between the laboratory alterations seen in subjects with coagulopathy due to sepsis-caused hepatic dysfunction rather than DIC [17]. This difference is especially important given the findings which propose that hepatitis is present in several subjects with SARS-CoV-2 infection, thus imitating the coagulopathy.

In any case, the clinical expressions of coagulopathy in these subjects can involve the most different organs and systems, from the heart, to the kidney, to the lungs, to the peripheral vessels. Older subjects and those with other diseases are at augmented danger of death from SARS-CoV-2, but younger subjects without other comorbidities may also have fatal problems such as thromboembolic complications [18]. Among other things, with regard to mortality, it should be borne in mind that subjects displaying with cardiac damage in the context of SARS-CoV-2 infection are more susceptible to coagulation alterations with respect to those without cardiac injury [19].

The limited data presented on thrombotic complications in subjects with COVID-19 propose that rates of venous thromboembolic events may be as high as 25 to 30%, especially in critically ill, mechanically ventilated subjects. Thrombotic complications also comprise stroke, acute limb ischemia, and acute coronary syndromes [20–23].

Several studies stated an augmented occurrence of VTE in subjects admitted to the ICU with SARS-CoV-2 infection. Klok et al. registered a 27% VTE occurrence and 3.7% arterial vascular thrombosis in spite of the employ of standard VTE prophylaxis with low-molecular-weight heparin (LMWH) [24], certainly a higher percentage with respect to the failure rate of 7.7% generally registered for VTE prophylaxis in ICU setting [25]. Cui et al. reported an analogous 25% frequency of VTE, but VTE prophylaxis was not provided in this population as VTE prophylaxis is not habitually used in Asia [26, 27].

SARS-CoV-2: pathogenetic mechanisms of coagulation alterations

Dehydration, an acute inflammatory condition, protracted immobilization during disease, existence of multiple cardiovascular risk factors such as diabetes, obesity or hypertension, previous coronary artery disease, ischemic stroke, peripheral artery disease, or VTE and classical genetic thrombophilia, such as heterozygous factor II and factor V Leiden mutation

are frequent comorbidities in SARS-CoV-2 hospitalized subjects, which possibly augment VTE risk.

However, other causal factors can still be identified (Table 1).

Inflammatory mediators

SARS-CoV-2 presents several correspondences with the SARS virus; nevertheless, SARS-CoV-2 has developed numerous characteristics that make it a more effectual agent for contagion than SARS-CoV. The most important receptor-binding domain of SARS-CoV-2 preserved the overall structure of the SARS-CoV binding domain, comprising 8 of the 14 residues being totally the same. However, the 3D conformation of the SARS-CoV-2 binding site displays that it is more compacted, has ameliorated binding ability, and possibly increased ACE-2 receptor binding affinity [66–69].

Additional distinction is that SARS-Cov-2 includes a polybasic (furin) cleavage site introduced at the boundary of the S1/S2 subunits of the spike S-protein12 able to increase the virus' capacity to internalize into the human cells.

After virus contact with the ACE-2 receptor in the presence of TMPRSS2, SARS-CoV-2 can go into the cells via endocytosis or membrane fusion [70–72]. Experimental model demonstrated that after engagement of SARS-CoV virus with ACE-2 receptor, there is an important decrease of ACE-2 in the endothelial cells [73]. This is probably part of the protection systems in response to the infection, to reduce viral growth and diffusion. Nevertheless, the possible effect of this engagement is that the physiological action normally performed by the receptor is also considerably reduced. This can cause unrestricted angiotensin II actions, comprising prothrombotic, proinflammatory, and prooxidant effects. Moreover, the onset of an endothelial damage due to the virus attachment to ACE-2 receptor may further augment VTE risk, while the delivery of inflammatory mediators and the use of drugs such as steroids and immunoglobulins in critical subjects may provoke an augmented blood viscosity [59, 60].

Numerous inflammatory mediators are involved in coagulative dysregulation during acute infection. Firstly, tissue factor (TF), the primary initiator of the blood coagulation cascade, provokes rapid hemostasis in case of organ injury

Table 1 Possible intrinsic and extrinsic causal factors of thromboembolic events in patients with SARS-CoV-2 infection

Intrinsic factor	Mechanism	Ref.
Endothelial activation	Release of VWF from Weibel-Palade bodies	[28, 29]
PAI-1 increase	Hypofibrinolytic state	[30]
Microvesicles	Delivery of procoagulant factors such as the TF or phosphatidylserine	[31, 32]
Increased thrombin	Platelet activation; activation of the coagulation system	[13, 33]
Increased LAC	Activation of endothelial cells; platelet activation; block of fibrinolysis; complement activation	[34]
NETs	Production of procoagulant elements; formation of microthrombi; stimulation of plasma kallikrein–kinin system; inhibition of ATIII; platelet stimulation	[33, 35–49]
Complement activation	Complement-mediated microvascular injury; leukocyte recruitment; activation of platelets and endothelial cells; increase of tissue factor and von Willebrand factor expression	[50]
Thrombocytosis	Augmented blood viscosity	[51–54]
Cytokine delivery	Vascular inflammation and endothelial activation	[28, 55]
Fibrinolysis block	Higher thrombin generation; prothrombotic state	[56–58]
Angiotensin II action	Prothrombotic, proinflammatory and prooxidant effects; induction of PAI-1 expression	[59–63]
Immobilization	Stasis, vessel wall dysfunction and alterations in clotting mechanisms (Virchow's triad)	[64]
Dehydratation	Augmented blood viscosity	[64]
Hypoxia	Increase of HIFs (increase of inflammation, blood viscosity, platelet activation, TF expression)	[30, 65]
Extrinsic risk factors	Mechanisms	Ref.
Steroid use	Activation of coagulation system and increase of vWF, factor VII, factor VIII, factor XI, and FBG; increase of platelet count	[60]
Immunoglobulin use	Augmented blood viscosity	[59]

through its receptor activity for factor VII. Inflammatory cytokines, such as tumor necrosis factor (TNF)-α, and endotoxin potently stimulate expression of TF on the cell surface of endothelium and leukocytes, specifically monocytes. TF stimulates pleiotropic inflammatory responses and gives a powerful contribution to hypercoagulable state [55].

Stimulation of cells like macrophages can also cause the delivery of cytokines, comprising IL-1β and IL-6, which will increase production of adhesion molecules able to induce vascular inflammation and endothelial activation [28]. With the decrease of ACE-2 and increase of angiotensin II, the generation of PAI-1 is also increased. This event causes an increased vascular inflammation and aggravates the prothrombotic condition. All these findings have been found in subjects with serious infection and laboratory evidence of augmented D-dimer and IL-6 concentrations.

Deficient coagulation inhibitors

Some findings propose that subjects with SARS-CoV-2 infection may acquire a condition of hypercoagulability as demonstrated by the thromboelastographic parameters, augmented factor VIII, fibrinogen, and von Willebrand factor. This condition could promote the onset of pulmonary embolism or deep vein thrombosis of the lower limbs in infected patients.

The motives for this hypercoagulability are unclear. In this type of patients, factor VIII, which is one of the most powerful stimulants of hypercoagulability, is intensely augmented, and the principal naturally occurring anticoagulants are normal (AT III) or even augmented (protein C) [16].

Moreover, damage of endothelial cells caused by SARS-CoV-2 provokes an augmented thrombin production and fibrinolysis block [56, 57].

Acute fibrinolysis shutdown has been reported in early sepsis and found to correlate to augmented morbidity and mortality. Fibrinolysis shutdown and organ failure have historically been associated with DIC [57].

In a recent report, fibrinolysis shutdown, as demonstrated by augmented D-dimer and complete failure of clot lysis at 30 min on thromboelastography, predicts thromboembolic complications and need for hemodialysis in critically ill patients with SARS-CoV-2 [58].

However, there are several limitations to this retrospective descriptive study. First, there was variability in the laboratory testing patterns based on intensivist preference. In addition, coagulation parameters were drawn at variable times of the patient disease processes. Studies done to evaluate for thromboembolic events were performed for clinical suspicion rather than routine screening, and therefore some events were likely not captured or had delays in diagnosis.

Furthermore, hypoxia can also induce thrombosis via not only augmenting blood viscosity but also via a hypoxia-inducible transcription factor-dependent system [65]. Hypoxia could be secondary to pneumonia, ARDS, hyperthermia (which may activate platelets and coagulation), and hypovolemia (due to gastrointestinal fluid loss). Vascular response to hypoxia is regulated essentially by the hypoxia-inducible transcription factors (HIFs); HIFs may stimulate further inflammation, thus augmenting blood viscosity and contributing to worsen hypercoagulability. Moreover, HIFs may directly activate platelets and coagulation factors, augmenting TF expression, augmenting PAI-1, and inhibiting the endogenous anticoagulant proteins [30].

As pointed out above, the action of SARS-CoV-2 infection on coagulation and fibrinolysis is believed to be controlled by several proinflammatory cytokines, similarly to what happens in cases of pneumonia due to other pathogens [74, 75]. The model of thrombosis is the pattern of interaction between coagulation and inflammatory state. All the subjects with coagulation alterations presented increased levels of IL6, and an evident correlation between IL6 and fibrinogen concentrations was reported. In fact, IL6 is a potent proinflammatory element, which stimulates fibrinogen and platelet production and tissue factor (TF) gene expression in different type of cells such as monocytes and endothelial. TF stimulates thrombin production, and all these elements cause the generation of a procoagulant profile that was evident in SARS-CoV-2 patients [76, 77].

Complement activation

However, numerous clinical and experimental data allow to hypothesize other mechanisms capable of conditioning the onset of thromboembolic events. In fact, more precise indications on the pathogenetic moments of thrombotic events of SARS-CoV-2 subjects arose from the autopsy findings of these subjects.

Dolhnikoff et al. have settled a system for executing ultrasound-based minimally invasive autopsies, and they used it in mortal cases of SARS-CoV-2 disease to define the pathogenesis of this infection. The pulmonary histological feature is an exudative and proliferative diffuse alveolar injury, with severe epithelial viral cytotoxic signs implicating alveolar and small airway epithelium, and the presence of a small lymphocytic penetration. Moreover, they detected a changing amount of small fibrinous thrombi in pulmonary arterioles. The presence of a great quantity of pulmonary megakaryocytes in the pulmonary capillaries are other signs of stimulation of the coagulation system. Their anatomo-pathological findings corroborate the present perception of hypercoagulative condition in these critically ill subjects [78].

However, surprising data come from analysis conducted by other authors, albeit on a small number of cases. Magro et al. studied pulmonary tissues from subjects with grave SARS-CoV-2 infection and respiratory failure. The feature of SARS-CoV-2 pneumonitis was essentially a pauci-

inflammatory septal capillary damage with relevant septal capillary luminal and mural fibrin accumulation. Yet, the most interesting aspect of their analysis was the discovery of relevant accumulations of terminal complement components C5b-9, C4d, and mannose-binding lectin-associated serine protease 2, in the micro-vessels, coherent with continuous, generalized stimulation of the alternative and lectin-based complement pathways. Furthermore, they found a co-localization of SARS-CoV-2 spike glycoproteins with C4d and C5b-9 in the interalveolar septa [79].

The complement system is a component of the innate immune response that protects against viral infections. Two experimental animal studies evaluated complement stimulation in coronavirus infections. In a murine model, animals were missing C3 and thus incapable to stimulate the common complement pathway. In this group, SARS-CoV infection gravity was reduced with less pulmonary alteration and inferior cytokine concentrations in spite of identical viral loads. In a different murine model of MERS-CoV infection, augmented levels of C5a and C5b-9 were reported in pulmonary tissues. Stopping C5a with a murine antibody reduced pulmonary injury with diminished cytokine response and viral proliferation [80, 81].

Confirmation for the participation of the lectin pathway (LP) in SARS-CoV-induced alterations derives from the finding that mannose-binding lectin connects with the SARS-CoV spike glycoprotein [82–84]. Even though reported experimentally only for SARS-CoV, with possible limitations regarding the possibility of applying this concept in the current pandemic [85], glycosylation sites for high-mannose elements with the ability to similarly engage mannose-binding lectin have been also recognized for SARS-CoV-2 [70].

Disproportionate complement activation happens in several pathologic conditions, provoking a systemic thrombotic microangiopathy (TMA). Atypical hemolytic uremic syndrome (aHUS) is an infrequent disease of uninhibited complement stimulation followed by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure [85]. This condition shows numerous similarities with the microangiopathic alterations found in some patients with SARS-CoV-2 infection. Based on these data, albeit limited to a small number of subjects, grave SARS-CoV-2 infection may provoke a catastrophic, complement-mediated thrombotic microvascular damage condition due to the activation of complement pathways and to a concomitant procoagulant condition [86, 87].

Neutrophil extracellular traps

Another interesting aspect detectable by the autopsy data obtained from patients suffering from SARS-CoV-2 infection was the high amount of intra-alveolar and septal neutrophils. SARS-CoV-infected animals also had higher degree of neutrophils in the lung. In humans, tissue neutrophilia may be due to the neutrophil chemoattractant ability of complement [88] and is correlated with a poorer outcome and is associated with the severity of disease [89–91]. The neutrophil-to-lymphocyte ratio is also an independent risk factor for more serious disease [9]. Although leukocytosis and neutrophilia are well-known characteristics of acute infection, in SARS-CoV-2 infection, neutrophilia could contribute to the genesis of a prothrombotic condition through the excessive production of neutrophil extracellular traps (NETs) [35].

In fact, neutrophils have a different, less known method of destroying pathogens: the generation of NETs [36]. NETs are complexes of nucleic DNA, histones, and nucleosomes ejected from the neutrophils that entrap pathogens. Crucial elements in the generation of NETs are enzymes such as neutrophil elastase (NE), which damages intracellular proteins and provokes nuclear fragmentation; gasdermin D which provokes pores in the membrane of the neutrophil, thus accelerating cell membrane rupture and the emission of DNA; and peptidyl arginine deiminase type 4 (PAD4), which citrullinates histones to ease the decondensation of the chromosomal DNA [37].

Even though NETs are useful in the protection against pathogens, collateral injury from continuous NET generation also provokes several negative situations, comprising those that happen during viral diseases [38]. Actually, disproportionate NET generation can promote micro-thrombosis, stimulate several inflammatory responses that damage contiguous tissues, and provoke a serious injury to lung, heart, and kidney [39], three organs frequently altered in SARS-CoV-2 infection.

NET may produce procoagulant elements correlated with plasma hypercoagulability and augmented risk of thrombosis in animal and human experimental models [40–42].

In fact, increased blood concentrations of NETs may justify hyperactive coagulation retrieved in SARS-CoV-2 subjects, and intravascular NETs have been demonstrated to have a crucial action in onset and progression of thrombotic events in arteries and veins. For example, NET concentrations correlate with thrombin levels, and when NETs are present in great quantities in blood, they can cause the closure of small vessels [43, 44]. In experimental models of septicaemia, intravascular NETs can cause the formation of microthrombi and provoke damage to different organs [45]. Moreover, a correlation between NETs and IL1β exists. If a NET–IL1β loop is activated in severe SARS-CoV-2, the accelerated generation of NETs and IL1β could accelerate respiratory alteration, the formation of microthrombi, and aberrant immune responses.

As far as the intimate mechanisms of action of NETs are concerned, NETs stimulate the plasma kallikrein–kinin system (the contact pathway of coagulation) through electrostatic relationships between the NET histones and platelet phospholipids [46]. Histones can also stimulate platelet activation by operating as ligands for the Toll-like receptors on platelets

[47]. Moreover, NE probably also operates by destroying the principal coagulation inhibitors such as tissue factor pathway inhibitor and AT III [48]. Moreover, there is probably a response loop by which thrombin causes platelet stimulation, and stimulated platelets then increase NET generation [33].

In animal models, destroying NETs with DNase I reestablishes normal perfusion of the heart and kidney [49].

A different reason for the hypercoagulability of these patients may be the occurrence of a great amount of circulating microvesicles. These elements are cytoplasmic microparticles derived from platelets or other cells, which contain procoagulant factors such as the TF or phosphatidylserine. Microvesicles are recognized factors of venous thromboembolism [31], while augmented amount of circulating microvesicles have been described in septic subjects [32], and it is consequently probable that they are also augmented in subjects with SARS-CoV-2 infection.

Platelet alteration

Finally, a further reason for hypercoagulability could lie in an alteration in the number of platelets. In SARS-CoV-2-infected patients, it is possible to detect both a reduction and an increase in platelets. A meta-analysis of nine reports has proposed that thrombocytopenia is notably correlated with the gravity of the SARS-CoV-2 infection [51]. Nevertheless, Qu et al. demonstrated that among hospitalized subjects with SARS-CoV-2 infection, those appearing with thrombocytosis had worse prognosis. Furthermore, the platelet-to-lymphocyte ratio at the time of platelet increase appeared as an independent prognostic factor for protracted hospitalization and may suggest a more relevant cytokine storm due to augmented platelet activation [52]. Yin et al. compared the coagulation parameters between SARS-CoV-2 infection and pneumonia provoked by different agents. Subjects with pneumonia caused by SARS-CoV-2 had greater platelet count than those caused by non-SARS-CoV-2 agents [53]. Nevertheless, as organ alteration is principally restricted in the lung, the coagulation aspect of severe SARS-CoV-2 infection might not be the same of the sepsis in general. Due to the augmented production of thrombopoietin subsequent to pulmonary inflammation, platelet number may not be a reliable marker for coagulopathy of SARS-CoV-2 infection [54].

Coagulation alterations in SARS-CoV-2 infection: management strategies

High blood pressure is a known risk factor for complications in patients with SARS-CoV-2. Since ACE-2 is the most important virus receptor, it is worth asking whether some drug classes (i.e., ACE inhibitors, angiotensin II receptor blockers) should be discontinued.

In a recent study conducted in patients with SARS-CoV-2, the viral load and lung injury were strongly associated with the circulating levels of angiotensin II [61].

ACE-2 down-regulation caused by SARS-CoV-2 might be remarkably disadvantageous in subjects with baseline ACE-2 deficiency due, for example, to older age or diabetes, hypertension, and heart disease. A further ACE-2 down-regulation provoked by the infection might increase the dysregulation between the adverse and the protective receptor axis, with augmented progression of inflammatory and thrombotic processes caused by angiotensin II hyperactivity unopposed by angiotensin [62], and numerous experimental models of lung injury caused by diverse triggers documented the causative relation between down-regulation of ACE-2 receptors and pulmonary inflammation provoked by an imbalance between angiotensin II over-activity and of antiotensin1–7 deficiency [63].

If we assume that viral-provoked ACE-2 deficiency and the resulting angiotensin II over-activity unopposed by angiotensin1–7 are relevant in the progression of the disease, then recombinant ACE-2, angiotensin1–7, and angiotensin II type 1 receptor blockers might be rational approaches in these subjects [92–94].

Moreover, based on what has been reported above on the pathophysiological mechanisms that regulate the state of hypercoagulation and thrombotic complications of patients suffering from SARS-CoV-2 infection, various therapeutic possibilities have been proposed (Table 2).

As far DIC, to date, its therapy has been direct on treatments to cure the principal-related disease [113]; this, of course, is inadequate in the case of SARS-CoV-2 infection, until more is discovered about efficient antiviral drugs for this new disease. However, the International Society of Thrombosis and Haemostasis has suggested a novel class of patients recognizing an earlier stage of sepsis-related DIC, named "sepsis-induced coagulopathy," and these subjects benefit from anticoagulant treatment [114].

Low-molecular-weight heparin (LMWH), or unfractionated heparin (UFH) should be chosen over direct oral anticoagulants for the potential interactions with antiviral and antibacterial (such as azithromycin) therapy [95].

LMWH is the most frequently employed anticoagulant also because of its anti-inflammatory action [96]. In fact, one of the better recognized non-anticoagulant capabilities of heparin, its anti-inflammatory effect, may also be crucial in this group of patients. The mechanisms of the anti-inflammatory action of heparin comprise blocking neutrophil chemotaxis and leukocyte migration, connecting to inflammatory cytokines, counterbalancing the positively charged peptide complement factor C5a, and reducing acute phase proteins [97–99]. A recent report stated that heparin can reduce the concentration of inflammatory biomarkers [100].

Table 2 Therapeutic possibilities for coagulative alterations in SARS-CoV-2 infection

Drug	Action	Effects	Ref.
Low-molecular-weight heparin	Anti-inflammatory action	Reduction of neutrophil chemotaxis; diminished leukocyte migration; effect on histones; action on NF-kB and MAPK pathways	[29, 95–104]
Unfractionated heparin	Anticoagulant properties Anti-inflammatory action	Interactions with antiviral therapy	[29, 95–104]
Thrombolytic agents	Elimination of microclots	Stimulation of endogenous plasmin	[105–107]
Complement inhibitors	Reduced pulmonary injury	Diminished cytokine response	[50, 79–81]
NE, PDA4, gasdermin 4 inhibitors (silvelestat, elafil, alvelestat, lonodelestat, CHF6333), DNAse 108–112]	NETs inhibition	Action on plasma-kallicrein-kinin system; reduction of inflammation; action on micro-thrombosis	[35, 45,
ACE inhibitors, angiotensin II receptor blockers	Reduction of inflammatory cytokines	Reduction of inflammatory and thrombotic processes evoked by angiotensin II hyperactivity	[92–94]

In addition to the pathogenic invasion, able to cause endothelial alterations, histones discharged from injured cells can also provoke endothelial damage [29]. Heparin can antagonize histones and so defend the endothelium [101, 102]. This protecting action can be expanded to the endothelial tight junctions as established in a sepsis model, where heparin reduced vascular leakage subsequent lipopolysaccharide-induced damage [103]. A different protective mechanism is via its action on histone methylation and the NF-κB and MAPK pathways [104]. Thus, heparin can influence the microcirculatory alteration and probably reduce organ injury.

If the employ of heparin seems to be the most correct therapeutic choice, various considerations must be made on the dosage to be used.

Rannuci et al. described coagulation parameters in SARS-CoV-2 subjects with acute respiratory distress syndrome. Patients received 4000 IU nadroparin twice daily. First findings were analogous to other studies, with an increased fibrinogen. However, in spite of normal clotting times on viscoelastic testing, other parameters revealed augmented clot firmness with above normal values for contributions from fibrinogen and platelets. For this reason, nadroparin dosing was augmented to 6000 IU or 8000 IU BID if BMI > 35 kg/m^2 [115]. The employ of an augmented dosage of nadroparin caused a relevant reduction in D-dimer concentrations even if all subjects still had levels above the normal range. Moreover, viscoelastic testing revealed reduced hypercoagulability after augmenting LMWH and diminutions in clot firmness as a result of a reduced contribution from fibrinogen and platelets.

In SARS-CoV-2 subjects, a risk-adapted method to increase the dosage of heparin should be carefully evaluated. Monitoring renal function and coagulation parameters should be performed.

Furthermore, as genetic risk factors of VTE differ considerably among ethnic populations, and the occurrence of VTE in Asian populations is smallest [116], a greater dose of LMWH could be administered in non-Asian subjects with grave SARS-CoV-2 infection.

Moreover, one potential challenge in the use of unfractionated heparin is the utility of the aPTT for monitoring heparin. In subjects with SARS-CoV-2, besides the intensity of heparin-based regimens, substantial heterogeneity in the aPTT response may be driven by high concentrations of factor VIII and fibrinogen or the presence of a lupus anticoagulant [34, 117]. Consequently, anti-factor Xa levels may need to be measured to ensure that a therapeutic heparin level is achieved [118].

In any case, the efficacy of anticoagulant treatment for sepsis-associated DIC is still debateable [119–121], although some reports proposed that septic subjects might just profit from early diagnosis and specific therapy [122, 123].

Caution should be also used for the employ of heparin in DIC associated with SARS-CoV-2 in subjects in treatment with veno-venous extracorporeal membrane oxygenation (VV-ECMO). In fact, an increased rate of intracranial hemorrhage in subjects receiving VV-ECMO was described [124, 125].

Finally, the stimulation of coagulation also provides compartmentalization of pathogens and decreases their diffusion

[105]. So, in infected subjects without relevant coagulopathy, anticoagulant therapy could lead to an increased risk of complications. This may justify the greater mortality of heparin users with respect to non-users in subjects with D-dimer ≤ 1 ULN, even though the difference was not statistically relevant.

In any case, augmenting heparin dosage alone is likely inadequate to modify prognosis in subjects with critical severe SARS-CoV-2 acute lung damage. Additional treatment with diverse drugs may be essential to reduce the thrombo-inflammatory condition and successive tissue damages that cause the prothrombotic modification leading to microvascular thrombosis or manifest VTE.

However, it should be noted that none of the therapeutic possibilities listed below have been validated by extensive controlled studies, and therefore the possibility of their use in the clinical setting should be considered only as a proposal to be explored.

A therapeutic possibility could be the concomitant administration of heparin and thrombolytic drugs in subjects with pulmonary embolism. Acute respiratory distress syndrome has been correlated with microclots in the lungs, while elimination of the microclots can be attained by stimulation of endogenous plasmin. In an old experimental animal model, Hardaway et al. evaluated fibrinolytic treatment in acute respiratory distress syndrome, achieving good results [106].

An opportunity could be the employ of bolus doses of alteplase (tPA) while subjects continue the therapeutic heparin therapy. Such an attempt employing greater bolus-dose tPA (100 mg) without maintaining anticoagulation is a different possibility, as mortality in SARS-CoV-2 acute respiratory distress syndrome is extremely high, while the risk of catastrophic bleeding from tPA in non-stroke subjects is about 1% [107].

A diverse chance could be the dipyridamole, a phosphodiesterase inhibitor that blocks platelet aggregation by augmenting intracellular levels of cyclic adenosine monophosphate. Dipyridamole has antiviral actions in vitro, specifically confirming the affinity of dipyridamole for a SARS-CoV-2 main protease [126]. In mouse models of viral pneumonia, dipyridamole administration stimulated interferon response and increased survival in infected mice.

To date, one study has examined dipyridamole in the therapy of SARS-CoV-2; 31 patients with viral infection were randomized to dipyridamole (150 mg three times a day for 7 days) versus control. In this small study, those treated with dipyridamole showed trends toward higher cure and hospital discharge rates. Augmented platelet counts and reduced D-dimer concentrations were also noted with dipyridamole treatment, attributed to infection resolution [64, 127].

Moreover, beyond their anticoagulant actions, direct oral anticoagulants (DOACs), especially factor Xa inhibitors, may exert anti-inflammatory actions in SARS-CoV-2. There is currently one registered clinical trial (C-19-ACS) evaluating low-dose rivaroxaban along with dual antiplatelet therapy, statins, and a proton-pump inhibitor in subjects with SARS-CoV-2 and a suspected acute coronary syndrome (NCT04333407) [128].

As reported above, the studies performed on critical SARS-CoV-2 patients revealed disproportionate complement stimulation that was accompanied by increased D-dimer, bilirubin and LDH, reduction of Hb and platelet count, cardiac and renal damage, and diffuse thrombotic microangiopathy. For this reason, complement inhibition may be a novel possibility in curing SARS-CoV-2 systemic thrombosis [50].

Finally, substances that target NETs are present or are in study. These substances comprise inhibitors of the enzymes or molecules essential for NET generation such as NE, PAD4, and gasdermin D. For instance, endogenous inhibitors of NET generation have been separated from umbilical cord plasma [108], and these could be used for the therapy of inflammatory diseases such as SARS-CoV-2 infection. The NET inhibitor sivelestat was accepted to treat ARDS, but it did not increase survival after ARDS in a meta-analysis of clinical trials [35], while a new group of powerful NE inhibitors, comprising elafil, alvelestat, lonodelestat (POL6014), and CHF6333, have started phase I testing.

DNase proteins, such as DNase 1–like 3, which is being developed to dissolve NETs [109], could enter clinical development soon. Dornase alfa is generally administered through nebulizers, but in several medical centers, these are precluded in SARS-CoV-2 due to the risk of aerosolizing virus and endangering healthcare workers. However, approaches exist that deliver aerosols in closed circuits for mechanically ventilated subjects. For non-intubated subjects, treatment can be safely nebulized in negative pressure rooms. In addition to their possible actions on mucous secretions, DNase treatments may also prevent the further progression to ARDS, as DNase I delivered through the airways increases survival in relevant animal models [110, 111].

In addition to directly targeting NETs, the NET–IL1β loop could be antagonized with approved drugs against IL1β, such as anakinra, canakinumab, and rilonacept [112].

Finally, recent reports indicated that the corticosteroid dexamethasone may reduce mortality of severe COVID-19 patients [129]. Dexamethasone would limit the production of and damaging effect of the cytokines but will also inhibit the protective function of T cells and block B cells from making antibodies, potentially leading to increased plasma viral load [130]. Probably, dexamethasone may be useful for the short term in severe, intubated, COVID-19 patients.

In conclusion, in spite of the evidence of a correlation between inflammation and coagulative alterations, no certain evidence is available of the effectiveness and safety of heparin or antiplatelet substances or other drugs on SARS-CoV-2 subjects, and several problems have to be resolved, such as the correct timing, doses, and associations.

Despite the uncertainties mentioned above, it is certainly possible to try to provide some indications for clinical practice. The employ of LMWH or fondaparinux at dosages suggested for prophylaxis of VTE is intensely recommended in all SARS-CoV-2-hospitalized patients; subjects with anticoagulant contraindications should be cured with limb compression. Prophylactic heparin treatment should be performed for all the hospitalization time and for 7–14 days after hospital discharge in presence of VTE risk factors. The employ of intermediate-dose LMWH could be used on an individual basis in subjects with numerous risk factors for VTE, while the employ of therapeutic doses of LMWH is at present not validated by sufficient evidence and cannot be suggested as a standard therapy for all SARS-CoV-2 subjects [131].

Although the violence of the pandemic may suggest the use of heroic treatments to reduce the frightening mortality that accompanies SARS-CoV-2 infection, we believe that experimental treatments should only be used within approved and controlled experimental protocols, the only ones that can provide useful and specify information on the validity of the treatments.

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