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SARS-CoV-2 infection and thrombotic complications: a narrative review

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Abstract

The current, global situation regarding the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic and its potentially devastating clinical manifestations, i.e. coronavirus disease 2019 (COVID-19), took the world by storm, as millions of people have been infected worldwide and more than 1,600,000 patients have succumbed. Infection induced by various respiratory viruses may lead to thrombotic complications. Infection-elicited thrombosis may involve a repertoire of distinct, yet interconnected pathophysiological mechanisms, implicating a hyperinflammatory response, platelet activation and triggering of the coagulation cascade. In the present review, we present current knowledge on the pathophysiological mechanisms that may underlie thrombotic complications in SARS-CoV-2 infection. Furthermore, we provide clinical data regarding the incidence rate of thrombotic events in several viral respiratory infections that cause acute respiratory distress syndrome, including SARS-CoV-2 infection and finally we summarize current recommendations concerning thromboprophylaxis and antithrombotic therapy in patients with thrombotic complications related to SARS-CoV-2 infection.

Keywords Acute respiratory distress syndrome · Antithrombotic therapy · COVID-19 · Endothelium · Inflammation · Respiratory viruses · SARS-CoV-2 · Thrombosis · Venous thromboembolism

Highlights

- SARS-CoV-2 infection is associated with an increased risk of arterial and venous thrombotic events.
- The pathophysiological mechanisms underlying thrombotic events in SARS-CoV-2 infection include platelet activation, triggering of the coagulation cascade, the formation of neutrophil extracellular traps (NETs) and "cytokine storm" syndromes.
- Antithrombotics, such as low-molecular-weight heparin or unfractionated heparin, are used for thromboprophylaxis or for the treatment of thrombotic events related to SARS-CoV-2 infection.
- More studies are required to fully elucidate the pathophysiological mechanisms responsible for thrombotic events in COVID-19 patients, as well as to increase the efficacy of the current antithrombotic treatment strategies. This will help reduce even more the incidence of such events.

Introduction

As of December 2020, approximately 70,000,000 people have been infected by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), whereas more than 1,600,000 have died from the coronavirus disease 2019 (COVID-19), according to the World Health Organization (https://www.who.int/emergencies/diseases/novel-coronavirus-2019, accessed on December 16, 2020).

SARS-CoV-2 infection occurs via its binding to the angiotensin-converting enzyme 2 (ACE2), expressed on various cell types, including type II pneumocytes, as well as macrophages and endothelial cells (ECs) [1]. Two proteins required for the entrance of SARS-CoV-2 into the target cells are the transmembrane protease serine 2 (TMPRSS2) and the main protein (Mpro) [2–5]. SARS-CoV-2 binding to ACE2 and TMPRSS2 occurs through the spike (S) protein, especially through the N-terminal domain of its S1 subunit

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[2]. Therefore, co-expression of ACE2 and TMPRSS2 on the target cells is a pre-requisite for cell infection. Infected cells undergo pyroptosis, a highly inflammatory type of cell death, which results in the release of damage-associated molecular patterns (DAMPs), inducing and perpetuating a hyperinflammatory response.

COVID-19 patients may exhibit coagulation abnormalities, resulting in a hypercoagulable state, and in an increased rate of thrombotic and thromboembolic events [6]. Indeed, in hospitalized COVID-19 patients, the rate of thrombotic events in intensive care units (ICU) is approximately 29.4%, whereas in non-ICU is 11.5% [7]. In this review, we provide insights on the pathophysiological mechanisms that may underlie coagulopathy and thrombotic complications in respiratory viral infections that induce acute respiratory distress syndrome (ARDS), primarily focusing on SARS-CoV-2 infection. The clinical data on the incidence rate of thrombotic events in several respiratory viral infections that cause ARDS is also presented. Finally, we summarize current recommendations concerning thromboprophylaxis and antithrombotic therapy in COVID-19 patients.

We independently searched the Medline bibliographic database. Any article considered potentially relevant by authors, was retrieved for full review. The search strategy involved the use of the following keywords: "Acute Respiratory Distress Syndrome", "Antithrombotic therapy", "COVID-19", "Endothelium", "Inflammation", "Respiratory viruses", "SARS-CoV-2", "Thrombosis", "Venous Thromboembolism", in any field (title, abstract and/or the main body) of papers. Exclusion criteria were articles written in any language apart from English.

Possible pathophysiological mechanisms underlying hypercoagulability and thrombotic complications in respiratory viral infections

Several respiratory viral infections induce hypercoagulability and are associated with increased risk of arterial and venous thrombosis. Notably, an association of viral acute respiratory infections, especially influenza, and acute myocardial infarction has been observed, whereas the incidence of venous thromboembolic events following influenza infection has also been reported [8, 9]. However, infection-related thrombotic events may occur in patients with an atherosclerotic background or undiagnosed cardiovascular disease [10]. In support of the association between respiratory viral infections and thrombosis are the results of a meta-analysis of randomized clinical trials showing that influenza vaccination is associated with a significant reduction in the rate of cardiovascular events, especially in high-risk patients who have experienced an acute coronary syndrome [11]. Accumulated evidence suggests a variety of possible cellular and molecular mechanisms that are accountable for the observed thrombotic complications. Among them, an overwhelming inflammatory response, in conjunction with platelet activation and a pro-coagulant phenotype seems to play a major role in the manifestation of respiratory viral infection-related thrombotic complications.

Viral respiratory infections are associated with the activation of platelets and the coagulation cascade [12, 13], thus increasing the incidence of thrombotic events. Platelets express on their surface several receptors, such as toll-like receptors (TLRs) and C-type lectin receptors, that recognize viruses as well as viral components, and commit platelets to respond to them [14]. A small study involving patients suffering from upper respiratory tract viral infections, reported higher platelet reactivity in these patients, expressed as adenosine diphosphate (ADP)-induced aggregation and P-selectin membrane expression, compared with platelets from healthy individuals [12]. Platelet P-selectin significantly contributes to the pro-thrombotic and pro-inflammatory platelet activities, through binding to its glycoprotein ligand-1 (PSGL-1), expressed on leukocytes, thus promoting monocyte and neutrophil activation [15]. In addition to P-selectin, activated platelets express and release a plethora of pro-inflammatory and pro-thrombotic mediators, such as CD40L, ADP, arachidonic acid (AA), von Willebrand factor (vWF) and chemokines, which mediate platelet interaction with leukocytes and ECs, thus inducing activation of these cells [15]. In addition to platelet activation, viral respiratory infections induce membrane expression of tissue factor (TF) by monocytes and ECs, through activation of nuclear factor kappa B, thus initiating the coagulation cascade, whereas they also induce the release of various pro-inflammatory cytokines, such as interleukin (IL)-1β and -8 [13].

SARS-CoV-2 infection and risk of thrombosis

SARS-CoV-2 infection and cellular components involved in thrombosis

SARS-CoV-2 infection and endothelial cell activation

Except for the lung epithelium, SARS-CoV-2 can also infect cells of other tissues, such as the vascular endothelium, heart and intestine, since ACE2 is expressed in these tissues too [16, 17]. Indeed, evidence suggests that blood vessel organoids contain RNA of the virus after in vitro SARS-CoV-2 infection [18], whereas ECs of the aforementioned tissues, obtained from SARS-CoV-2-infected patients, contain the virus, and histological samples of COVID-19 patients have revealed EC inflammation and death [19]. The abundant

expression of ACE2 receptors on ECs enhances their vulnerability to SARS-CoV-2 binding, membrane fusion and cell entry, thus inducing endothelial dysfunction and endotheliitis. Furthermore, SARS-CoV-2-infected patients exhibit increased concentration of pro-inflammatory factors, including IL-1β, IL-6, monocyte chemoattractant protein-1 (MCP-1) and interferon γ, which adversely affect endothelial integrity and functionality and lead to the endothelial expression of molecules such as vWF, intercellular adhesion molecule-1 (ICAM-1), P- and E-selectin [20, 21], which in turn results in platelet and leukocyte attraction and activation [22, 23], as well as in complement activation. Moreover, the hypoxia that these patients suffer, leads to overexpression of TF via hypoxia-inducing factors, which can trigger the coagulation cascade [24]. All the above data advocate to the display of a pro-coagulant and pro-thrombotic phenotype, related to the endothelial dysfunction and endotheliitis caused by SARS-CoV-2.

SARS-CoV-2 infection and platelet activation

Thrombocytopenia is a characteristic feature in patients exhibiting severe COVID-19. Indeed, the results of a meta-analysis demonstrated that thrombocytopenia is associated with a fivefold increased risk of severe disease, albeit it is not a common finding in non-severe COVID-19 [25]. Importantly, platelets express ACE2, rendering them a target cell to SARS-CoV-2 infection and leading to their activation [26]. SARS-CoV-2-activated platelets secrete a repertoire of chemokines, e.g. platelet factor 4, regulated on activation, normal T expressed and secreted (RANTES), CCL3 and -7 and CXCL1, -5 and -7, which potentiate the recruitment of leukocytes, granting platelets a pro-inflammatory phenotype in the setting of SARS-CoV-2 infection [25]. Furthermore, activated platelets secrete inorganic polyphosphate, which activates the contact pathway, as well as high-mobility group box-1, which potentiates the recruitment of monocytes, the membrane expression of monocyte TF and the shedding of monocyte-derived TF-bearing microparticles, that in turn leads to activation of the coagulation cascade [25]. Moreover, platelets play a role in modulating the adaptive immunity, since they participate in the recruitment and proliferation of T-cells [27, 28], as well as they increase the production of immunoglobulins from B-cells [29].

SARS-CoV-2 infection and neutrophil extracellular traps

Activated neutrophils can form neutrophil extracellular traps (NETs), a web-like material structured from DNA and a multitude of proteins [30]. The process of NET formation is termed "NETosis". NETs display pro-inflammatory properties, since they are produced and participate in the pathogenesis of sterile and non-sterile inflammatory conditions, including atherogenesis, arterial and venous thrombosis [31]. Although NETosis is a beneficial mechanism of innate immune response when properly controlled, persistent NETosis can be detrimental to the host, since NETs bear multiple proteases that can be harmful to the endothelium and other tissues [32, 33]. NETs are also generated in response to viruses, such as influenza [34]. In this regard, several studies reported that NETs are also employed in response to SARS-CoV-2 [35–38]. Indeed, COVID-19 is associated with neutrophil infiltration to the lungs, lung injury, microthrombosis in the lung vasculature and increased markers of NETosis, such as myeloperoxidase-associated DNA and citrullinated histone H3, in the serum of COVID-19 patients [35–38]. NETs can be formed directly in the presence of DAMPs or pathogen-associated molecular patterns, or in response to cytokines, such as IL-8 [30]. Additionally, NETs can be formed indirectly by platelets activated either via classic platelet agonists (e.g. thrombin, ADP, AA) [39–41] or via other receptors (e.g. TLR4) [42]. Once formed, NETs express pro-coagulant and pro-thrombotic effects inducing platelet activation [40, 43, 44], as well as through the accumulation of pro-thrombotic molecules such as fibrin, vWF [43] and TF on their structure [40]. NETs also activate the contact pathway [25] and promote the gene expression of coagulation factors [45]. Hence, aberrant NETosis has adverse consequences to the host and may contribute to thrombotic complications in COVID-19 patients.

SARS-CoV-2 infection and non-cellular components involved in thrombosis

SARS-CoV-2 infection and "cytokine storm" syndromes

Another factor contributing to thrombotic complications in SARS-CoV-2 and other respiratory viral infections are the "cytokine storm" syndromes, characterized by elevated concentrations of various cytokines, including IL-1β, -2, -6, -7, granulocyte colony-stimulating factor, MCP-1, tumor necrosis factor-α and ferritin [46–48]. Cytokine storm syndromes may activate the coagulation cascade and on the other hand, coagulation factors can act as triggers of the cytokine storm [46–48]. Moreover, NETs can aggravate the overproduction of cytokines, as well as the pro-coagulant and pro-thrombotic status [37, 38]. Ultimately, the overproduction of cytokines, as well as the development of thrombi, are crucial for multi-organ injury [47, 48], such as lung, cardiac and hepatic injury, and eventual failure, which may lead to death.

SARS-CoV-2 infection and complement activation

The nucleocapsid (N) protein of SARS-CoV-2 binds to the mannose-binding lectin-associated serine protease (MASP)-2, which is expressed on the microvasculature, thus leading to complement activation [25]. This activation potentiates the aforementioned mechanisms through the overexpression of endothelial and monocyte TF, as well as through increasing platelet activation. It also enhances endothelial inflammation, thus further increasing the production of pro-inflammatory cytokines from ECs, such as IL-1, -6, -8, RANTES and MCP-1. Activation of the complement component C3 is associated with activation of the contact pathway and may play an important role in disease pathogenesis and exacerbation [49]. Consistent with the above results is the observation that deletion of C3 in mice infected with mouse-adapted severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) is associated with reduced neutrophil and monocyte numbers, as well as reduced cytokine levels in these animals [49], suggesting the participation of C3 in the inflammatory response.

SARS-CoV-2 infection and thrombin generation

Activation of the contact pathway, as well as the increased expression of TF, through the above described mechanisms, lead to enhanced thrombin generation in COVID-19 patients.

Thrombin is an important protease in thrombosis, since it cleaves fibrinogen to produce fibrin and also activates platelets through protease-activated receptor (PAR)-1 and -4 [50]. These receptors are expressed in all tissues and mediate a variety of cellular effects, including endothelial and leukocyte activation, thus promoting a pro-inflammatory phenotype. In this regard, thrombin-induced activation of ECs through PAR-1 upregulates platelet-activating factor, MCP-1, IL-6 and -8, as well as P- and E-selectin and ICAM-1, which enhance the recruitment of leukocytes to the endothelium and further leukocyte activation. Ultimately, the activation of platelets, ECs and leukocytes leads to thrombin generation via a positive feedback loop, which plays an important role in the thrombotic clinical manifestations observed in severe COVID-19 patients, such as ischemic stroke, pulmonary embolism (PE) and deep vein thrombosis (DVT) [25].

SARS-CoV-2 infection and antiphospholipid syndrome

Another possible factor contributing to the thrombotic complications observed in respiratory viral infections, such as those caused by influenza A/H1N1 and SARS-CoV-2, is antiphospholipid syndrome (APS) [51]. In this regard, antiphospholipid antibodies have been identified in COVID-19 patients [52]. Antiphospholipid antibodies in COVID-19 patients are predominantly directed against beta-2-glycoprotein I, but to a different epitope compared to the one targeted by antiphospholipid antibodies of individuals with established, non-COVID-19-related APS [53].

In COVID-19-related APS, increased concentrations of antiphospholipid antibodies have been associated with increased platelet numbers, worse respiratory disease manifestation, as well as nephrological abnormalities [54]. Importantly, increased levels of antiphospholipid antibodies in COVID-19 patients have been also associated with increased NETosis [54]. Moreover, IgG antiphospholipid antibody fractions from COVID-19 patients induced NETosis in neutrophils from control individuals, a finding also observed in patients with non-COVID-19-related APS, whereas administration of these fractions to mice resulted in venous thrombosis [54]. Indeed, previous reports suggested that NETs are linked to the pathogenesis of APS [55]. However, other researchers suggested that antiphospholipid antibodies are not frequent in COVID-19 patients and they are not responsible for the occurrence of major thrombotic events in these subjects [53].

A comprehensive illustration of the above described mechanisms of thrombotic complications during respiratory viral infections are presented in Fig. 1.

Main clinical data involving thrombotic complications in respiratory viral infections

The thrombotic complications reported in COVID-19 patients [56–59] are a common feature of respiratory viral infections, like those caused by influenza viruses [9, 60–62] and other betacoronaviruses, including SARS-CoV-1 and Middle Eastern respiratory syndrome coronavirus (MERS-CoV) [63]. The clinical data of several studies, involving thrombotic complications in various respiratory viral infections, is summarized in Table 1.

Results from a recent study involving 183 SARS-CoV-2-infected patients, demonstrated that 21 (about 11.5%) deceased, whereas among the non-survivors 15 (about 71.4%) developed overt disseminated intravascular coagulation (DIC) [56]. In another study involving 81 COVID-19 severe cases admitted to the ICU, 20 (about 25.0%) developed venous thromboembolism (VTE), of which 8 (40.0%) did not survive [57]. Similar results were reported in 184 COVID-19 patients who were admitted to the ICU and were receiving thromboprophylaxis. The cumulative incidence of the composite outcome of VTE or arterial thrombotic events in these patients was 31% (27% VTE and 3.7% arterial thrombosis). Among them, PE was the predominant thrombotic event (25 cases; about 80.6%), whereas all arterial thrombosis cases were ischemic strokes [58]. In another report involving 25 COVID-19 patients, 7 (28%) developed

PE [59]. A multi-national meta-analysis of 17,799 hospitalized COVID-19 patients from 11 countries demonstrated that the total risk of stroke is 0.5%, with a pooled risk of 0.9%, whereas the need for mechanical ventilation support and the history of ischemic heart disease of the patients are independent prognostic factors of stroke [64]. Finally, in a more recent meta-analysis, it was demonstrated that major thromboembolic events, and especially PE, were particularly evident in COVID-19 patients admitted to the ICU [65].

Regarding influenza infection, it was reported that, among 119 hospitalized patients with H1N1 influenza A, 7 (about 5.9%) experienced a thrombotic event [60]. In another report, which involved 11,208 patients who suffered an acute myocardial infarction, 3927 (about 35.0%) had an acute respiratory infection, including influenza [61]. Individuals with at least one indicator of influenza were more likely to develop myocardial infarction compared to those without any influenza indicators ($p = 0.012$), suggesting that influenza may constitute a stronger trigger for myocardial infarction than other respiratory infections [61]. Furthermore, it was documented that, among 252 hospitalized patients with confirmed H1N1 influenza A infection, 20 (about 7.9%) became critically ill and required admission to the ICU. Among them, 5 (25.0%) experienced a thrombotic event [9]. A more recent study reported that, among 36 patients

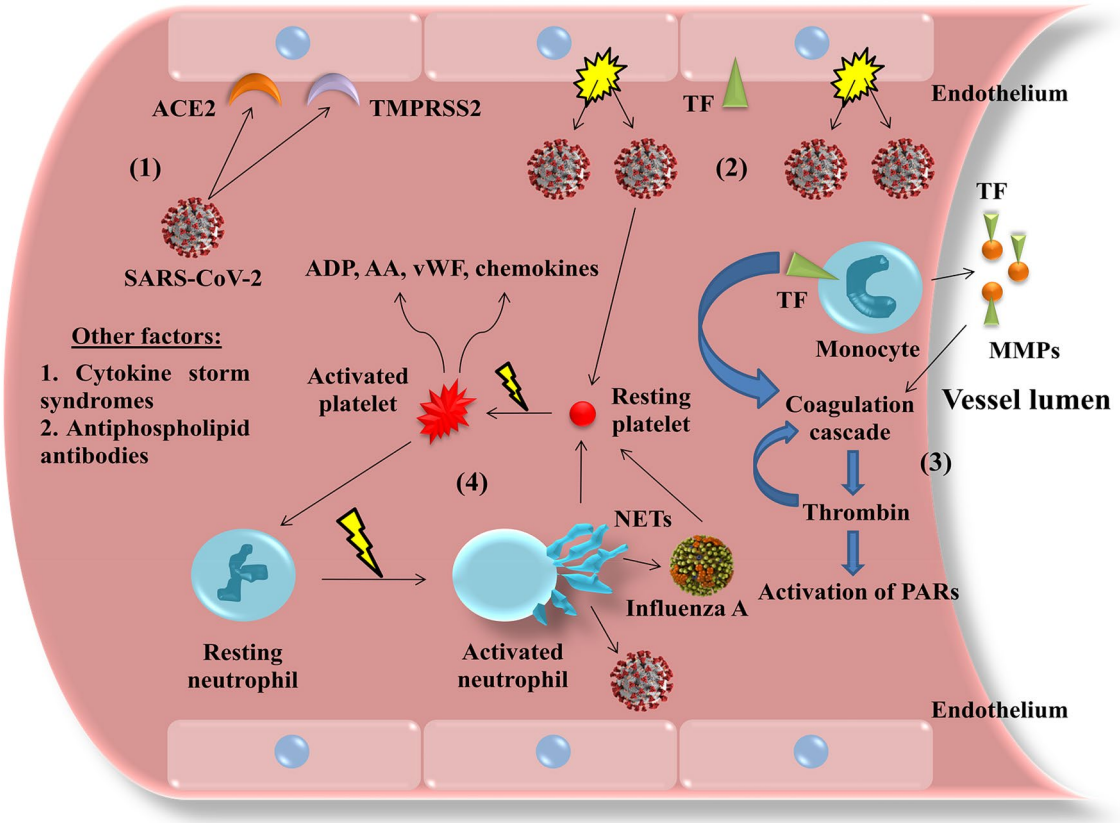

Fig. 1 Possible pathophysiological mechanisms implicated in thrombotic complications during respiratory viral infections. The presence of viruses, such as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and influenza A, triggers a series of cellular and molecular events that may be accountable for thrombotic complications in such infections. For example, SARS-CoV-2 enters endothelial cells via simultaneous binding to angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) (1), causing widespread endothelial disruption (2). Moreover, respiratory viral infections induce the membrane expression of tissue factor (TF) by endothelial cells, monocytes and monocyte-derived microparticles (MMPs), thus initiating the coagulation cascade which culminates in thrombin generation, which activates protease-activated receptors (PARs) and enhances the coagulation cascade in a positive feedback loop (3). Thrombin and other platelet agonists (e.g. adenosine diphosphate [ADP] and arachidonic acid [AA]), as well as viruses directly, activate platelets to express on their surface and release a plethora of pro-inflammatory and pro-thrombotic mediators, e.g. P-selectin and CD40L (not shown), more ADP and AA, von Willebrand factor (vWF) and various chemokines, which in turn activate endothelial cells and leukocytes. Notably, activated neutrophils form neutrophil extracellular traps (NETs), which arrest viruses but also bear pro-thrombotic properties, for example by activating more platelets in a vicious cycle (4). Other factors that contribute to the manifestation of a pro-thrombotic phenotype are the existence of cytokine storm syndromes (i.e. an overwhelming rise of cytokine levels, such as interleukins and other pro-inflammatory molecules) and possibly antiphospholipid antibodies, in a virus-related antiphospholipid syndrome

admitted to the hospital with H1N1 influenza A infection, 16 (about 44.4%) developed VTE [62].

Concerning SARS-CoV-1-infected patients, a study reported that, among 138 individuals, 44.8% had thrombocytopenia [66]. Another study demonstrated small vein thrombosis in 3 autopsied patients with SARS-CoV-1 [67]. Similarly, the presence of fibrin thrombi was reported in 1 among 6 autopsied SARS-CoV-1 patients [68]. In another study, the existence of hematologic abnormalities, including thrombocytopenia, at a rate of up to 45% in adults and 50% in children with SARS-CoV-1, was reported [69]. A retrospective analysis demonstrated that, among 157 SARS-CoV-1-infected patients, 87 (about 55.4%) developed thrombocytopenia, whereas 4 patients (about 2.5%) developed DIC [70]. Finally, in another study, the incidence of large artery ischemic stroke in 5 out of 206 SARS-CoV-1-infected patients (about 2.4%), was demonstrated [71].

Similarly to the above data, thrombotic vascular events have been also reported in MERS-CoV-infected patients. According to previously published results, thrombocytopenia was evident in 17 of 47 individuals (about 36.2%) with confirmed MERS-CoV infection [72], whereas in another study thrombocytopenia was more pronounced in MERS-CoV-infected patients (about 57.1%, i.e. in 4 out of 7 individuals) [73]. Other investigators reported a case of MERS-CoV-associated fatality which had presented DIC [74], whereas in another study, DIC was evident in 1 among 2 cases of MERS-CoV-related neurologic complications [75]. Finally, in a review article it was reported that the mortality rate among MERS-CoV-infected patients was about 30%, whereas the corresponding rate in SARS-CoV-1-infected patients was 9.6% [76]. Importantly, DIC was one of the major complications in MERS-CoV-infected patients [76]. Due to the heterogeneous rates of thrombotic events in the above studies, it is difficult to draw a definite conclusion as to whether the prevalence of SARS-CoV-2-induced coagulopathy and thrombotic complications is greater, or not, than those related to other respiratory viral infections.

Thromboprophylaxis and anticoagulant therapy in thrombotic complications related to respiratory viral infections

The use of antithrombotics as thromboprophylaxis or to treat thrombotic events is a common practice in patients with respiratory viral infections. Notably, in influenza A/H1N1-infected patients, even empirical anticoagulation therapy using heparin reduced the incidence of thromboembolic events in critically-ill subjects, without increasing the bleeding risk [62]. Moreover, in 184 severe COVID-19 patients the cumulative incidence of the composite outcome

Table 1 Main clinical data involving thrombotic complications in various viral infections

Viral infection	Thrombotic complication(s)	Prevalence (patient numbers and rates)	References
SARS-CoV-2	Overt DIC	21 of 183 (11.5%)	[56]
	VTE	20 of 81 (25.0%)	[57]
	VTE or AT	31 of 184 (31%*)	[58]
	PE	7 of 25 (28%)	[59]
	VTE PE	16 of 71 (22.5%) 7 of 71 (9.9%)	[77]
	VTE	18 of 26 (69.2%)	[78]
	SIC	97 of 449 (21.6%)	[79]
Influenza A	VTE or AT	7 of 119 (5.9%)	[60]
	MI	3927 of 11,208 (35.0%)**	[61]
	Thrombotic events	5 of 252 (2.0%)	[9]
	VTE	16 of 36 (44.4%)	[62]
SARS-CoV-1	Small vein thrombosis	3 autopsies	[67]
	Presence of thrombi	1 of 6 autopsies (17.0%)	[68]
	DIC	4 of 157 (2.5%)	[70]
	Ischemic stroke	5 of 206 (2.4%)	[71]
MERS-CoV	DIC	1 autopsy	[74]
	DIC	1 of 2 patients with neurologic complications (50%)	[75]

*Corresponds to a cumulative incidence

**Not all of these cases refer to influenza, but rather to an acute respiratory infection, including influenza

AT arterial thrombosis, *DIC* disseminated intravascular coagulation, *MI* myocardial infarction, *MERS-CoV* Middle Eastern respiratory syndrome coronavirus, *PE* pulmonary embolism, *SARS-CoV* severe acute respiratory syndrome coronavirus, *SIC* sepsis-induced coagulopathy, *VTE* venous thromboembolism

Table 2 Ongoing randomized, controlled trials of antithrombotic therapy in hospitalized patients with COVID-19

Trial full name	Trial registration number (ClinicalTrials.gov)	Actual/estimated number of participants	Aim of the trial
Austrian coronavirus adaptive clinical trial (COVID-19) (ACOVACT)	NCT04351724	500 subjects	Rivaroxaban vs. LMWH, for sustained clinical improvement (substudy of ACOVACT)
Comparison of two doses of enoxaparin for Thromboprophylaxis in hospitalized COVID-19 patients (X-Covid 19)	NCT04366960	2712 Subjects	Enoxaparin twice daily vs. enoxaparin once daily, for prevention of VTE
Intermediate or prophylactic-dose anticoagulation for venous or arterial thromboembolism in severe COVID-19: A cluster based randomized selection trial (IMPROVE-COVID)	NCT04367831	100 ICU Subjects	Intermediate vs. prophylactic dose of enoxaparin or UFH, for prevention of thrombotic events in critically-ill patients
Antithrombotic therapy to ameliorate complications of COVID-19 (ATTACC)	NCT04372589	3000 Subjects	LMWH or UFH vs. standard-of-care anticoagulation, for reduction of intubation or mortality
Trial evaluating efficacy and safety of anticoagulation in patients with COVID-19 infection, nested in the corimmuno-19 cohort (CORIMMUNO-COAG)	NCT04344756	808 Subjects	Tinzaparin or UFH vs. standard-of-care anticoagulation, to test the efficacy and safety of anticoagulation in COVID-19 patients
Weight-adjusted vs fixed low doses of low molecular weight heparin for venous Thromboembolism prevention in COVID-19 (COVI-DOSE)	NCT04373707	602 subjects	Weight-adjusted vs. low prophylactic dose of LMWH, for prevention of VTE
Full anticoagulation versus prophylaxis in COVID-19: Coalizao action trial (ACTION)	NCT04394377	600 Subjects	Rivaroxaban (followed by enoxaparin/UFH when needed) vs. enoxaparin, to test the effect of full vs. prophylactic anticoagulation
Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care as a Rapid Response to the COVID-19 Pandemic (RAPID COVID COAG)	NCT04362085	462 Subjects	Therapeutic anticoagulation with enoxaparin or UFH vs. standard-of-care, for prevention of thromboembolic events and COVID-19 progression
A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care as a Rapid Response to (SARS-CoV-2) COVID-19 Pandemic (RAPID-BRAZIL)	NCT04444700	462 Subjects	Enoxaparin vs. standard-of-care, for prevention of thromboembolic events and COVID-19 progression
Safety and Efficacy of Therapeutic Anticoagulation on Clinical Outcomes in Hospitalized Patients With COVID-19	NCT04377997	300 Subjects with elevated D-dimer levels	Therapeutic vs. standard-of-care anticoagulation with enoxaparin, to test the efficacy and safety of therapeutic anticoagulation in patients with elevated D-dimer levels
High Versus Low LMWH Dosages in Hospitalized Patients With Severe COVID-19 Pneumonia and Coagulopathy (COVID-19 HD)	NCT04408235	300 Subjects with severe COVID-19, not requiring invasive mechanical ventilation	High- vs. low-dose enoxaparin, to test the efficacy and safety of high vs. low LMWH doses
Preventing COVID-19 Complications With Low- and High-dose Anticoagulation (COVID-HEP)	NCT04345848	200 Subjects with severe COVID-19	Therapeutic vs. prophylactic doses of enoxaparin or UFH, for risk reduction of arterial and venous thrombosis, DIC and mortality
Clinical Trial on the Efficacy and Safety of Bemiparin in Patients Hospitalized Because of COVID-19	NCT04420299	120 Subjects	Therapeutic vs. prophylactic dose of bemiparin, for prevention of arterial or venous thrombotic events or COVID-19 progression

Table 2 (continued)

Trial full name	Trial registration number (ClinicalTrials.gov)	Actual/estimated number of participants	Aim of the trial
Systemic Anticoagulation With Full Dose Low Molecular Weight Heparin (LMWH) Vs. Prophylactic or Intermediate Dose LMWH in High Risk COVID-19 Patients (HEP-COVID Trial)	NCT04401293	308 high-Risk COVID-19 subjects	Full dose vs. prophylactic/intermediate dose of LMWH or UFH, for reduction of arterial and venous thromboembolic events and all-cause mortality
InterMediate ProphylACtic Versus Therapeutic Dose Anticoagulation in Critically Ill Patients With COVID-19: A Prospective Randomized Study (The IMPACT Trial)	NCT04406389	186 Critically-ill subjects	Therapeutic vs. intermediate dose of anticoagulation, for mortality reduction
Prevention of Arteriovenous Thrombotic Events in Critically-Ill COVID-19 Patients Trial (COVID-PACT)	NCT04409834	750 Critically-ill subjects	To test the efficacy and safety of full-dose vs. standard prophylactic dose anticoagulation and of antiplatelet vs. no antiplatelet therapy for prevention of venous and arterial thrombotic events
Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Disease 2019 (COVID-19) Trial (ACT-COVID19)	NCT04324463	4000 Subjects	Combination of aspirin and rivaroxaban vs. standard-of-care, to reduce the clinical progression of COVID-19
Preventing Cardiac Complication of COVID-19 Disease With Early Acute Coronary Syndrome Therapy: A Randomised Controlled Trial. (C-19-ACS)	NCT04333407	3170 Subjects	Antithrombotic and hypolipidemic drugs vs. placebo, for prevention of cardiovascular complications related to COVID-19
Effect of Anticoagulation Therapy on Clinical Outcomes in COVID-19 (COVID-PREVENT)	NCT04416048	400 Subjects with moderate to severe COVID-19	Rivaroxaban vs. standard-of-care, for prevention of arterial and venous thrombotic events, all-cause mortality or intubation and invasive ventilation
The Utility of Camostat Mesylate in Patients With COVID-19 Associated Coagulopathy (CAC) and Cardiovascular Complications	NCT04435015	200 Subjects	Camostat mesylate vs. placebo, to test the effect of camostat mesylate on myocardial injury and COVID-19 progression
Trial of Open Label Dipyridamole- In Hospitalized Patients With COVID-19 (TOLD)	NCT04424901	100 Subjects	Dipyridamole vs. standard-of-care, for treatment of respiratory tract infection and circulatory dysfunction
Dipyridamole to Prevent Coronavirus Exacerbation of Respiratory Status (DICER) in COVID-19 (DICER)	NCT04391179	80 Subjects	Dipyridamole vs. placebo, for prevention of exacerbation of respiratory status
Fibrinolytic Therapy to Treat ARDS in the Setting of COVID-19 Infection	NCT04357730	60 Subjects with severe respiratory failure	Alteplase vs. standard-of-care, for treatment of ARDS
Impact of Tissue Plasminogen Activator (tPA) Treatment for an Atypical Acute Respiratory Distress Syndrome (COVID-19) (AtTAC)	NCT04453371	50 Subjects	Alteplase vs. placebo, for treatment of severe atypical ARDS
Prasugrel in Severe COVID-19 Pneumonia (PARTISAN)	NCT04445623	128 Subjects	Prasugrel vs. placebo, for prevention of severe COVID-19-related pneumonia
Dociparstat for the Treatment of Severe COVID-19 in Adults at High Risk of Respiratory Failure	NCT04389840	524 Subjects with severe COVID-19	Dociparstat vs. placebo, to test the efficacy and safety of dociparstat in the treatment of acute lung injury
Anticoagulation in Patients Suffering From COVID-19 Disease The ANTI-CO Trial	NCT04445935	100 Subjects	Bivalirudin injection vs. standard-of-care, for improvement of oxygenation

Table 2 (continued)

Trial full name	Trial registration number (ClinicalTrials.gov)	Actual/estimated number of participants	Aim of the trial
Nebulized Heparin for the Treatment of COVID-19 Induced Lung Injury	NCT04397510	50 Subjects	Nebulized heparin vs. placebo, for reduction of severity of lung injury

ARDS acute respiratory distress syndrome, *DIC* disseminated intravascular coagulation, *ICU* intensive care unit, *LMWH* low-molecular-weight heparin, *UFH* unfractionated heparin, *VTE* venous thromboembolism

of venous or arterial thrombosis was 31%, despite rigorous thromboprophylaxis [58]. This suggests that high prophylactic doses should be administered to such patients, in spite of the absence of relevant recommendations [58]. Similarly, in another study involving 71 COVID-19 patients under adequate thromboprophylaxis, who were not admitted to the ICU, a VTE incidence of about 22.5% was reported [77]. Authors concluded that heparin thromboprophylaxis should be aggressive and under the guidance of D-dimer levels, which may have a predictive value for VTE, with a cut-off value of 1.0 μg/mL [77]. In accordance with the above results, an additional study reported that COVID-19 patients receiving prophylactic anticoagulation had significantly higher rates of VTE compared to those receiving therapeutic anticoagulation with either low-molecular-weight heparin (LMWH) or unfractionated heparin (100% vs. 56% respectively, $p=0.03$) [78]. Finally, other investigators found that administration of unfractionated heparin or LMWH improves the clinical outcome of COVID-19-associated thrombotic complications [59, 79].

In light of this data, the International Society of Thrombosis and Haemostasis (ISTH) has recommended the use of prophylactic doses of LMWH in all hospitalized COVID-19 patients (whether they have severe disease or not), in the absence of any contraindications [80]. LMWH should also prevent VTE incidence in critically-ill patients [80]. Moreover, the anti-inflammatory properties of LMWH would probably benefit patients from cytokine storm syndromes [80]. Other guidelines suggest thromboprophylaxis with the use of standard dose of unfractionated heparin or LMWH (or intermediate dose of LMWH), unless there are contraindications, in all non-critically-ill, hospitalized patients [81]. In critically-ill patients, prophylactic doses of unfractionated or LMWH should be considered, whereas intermediate doses of LMWH should be given to high-risk patients [81]. In therapeutic, and not prophylactic settings, administration of LMWH should be considered in hospital, whereas direct oral anticoagulants (DOACs) are recommended after hospital discharge [81]. According to the CHEST guidelines, administration of LMWH or fondaparinux is preferred over unfractionated heparin, in acutely-ill, hospitalized COVID-19 patients, in the absence of contraindications, whereas administration of unfractionated heparin is preferred over DOACs [82]. Moreover, in the absence of any contraindications, LMWH is preferred over unfractionated heparin, in critically-ill, COVID-19 patients, whereas administration of LMWH or unfractionated heparin is preferred over fondaparinux or DOACs [82]. The same guidelines recommend administration of standard doses of anticoagulants over intermediate or full-dose treatment, in both acutely-ill or critically-ill COVID-19 patients [82]. Continuation of thromboprophylaxis in COVID-19 patients after hospital discharge is not recommended, unless a net benefit is

recognized and there is low bleeding risk [82]. Ongoing randomized, controlled trials on antithrombotic therapy in hospitalized COVID-19 patients are summarized in Table 2. These trials will demonstrate the possible clinical usefulness of this therapy in terms of efficacy and safety, not only in the prevention of thrombotic events, but also in the overall clinical management of these patients.

Concluding remarks and future directions

Patients suffering from respiratory viral infections are at increased risk of manifesting a thrombotic event, of arterial and/or venous origin. However, due to the fact that the available evidence regarding respiratory virus-related thrombotic complications has not been analyzed collectively and in a head-to-head comparison with other viruses, there cannot be a safe conclusion as to whether SARS-CoV-2 is responsible for a worse rate of thrombotic manifestations, compared to other respiratory viruses, or not. These thrombotic events are attributed to various cellular and molecular mechanisms, mainly involving the interplay between a hyperinflammatory response, as well as the activation of platelets and the coagulation cascade. Thus, patients at risk of such events receive antithrombotic drugs either as thromboprophylaxis or as treatment therapy.

In the case of SARS-CoV-2, in addition to current recommendations, ongoing randomized, controlled trials on antithrombotic therapy in hospitalized COVID-19 patients will demonstrate the possible clinical usefulness of this therapy regarding its efficacy and safety, not only in the prevention of thrombotic events, but also in the overall clinical management of these patients.

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