REVIEW

COVID-19 and thrombosis: Clinical features, mechanism of disease, and therapeutic implications

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ABSTRACT

COVID-19 is a viral respiratory illness caused by the SARS-CoV-2 infection. In addition to lung disease, clinical complications of COVID-19 include myocardial damage and ischemia-related vascular disease. Severe manifestations and poor prognosis in these patients are associated with a hypercoagulable state predisposing to thrombotic-related complications and eventually death. However, these clinical features can also occur in other forms of pneumonia, such as community-acquired pneumonia (CAP), which, is also complicated by vascular diseases and characterized by platelet activation. Platelets play a pivotal role in these settings as bacteria and viruses may induce activation via Toll-like receptors (TLRs) in CAP patients and different and multiple pathways, including ACE2-AngII axis and/or TLRs, in COVID-19 patients. Despite evidence confirming the implication of platelet activation in both settings, their contribution to the thrombotic process is still under investigation. Thus, in this review, we (1) compare the thrombotic features of SARS-CoV-2 infection and CAP, (2) analyze the putative mechanisms accounting for venous and arterial thrombosis in SARS-CoV-2 infection, and (3) discuss the potential anticoagulant armamentarium to counteract thrombosis.

Key words: anticoagulation, COVID-19, platelets, SARS-CoV-2 infection, thrombosis

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INTRODUCTION

COVID-19 is a pandemic that so far has affected millions of individuals worldwide and greatly increased the risk of morbidity and mortality. Classical clinical features of COVID-19 are represented by the SARS--CoV-2 infection, which is characterized by bilateral ground-glass pneumonia. Pneumonia by COVID-19 may be a serious disease needing mechanical ventilation and intensive care unit (ICU) treatment in old patients or patients with comorbidities, such as coronary heart disease, cardiac failure and arrhythmia, risk factors for atherosclerosis, and chronic obstructive pulmonary disease (COPD) [1]. Even if lung disease with its sequelae greatly contributes to the enhanced risk of morbidity and mortality, other clinical features may also contribute to worsening clinical outcomes. Thus, patients with the SARS-CoV-2 infection may experience thrombosis in the venous and arterial circulation, which can aggravate the disease and eventually increase the mortality risk [2]. In accordance with this, analysis of global clotting laboratory tests consistently showed an enhanced circulating level of D-dimer, which results from fibrin degradation by plasmin and, thereby, is considered a marker of hypercoagulation state in patients with the SARS-CoV-2 infection [3]. Changes in other global clotting tests have been also reported, such as prolonged/shortened prothrombin

time (PT), activated partial thromboplastin time (aPTT), or thrombocytopenia, which suggest that the SARS-CoV-2 infection could be complicated by disseminated intravascular coagulation (DIC). However, this complication has been far demonstrated also because its prevalent clinical feature, i.e, bleeding complications, is rare in the SARS-CoV-2 infection. Therefore, there is consensus that the SARS-CoV-2 infection is essentially complicated by a hypercoagulation state, which is responsible for thrombosis in both venous and arterial circulation [4]. This is of scientific interest as other forms of pneumonia such as, for instance, community-acquired pneumonia (CAP), is complicated by thrombosis essentially in the arterial circulation. Thus, this review aims to compare the thrombotic features of the SARS-CoV-2 infection and CAP, to analyze the putative mechanisms accounting for venous and arterial thrombosis in the SARS-CoV-2 infection, and discuss the potential anticoagulant armamentarium to counteract thrombosis.

THROMBOTIC FEATURES IN SARS-COV-2 AND CAP

There is a growing body of evidence that clotting, platelet activation, and inhibition of anticoagulant factors may occur in infectious diseases caused by bacteria or viruses [5]. Clinical evidence has been documented in patients with CAP, which may be caused by viruses as well as bacteria [6]. During the hospital stay, patients with CAP may experience myocardial infarction (MI) and stroke, which occur prevalently in old patients or those with serious disease severity [7]. In a large, prospective, multicenter study conducted on more than 1000 patients, MI and stroke were detected in 11% of CAP patients [8]; notably, such complications were a warning sign of poor outcome in short- and long-term follow-up, suggesting the need for appropriate prevention of these vascular diseases [9, 10]. Conversely, there is no consensus as to whether CAP is complicated by venous thrombosis. In the prospective observational study, we did not observe symptomatic venous thrombosis (VT) in CAP, but we could not exclude a coexistence of asymptomatic VT [11].

At variance with CAP, early data on COVID-19 demonstrated that venous thrombosis is the principal thrombotic feature of SARS-CoV-2; clinical presentations of VT are essentially deep venous thrombosis (DVT) and pulmonary embolism (PE). Mackman et. al analyzed 15 studies from different countries and showed that venous thrombo-embolism was the most frequently reported vascular complication with a very large rate from 0.9% to 69%. On the other hand, the rate of arterial thrombosis was scarcely represented with an incidence of 2.8%–3.8% [12]. This apparent discrepancy between venous and arterial thrombosis was disproved by a study in a small group of 73 patients, of whom 17 (23%) experienced an almost similar distribution of venous and arterial thrombosis [13]. Furthermore, a large prospective study conducted in 3 334 COVID-19 patients showed an occurrence of thrombotic events in 533 (16%) during hospitalization — 207 events were in the venous tree (6.2% were venous; 3.2% PE and 3.9% DVT) and 365 (11%) in the arterial one (8.9% MI, 1.6% stroke and 1% thromboembolism) [14]. A similar rate of thrombosis was reported in a smaller group of COVID-19 patients, where the incidence rate during hospitalization was roughly 20% with an equal distribution between venous and arterial thrombosis [15–17]. Regarding the clinical features of arterial thrombosis, MI is the most frequent complication while stroke and arterial thromboembolism are less frequent [18].

Identification of patients at higher risk of thrombosis is an important challenge in the management of COVID-19 patients as it implies their treatment with or without an anticoagulant to prevent the thrombotic risk and eventually lower the mortality rate [19]. There is some evidence that age, sex, and comorbidities, including coronary heart disease, COPD, diabetes, and obesity predispose to thrombosis [20]. Scores, such as pneumonia severity index (PSI) or CURB65, applied to measure disease severity, are also good indicators of poor outcomes, but their relatively low sensitivity precludes their use as thrombosis predictors [21]. There is consistent evidence that patients needing mechanical ventilation or ICU are at higher risk of thrombosis and prescription of anticoagulant at this stage of the disease is mandatory [22]. However, it would be more clinically relevant to identify patients at risk of thrombosis in the early phase of the disease, where therapeutic prophylaxis could prevent thrombosis and its sequelae. So far we have limited information to implement laboratory and/or clinical scores. Some scores such as the PADUA or IMPROVE have been tested in the COVID-19 population to predict thrombosis but, due to the lack of a validation cohort or the analysis of variables, these scores do not fully reflect the clinical picture of the COVID-19 population, and their implementation into clinical practice is difficult [23, 24]. Among the laboratory variables, D-dimer may represent a useful marker of incipient thrombosis and data are consistent its elevation is closely associated with thrombosis in COVID-19 [14]. Among 2377 patients hospitalized for COVID-19, Berger et al. reported D-dimer elevation in 1823 patients (76%). The patients with elevated levels of D-dimer were at higher risk to experience a critical illness, thrombosis, and death and, interestingly, the magnitude of D-dimer progressively increased the thrombotic risk with values >2000 ng/ml and was significantly associated with thrombosis [25]. The relevance of this interesting finding was undermined by the fact that 10% of patients with negative D-dimer were also at risk of thrombosis suggesting that D-dimer alone is not useful for thrombotic prediction. Serum albumin is another biomarker potentially useful for thrombosis prediction. Albumin is an acute reactant protein with powerful antioxidant properties related to its richness in thiol groups and with anticoagulant and antiplatelet activity likely related to its antioxidant property; thus, its administration to patients with low serum albumin resulted in platelet aggregation inhibition [26]. Albumin is usually reduced in acute infections because of its involvement as an

anti-inflammatory molecule [27]. Consequently, albumin is severely lowered in COVID-19 patients with values <35 g/l in most patients with critical illness or needing ICU [28]. This finding may be of interest in exploring the thrombotic risk of COVID-19 as previous studies in the general population on patients at risk of cardiovascular disease reported a close association between serum levels <35 g/l and thrombosis [29]. In line with this, we found that serum levels <35 g/l were significantly associated with D-dimer elevation and an increased risk of thrombosis and death [13, 28]. In a preliminary study including a small group of COVID-19 patients, we found that albumin infusion at a dosage of 80 g/day for 3 days followed by 40 g/day in the following 4 days resulted in a significant reduction of D-dimer [30]. The mechanism accounting for low serum albumin in COVID-19 may be complex including not only its consumption as an anti-inflammatory molecule but also impaired liver synthesis, loss from concomitant renal disease, or impaired nutritional status [31, 32]. Taken together, the data reported here suggest that these two variables, i.e. serum albumin and D-dimer, may be of interest for future stratification of the thrombotic-risk patients not only in COVID-19 but also in other infectious diseases.

THE MECHANISM OF DISEASE

In addition to macrovascular thrombosis in the venous and arterial circulation, the SARS-CoV-2 infection is characterized by micro-thrombosis occurring in the alveolar-capillary district, where endothelial swelling along with platelet and leucocyte infiltration concur to thrombotic process [33]. Platelet-fibrin thrombi are quite common in autopsy studies performed in lungs taken from SARS-CoV-2 patients; they are detected in 80%–100% of specimen examined [34]. Thus, at least 3 cellular lines, namely platelets, leucocytes, and endothelial cells, are involved in the thrombotic mechanism of thrombosis in COVID-19.

Platelet activation is the key feature of SARS-CoV-2 as documented by early studies reporting the occurrence of thrombocytopenia as a hematological complication in COVID-19 patients [35]. Thrombocytopenia, approximately 100 000/μl, was detected in 5%–18% of the SARS-CoV-2 population, mostly in patients with severe disease, and was associated with poor survival, which, nonetheless, was not confirmed in following studies [3].

Thrombocytopenia has been interpreted as a consequence of its activation and rapid turnover, and experimental studies consistently showed that platelets are over-activated in SARS-CoV-2 [36–38]. Several markers of ex vivo platelet activation, such as platelet aggregation, platelet biosynthesis of thromboxane B2, or platelet spreading on collagen under flow condition consistently showed that platelets are over-activated. These changes were more frequently observed in patients with severe disease and needing ICU [39].

Previous studies demonstrated that viruses and bacteria may directly or indirectly interact with platelets so eliciting activation [40–42]. Koupenova et al. [43] reported that influenza A virus localizes in platelets and elicits C3 release-dependent neutrophil-DNA release and aggregation via Toll-like receptor 7 (TLR7). Recent studies suggested that this pathway may be implicated in the thrombotic process via Spike protein interaction with TLR4 and eventually activation of cells implicated in the thrombotic process, such as monocytes and leucocytes [44, 45]. Likewise, we found that platelets from SARS-CoV-2 over-express TLR4, which suggests that this may be a potential mechanism accounting for platelet activation [46]. Thus, TLR4 activation yields up-regulation of NOX2, the most important cellular producer of reactive oxidant species (ROS) such as hydrogen peroxide generation [47, 48]. NOX2 is a key enzyme of the innate immune system, which, intriguingly, is also localized in endothelial cells and platelets [49, 50]. Human models characterized by the absence of NOX2 (chronic granulomatous disease) demonstrated that NOX2 is a powerful vasoconstrictive molecule (NO) [51] and favors platelet activation via the production of F2-isoprostanes and NO inactivation [49]. The behavior of NOX2 has been studied in SARS-CoV-2 patients via analysis of its soluble form, which derives essentially from leucocyte and platelet activation, which shows that the enzyme is over-activated with a close relation with thrombotic events occurring during hospitalization [52].

An alternative mechanism of platelet activation may occur via Spike protein binding to angiotensin-converting enzyme 2 (ACE2) upon its cleavage by a serine protease, i.e. TMPRSS2 [36]. COVID-19 RNA has been detected in platelets from patients with severe and non-severe COVID-19, but it is still unclear if this occurs via the Spike protein-ACE2 axis (Figure 1) as there is no agreement that platelets express ACE2 [36, 39]. Assuming, however, that Spike protein binds to ACE2, which results in expression downregulation and loss of function, this would be associated with human angiotensin II (Ang II) up-regulation as ACE2 degrades Ang II to Ang 1–7 [53]. The ensuing elevated serum levels of Ang II [54, 55] could have potentially deleterious effects as Ang II is implicated in artery dysfunction via NOX2-mediated ROS over-production [56] and plays a direct role in platelet activation [57, 58]. Also, viral particles and RNA viruses could activate platelets via platelet FcγRIIA interaction upon viral particle opsonization by antibodies [43]. However, this would occur at a later stage of the disease with no relation to the early thrombotic events [59].

Finally, overproduction of inflammatory pro-aggregating cytokines such as, for example, tumor necrosis factor α (TNFα) [60], could be another important stimulus for platelet activation as it behaves as a pro-aggregating molecule and is elevated in patients affected by COVID-19 [61]. Further research is necessary to explore this hypothesis.

Despite these experimental data supporting the role of platelets in the thrombogenesis of SARS-CoV-2, few studies found a relationship between platelets and thrombosis in SARS-CoV-2. Barrett et al. reported that soluble CD40L,

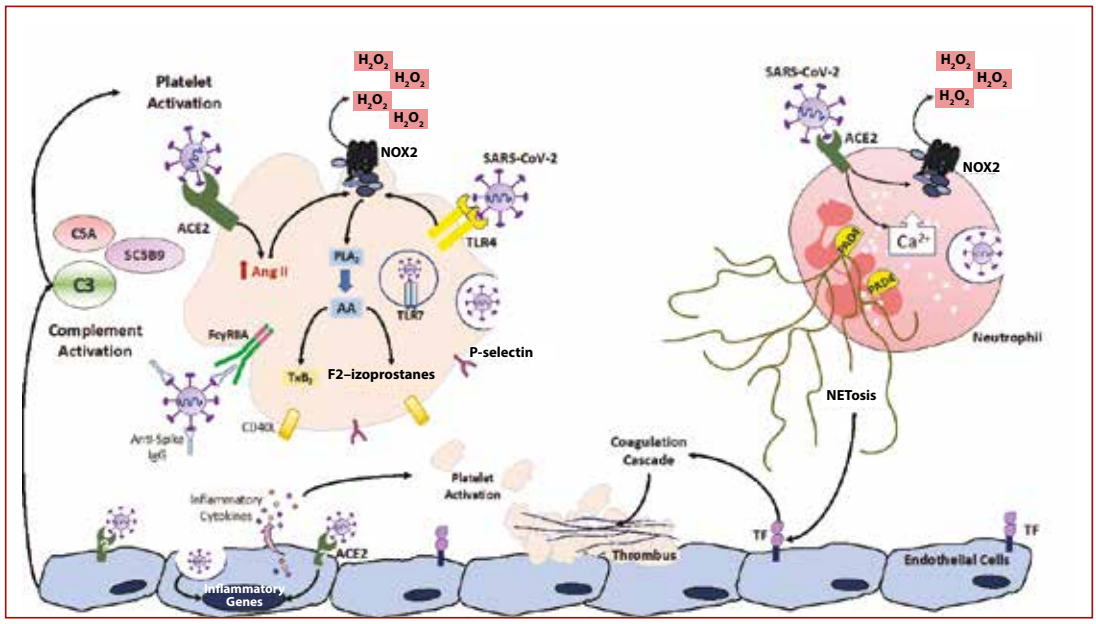

Figure 1. Pathophysiological mechanisms implicated in the thrombotic process mediated by SARS-CoV-2. SARS-CoV-2 produces a series of cellular and molecular events that may be implicated in thrombotic complications. In particular, SARS-CoV-2 enters platelets, endothelial cells, and leukocytes via binding to ACE2, TLR4, and via endocytosis, causing activation of intra-signaling pathways. SARS-CoV-2 may activate platelets by ACE2 or TLR4, which, in turn, induce NOX2-mediated oxidative stress and increase TXB_2, P-selectin, and CD40L, further activating platelets, endothelial cells, and leukocytes. In addition, SARS-CoV-2 induces the membrane expression of TF by endothelial cells, thus initiating the coagulation cascade. Moreover, SARS-CoV-2 elicits NETs-derived neutrophils that arrest viruses but also have pro-thrombotic properties. Finally, the complement activation cascade amplifies platelet and leukocytes activation and endothelial dysfunction associated with vascular thrombosis in SARS-CoV-2 infection

Abbreviations: ACE2, angiotensin-converting enzyme 2; Ang II, angiotensin-converting enzyme II; AA, arachidonic acid; CD40L, CD40 ligand; H_2O_2, hydrogen peroxide; NETs, neutrophil extracellular traps; PAD4, protein arginine deiminase 4; PLA_2, phospholipases A_2; TLR4, toll-like receptor 4; TF, tissue factor; TXB_2, thromboxane B_2

P-selectin, and serum TXB_2 were independently associated with thrombosis or death. Multiple regression analyses showed, however, that only TXB_2 was independently associated with thrombosis [62]. Further data are, therefore, necessary to elucidate the relationship between platelet activation and thrombosis in COVID-19 patients.

Leukocyte activation is another mechanism potentially implicated in the thrombogenesis of SARS-CoV-2. A massive presence of leukocytes has been detected in autoptic studies performed in SARS-CoV-2 infected patients [63, 64], which may result in thrombus growth as, upon activation, leucocytes may generate NETs, which comprise of DNA and histones and are released upon neutrophil stimulation by patterns recognition receptors or chemokines [65]. Such release requires the formation of ROS and calcium mobilization, which activate protein arginine deaminase 4 (PAD4) to deaminate arginine residues on histones [66]. Autoptic studies in patients with COVID-19 demonstrated the presence of platelets, neutrophils, and NETs in the lung and structures consistent with blood vessels, which suggests that platelet-neutrophil interaction may lead to NETs formation and eventually thrombosis [67–69]. Thus, NETs are powerful prothrombotic molecules via expression of tissue factor (TF), a glycoprotein that converts factor X to Xa [71, 71]. Notably, a significant correlation between circulating NETs and thrombin-antithrombin complexes was detected in the blood of patients with COVID-19 [72]. Also, platelet-rich plasma from SARS-CoV-2 infected subjects co-incubated with normal neutrophils increased the levels of TF mRNA and generated NETs expressing TF [72].

Endothelial dysfunction/damage is another factor contributing to thrombosis in SARS-CoV-2. Electron microscopy of endothelial cells (EC) revealed endothelium congestion with leakage of end-cellular material in the lumen suggesting that SARS-CoV-2 elicits a sort of inflammation-induced endothelitis [73]. Thus, electron microscopy studies showed that the COVID-19 localizes within the endothelial cells, where it can induce cell apoptosis and, eventually, functional changes [74]. It is unclear, however, how COVID-19 gets access to EC as it is uncertain whether ACE2 is expressed by EC [75]. Conversely, pericytes do express ACE2, and studies in alveolar capillaries by SARS-CoV-2-infected lungs showed a marked decrease of these cells, which may also contribute to thrombosis. An important input has been provided by Canzano et al. [76] who showed a marked impaired endothelial biosynthesis of two crucial vasodilator and antiaggregant molecules, such as nitric oxide and prostacyclin (prostaglandin I2, PGI2), which may represent a key factor for platelet activation and thrombus growth.

Finally, endothelial perturbation and vascular thrombosis can also be promoted by the complement system activation. Regardless of the initial activation step, the cleavage of C3, subsequent C5 activation (C5a), and the membrane attack complex formation (MAC/C5b-9) drive neutrophil activation and inflammation that eventually leads to endothelial damage. Several studies analyzed the complement activation in COVID-19 patients, and all three pathways seem to be implicated [77]. Indeed, COVID-19 patients showed higher levels of C4d (classical pathway) [78], C5a and sC5b-9 [78–82] (alternative pathway), and mannose-binding lectin (MBL) pathway [79]. Moreover, enhanced complement activation was more prevalent in patients with severe COVID-19 [80, 82] and associated with biomarkers of endothelial injury [80] and hypercoagulability [80, 83].

Besides increased systemic concentrations of complement components, some evidence showed increased local multi-organ complement deposition in the lung and skin [83], kidney, and liver [77, 84] (Figure 1).

THERAPEUTIC IMPLICATIONS

Based on the clinical presentation of SARS-CoV-2 infected patients, anticoagulants (ACs) have been the first-choice treatment to prevent thrombosis and possibly death. ACs have been given as prophylactic or intermediate-full dosage in COVID-19, and low-molecular-weight heparin (LMWH) was the anticoagulant most extensively used. However, several caveats regarding the usefulness of the therapeutic approach remain, especially considering their use in the cases of severe or non-severe disease such as, for instance, in the ICU vs. non-ICU patients with COVID-19. A recent consensus from the American Society of Hematology recommends the use of a prophylactic dose of LMWH whatever the clinical presentation is while the International Society on Thrombosis and Haemostasis suggests the use of a higher dosage in case of severe critical illness [85, 86]. The clinical studies did not show a greater benefit of using a high dosage of AC, therefore, until new data are reported, the choice of prophylactic dosage of AC is advisable. This issue has been recently addressed by Spyropoulos et al. [87] who randomized 557 COVID-19 patients into a group with a prophylactic/intermediate dosage of LMWH and a group with therapeutic doses of heparin. The patients suffered from severe disease as depicted by D-dimer >4 times higher the upper limits of normal or sepsis-induced coagulopathy score >4 or greater [87]. Spyropoulos et al. found that therapeutic dosage lowered the risk of major thromboembolism and death but was not superior to the other two dosages in ICU patients.

Despite the beneficial effect of LMWH, the thrombotic risk remains elevated, which suggests the need for implementing suppletive therapeutic approaches. It could be argued, for instance, that the robust evidence in favor of coincident platelet activation might suggest combining AC with an antiplatelet drug such as aspirin. We have very little data regarding the effectiveness of aspirin in COVID-19. Chow et al. [88] studied 420 COVID-19 patients, 314 (76.3%) aspirin-free and 98 (23.7%) on aspirin within 24 hours from admission or 7 days prior to admission and reported that aspirin use was independently associated with decreased risk of mechanical ventilation (–46%), ICU admission (–43%), and in-hospital mortality (–47%) while no differences in major bleedings or thrombosis were detected between aspirin users and non-users [88]. This finding, however, must be considered with caution and further studies are necessary to assess if aspirin alone or in combination with AC may lower the thrombotic risk in SARS-CoV-2. Considering, however, that the association of AC with aspirin increases the risk of bleeding, an alternative antiplatelet approach could be considered. We have previously reported, for instance, that glucocorticoids exert an antiplatelet activity by lowering the platelet biosynthesis of TXB_2, which may provide a plausible interpretation to why glucocorticoids reduce the risk of MI in CAP patients [89]. It is worth noting that a recent study reported that glucocorticoids improved survival in COVID-19, but it was not investigated if this beneficial effect could be mediated by changes in the thrombotic risk [90].

TLRs may be another target to inhibit platelet function in COVID-19 patients. Thus, platelets from SARS-CoV-2 infected subjects over-express TLR4, which suggests that TLR4 inhibition may be of potential benefit [46]. This hypothesis is supported by the fact that TLR4 has an important role as a thrombosis stimulus as shown by an experimental model of low-grade endotoxemia-induced arterial thrombosis where an inhibitor of TLR4 significantly reduced thrombus growth [91].

Inhibition of NOX2 may be another intriguing therapeutic perspective as NOX2 has a prominent role in platelet ROS formation and platelet activation [92], and the previous study reported a significant association between its activation and thrombosis in SARS-CoV-2 [52].

Albumin may be another option due to its known antioxidant property. A pilot study in patients with cirrhosis and low serum levels of albumin reported a significant reduction of platelet activation as early as after 3 days of albumin supplementation [26], and a pilot study in COVID-19 patients demonstrated that its infusion for 7 days reduced the levels of D-dimer [30]. Moreover, ACE2 administration or inhibition of Spike protein may represent an interesting therapeutic approach as the experimental study demonstrated that both treatments have a negative effect on thrombus growth [36].

Finally, complement activation has been suggested as a novel therapeutic target. The administration of anti-C5 monoclonal antibody eculizumab led to a marked decline in D-dimer levels, alone [93] or in combination with ruxolitinib, a JAK1/2 inhibitor [94]. Moreover, eculizumab reduced neutrophil counts [93] and C-reactive protein levels [95]. Other C5-blocking monoclonal antibodies include tesidolumab (LFG316), which improved oxygenation and

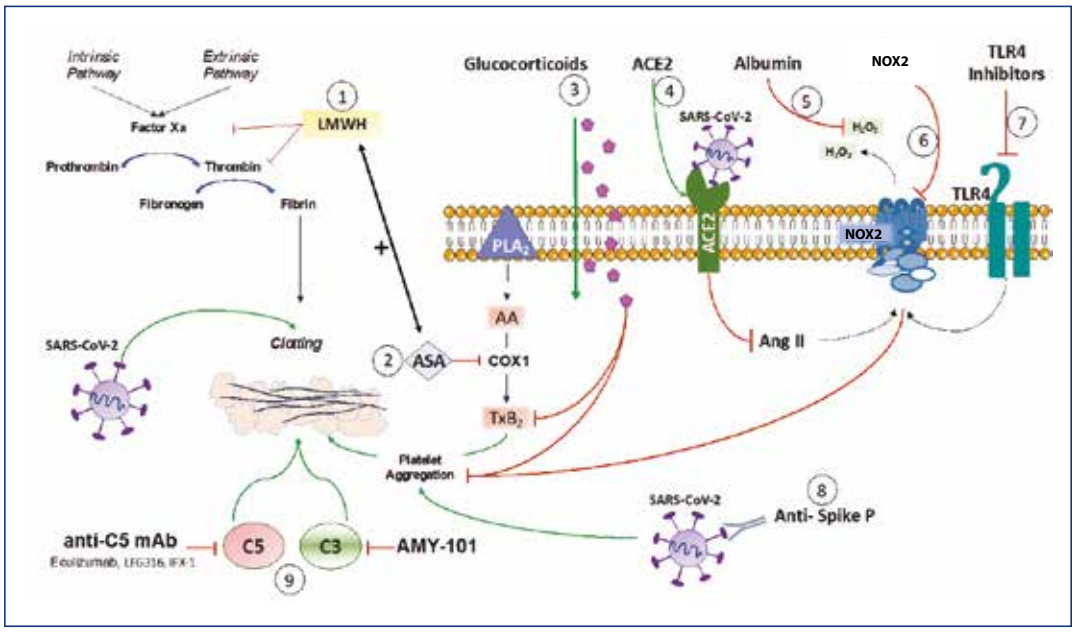

Figure 2. Antithrombotic therapy strategies in COVID-19. Therapeutic approaches to inhibit thrombotic process in COVID-19 patients include (1) anticoagulants (ACs) such as LMWH alone or in association with (2) aspirin, (3) glucocorticoids, (4) ACE2 agonists, (5) Albumin supplementation, inhibitor of (6) NOX2, (7) TLR4, (8) spike protein (P), and (9) complement components. Green arrows: activation pathway. Red arrows: inhibition pathway

Abbreviations: ASA, aspirin; AA, arachidonic acid; Ang II, angiotensin II; ACE2, angiotensin-converting enzyme 2; COX1, cyclooxygenase-1; H_2O_2, hydrogen peroxide; LFG316, tesidolumab; LMWH, low-molecular-weight heparin; IFX-1, vilobelimab; PLA2, phospholipases A2; TLR4, toll like receptor 4

reduced the arterial partial pressure of carbon dioxide ($PaCO_2$) [96], and vilobelimab (IFX-1), which was tested in phase 2 randomized controlled trial demonstrating its safety and tolerability in patients with severe COVID-19 [97].

Another approach is the use of compstatins (Cp40/AMY-101), highly selective and potent C3 inhibitors. Preliminary clinical results of the administration of AMY-101 indicate a reduction of the systemic hyper-inflammation by reducing C-reactive protein and IL-6 levels and a marked improvement of lung function [98, 99].

CONCLUSIONS

Experimental and clinical studies consistently showed that platelets are activated in CAP and COVID-19 and could play a role in precipitating vascular diseases, which complicates the clinical course of both diseases. The mechanism of platelet and clotting activation may include different and multiple pathways, which appear to be more complex in the case of COVID-19, where the virus might bind to the cells using several entry mechanisms such as the ACE2-AngII axis and/or TLRs (Figure 2). If confirmed, inhibition of these two pathways may be a tool to develop novel antiplatelet strategies. Conversely, it is still unclear if, in the case of CAP, one or more cellular line activation is implicated in the thrombotic process. However, the lower risk of thrombosis, as well as the peculiar thrombosis typical of CAP, suggests that CAP and COVID-19 do not share similar thrombotic mechanisms, with COVID-19 being more frequently complicated by both venous and arterial thromboses while the vascular disease is less frequent in CAP and localized prevalently in the arterial circulation. These findings may have an impact on the antithrombotic strategy as antiplatelet drugs, such as aspirin, could be the first choice for CAP treatment unless the disease severity entails alternative treatment. In the case of COVID-19, the typology of vascular disease indicates AC as the first choice while the contemporary use of antiplatelet drugs is still debated, given the potential bleeding risk. Experimental data, however, support the thesis/assumption that platelets contribute to the thrombotic process and, considering the still elevated residual risk of thrombosis and death, despite AC treatment, a combination of antiplatelet treatment may be an important option to improve clinical outcomes in COVID-19. In this last context, a novel therapeutic combination is needed as the classic combination of AC with antiplatelet drugs, such as aspirin or clopidogrel, is not effective and potentially harmful. Future studies should be launched to develop novel antithrombotic strategies in COVID-19.

Article information

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