Prognostic Significance of the Coagulation and Complement Systems in Critical COVID-19 Infection

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Abstract: Infection with the SARS-CoV-2 virus (COVID-19 disease) can cause a wide range of clinical situations – from an asymptomatic state to fatal outcomes. In cases of serious clinical manifestations, the underlying mechanisms involve a number of immune cells and stromal cells as well as their products such as pro-inflammatory interleukin-6 and tumour necrosis factor-alpha that ultimately cause the cytokine storm. The situation of overproduction of pro-inflammatory cytokines is somewhat similar to, though in a mild form, health conditions in obesity and related metabolic disorders like type-2 diabetes, which are also considered important risk factors for severe illness in COVID-19. Interestingly, neutrophils perhaps play a significant role in this pathogenesis. On the other hand, it is thought that COVID-19-related critical illness is associated with pathological hyperactivity of the complement system and coagulopathy. Although the precise molecular interactions between the complement and coagulation systems are not clear, we observe an intimate cross-talk between these two systems in critically ill COVID-19 patients. It is believed that both of these biological systems are connected with the cytokine storm in severe COVID-19 disease and actively participate in this vicious cycle. In order to hinder the pathological progression of COVID-19, a number of anticoagulation agents and complement inhibitors have been used with varying success. Among these drugs, low molecular weight heparin enoxaparin, factor Xa inhibitor apixaban, and complement C5 inhibitor eculizumab have been commonly used in patients with COVID-19. Our overall experience might help us in the future to tackle any such conditions.

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Introduction

In the latest coronavirus (COVID-19) pandemic, where the causative agent SARS-CoV-2 has been spreading and evolving currently in a milder form, an important pathogenesis-related issue is the understanding of the specific role of the immune system. Although only a small percentage of COVID-19 patients usually develop serious clinical manifestations, different studies have reported a condition of hyper-inflammation or cytokine storm that could produce a grave condition, the acute respiratory distress syndrome (ARDS) (de la Rica et al., 2020). It is believed that imbalanced production of various cytokines and their dysregulated or excess activities are responsible for the adverse clinical outcomes; and this cytokine storm can affect other organs besides the lungs, leading to multi-organ failure.

Perhaps, one of the most important cytokines, which may participate prominently in the above-mentioned hyper-inflammation, is interleukin-6 (IL-6). Interestingly, in one study, the mean IL-6 concentration was shown to be 2.9-fold higher in patients with complicated COVID-19 than patients with uncomplicated illness (Coomes and Haghbayan, 2020). IL-6 is a pleiotropic cytokine, mainly produced by a number of stromal cells and immune cells, including monocytes or macrophages, and it has multifaceted effects on inflammation and immune responses. Many investigators believe that SARS-CoV-2 induces the biosynthesis of IL-6 along with other pro-inflammatory cytokines, which are the significant mediators for lung injury, disease severity, and mortality (Hedrick et al., 2020). On the other hand, pro-inflammatory cytokines such as IL-6 and tumour necrosis factor α (TNF-α) probably play a significant role in obesity and insulin resistance (Bastard et al., 2006). Remarkably, both obesity and insulin resistance (or type-2 diabetes) are considered as risk factors for the development of severe disease, and mortality in SARS-CoV-2 infection (Cevik et al., 2020).

Studies have shown cooperation between IL-6 and neutrophil functions (Fielding et al., 2008; Mateer et al., 2018). In a study in Italy, bronchoalveolar lavage was examined from 33 adult patients with SARS-CoV-2 infection (Pandolfi et al., 2020). The patients admitted to the intensive care unit (ICU) showed higher IL-6 and IL-8 levels, as well as a marked increase in neutrophils and decreased lymphocyte count. Similarly, another study on 364 patients with COVID-19 from Wuhan, China (from this place, SARS-CoV-2 spread) found higher blood levels of IL-6 and neutrophils among severe and critical patients compared to patients with mild symptoms (Li et al., 2020). Of note, Godkin and Humphreys (2020) have commented that the elevated level of neutrophils along with the raised concentrations of IL-6, IL-10, and C-reactive protein (CRP) suggest a very significant role of innate cells (like neutrophils) in the pathogenesis of severe disease in SARS-CoV-2 infection. Consequently, it could be assumed that neutrophils may intensify disease-associated injury (Borges et al., 2020). Moreover, besides the movement to the site of inflammation for phagocytosis of pathogenic agents including viruses, neutrophils can

modify the adaptive immune responses by supporting bidirectional cross-talk with T-lymphocytes.

The neutrophil to lymphocyte ratio (NLR) is an indicator of inflammation. Several studies have demonstrated that an increase in NLR was associated with a higher risk for disease severity and death among COVID-19 patients (Basbus et al., 2020; Liu et al., 2020; Tatum et al., 2020). On the other hand, activated neutrophils can release neutrophil extracellular traps (NETs) that are net-like structures composed of chromosomal DNA, histones, and cytoplasmic proteins, including enzymes like myeloperoxidase (MPO) and neutrophil elastase. Interestingly, NETs confine invading microorganisms. However, the overproduction of NETs induces lung injury (Grabcanovic-Musija et al., 2015). After analysing the production of NETs from 32 patients with COVID-19, the investigators concluded a possible detrimental role of NETs in the disease course (Veras et al., 2020). Specifically, they detected higher concentration of NETs in tracheal aspirate, lung tissue, and plasma. Interestingly, a study on 25 patients with COVID-19 in Greece observed that complement activation potentiated the NETs and thrombotic pathway during SARS-CoV-2 infection (Skendros et al., 2020). Of note, complement components C3a and C5a activate neutrophils, monocytes, endothelial cells, and platelets leading to the release of pro-inflammatory cytokines that promotes coagulopathy (Lim and Mcrae, 2021). Furthermore, analyses of clinical specimens from critical COVID-19 patients revealed that complement proteins were upregulated along with IL-6 (which is possibly a marker of disease severity) (D'Alessandro et al., 2020; Alosaimi et al., 2021). A precise knowledge of SARS-CoV-2 infection-related different factors, e.g., immune cells, complement components, pro-inflammatory cytokines, and coagulation proteases, as well as their interactions, would be helpful to understand the underlying pathology of disease severity.

The complement system in COVID-19

We know that complement proteins have a vital function in the immune system in order to protect our health against different pathogenic microorganisms; however, its hyperactivity or disturbances in its normal function can cause tissue damage. Unlike the high mortality rate of MERS-CoV infection (approximately 35%), lower disease severity and death rates have been noticed in COVID-19 cases. It is important to remember that a significant role of the complement system was detected in MERS-CoV infection. Of note, apart from the latest outbreak of SARS-CoV-2, the two other recent outbreaks were due to similar coronaviruses – SARS-CoV (or SARS-CoV-1) and MERS-CoV, which started in China and Saudi Arabia, respectively. Nonetheless, in a study on a DPP4 transgenic (hDPP4-Tg) mouse model (with MERS-CoV infection), the investigators observed that MERS-CoV infection induced over-activation of complement components, which perhaps contributed to pyroptosis, i.e., inflammatory apoptosis, and overall hyper-inflammation (Jiang et al., 2019). In another study on C57BL/6J mice, the investigators utilised C3

knockout/null (C3$^{-/-}$) mice of the matching genetic background (Gralinski et al., 2018). It is notable that the principal complement component C3 plays a central role in complement activation pathways. However, in this study, mice were infected with SARS-CoV-1. Compared to C57BL/6J control mice, the investigators noticed that SARS-CoV-1-infected C3$^{-/-}$ mice displayed significantly less disease severity and a reduced amount of respiratory dysfunction in spite of equivalent viral loads in the lungs of both controls and C3$^{-/-}$ mice. Interestingly, a smaller quantity of neutrophils and monocytes were present in the lungs of C3$^{-/-}$ mice in comparison with C56BL/6J control mice. Furthermore, a reduced amount of lung damage, as well as diminished levels of cytokines were found in both lung tissue and serum samples of C3$^{-/-}$ mice relative to controls. Consequently, this study explained that the involvement of the complement system was associated with lung injury, disease severity, and a systemic pro-inflammatory reaction in cases with SARS-CoV-1 infection (Gralinski et al., 2018). With these above-mentioned examples, it could be said that the complement system also has a significant role in the immune response to SARS-CoV-2 infection, disease severity, and associated hyper-inflammation that adversely affects the functions of multiple organs.

Generally, we know that the complement system functions through 3 pathways: the classical, lectin, and alternative pathways. However, there is another extrinsic pathway where coagulation-related proteases such as thrombin, factor XIIa, plasmin, as well as kallikrein are involved (Figure 1). Moreover, it has been believed that the coagulation factors Xa and XIa, and also plasmin may cleave both C5 and C3, and intensely generate C5a and C3a (i.e., anaphylatoxins) (Amara et al., 2008). It is worth mentioning that initial studies have suggested that the complement system plays a key role in the coagulopathy of severe COVID-19 (Lo et al., 2020). After
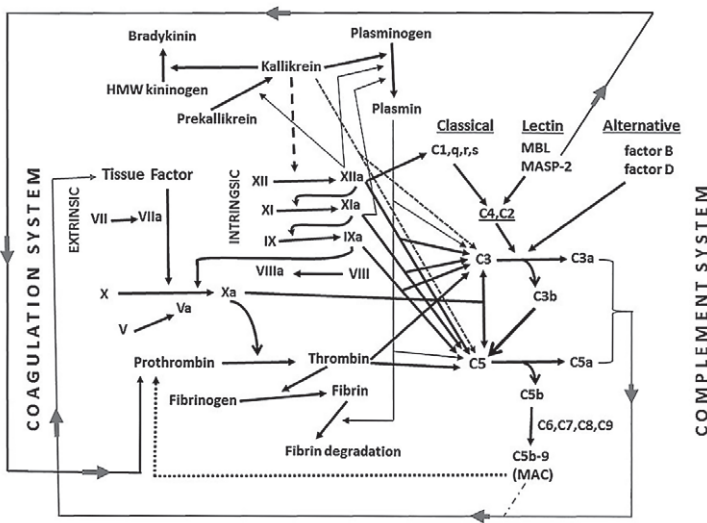

Figure 1 – Interactions between the complement and coagulation systems (MBL – mannose-binding lectin; MASP-2 – mannan-binding lectin serine protease-2; MAC – membrane attack complex [terminal complement complex, i.e., C5b + C6 + C7 + C8 + C9]).

analysing post-mortem lung tissue samples from 5 patients with severe COVID-19 characterised by respiratory failure, the investigators observed significant deposits of terminal complement components C5b-9 (membrane attack complex/MAC), C4d (a split product), and mannose binding lectin (MBL)-associated serine protease (MASP-2) in the microvasculature, along with systemic activation of the complement pathways (Magro et al., 2020). Perhaps, the normal functions of the complement system could be imbalanced in response to the overstimulation of different immune-associated cells such as neutrophils and monocytes or macrophages. Conversely, complement components such as anaphylatoxins (C3a and C5a) and opsonins (C3b, C1q, MBL) can also influence macrophage responses (Bohlson et al., 2014).

The coagulation system in COVID-19

Overall, the complement system's functional abnormalities can cause a number of health problems such as recurrent microbial infections, autoimmune diseases, hereditary angioedema, and atypical haemolytic-uremic syndrome (aHUS) (Tichaczek-Goska, 2012). Activated complement components may mediate hyper-inflammation, coagulation, and tissue damage – all these pathological features can be seen in critical patients with SARS-CoV-2 infection (Figure 2). As mentioned earlier, the presence of coagulopathy is a common feature of severe COVID-19 (Gómez-Mesa et al., 2021). A study on 148 patients with COVID-19 noticed that
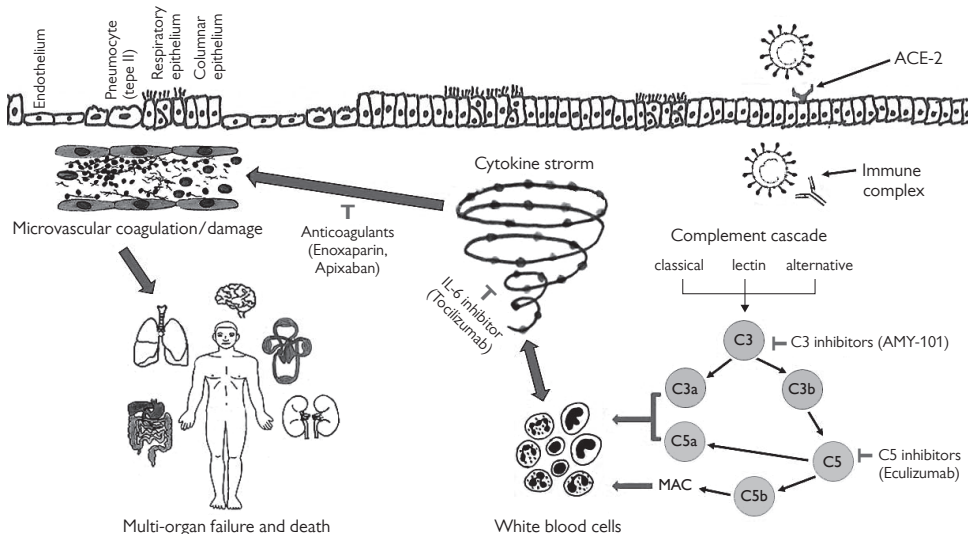

Figure 2 – Inflammatory response via complement activation in COVID-19 disease (ACE-2 – angiotensin converting enzyme-2 [receptor for the SARS-CoV-2 viral entry]; C3a and C5a – anaphylatoxins, primarily induce pro-inflammatory responses; MAC – membrane attack complex; cytokine storm – associated with the elevated levels of several cytokines that include interleukin-1β [IL-1β], IL-6, TNF-α, and macrophage inflammatory protein [MIP]).

the high plasma levels of soluble MAC (or sC5b-9) correlated with von Willebrand factor (vWF) and paralleled disease severity, but these levels diminished during disease remission (Cugno et al., 2021). Another study on 25 patients showed higher plasma levels of NETs, and sC5b-9, as well as increased tissue factor (TF) activity in patients (Skendros et al., 2020). Moreover, patients' neutrophils displayed elevated TF expression and released NETs carrying active TF. In a study conducted by D'Alessandro et al. (2020), several peptides related to both the complement and coagulation systems were increased in COVID-19 patients' sera. The study included 33 COVID-19-positive patients and 16 control subjects (SARS-CoV-2 negative by nasopharyngeal swab). On the other hand, a study examined blood samples from 102 COVID-19-positive patients and 26 negative controls from New York. The investigators applied RNA sequencing and high-resolution mass spectrometry to record 219 molecular features that are relevant to COVID-19 status and severity (Overmyer et al., 2021). They observed increased expression of genes and/or proteins associated with the neutrophil function (like MPO – linked to NETs formation), neutrophil degranulation, platelet activation, vWF, and complement activation. Similarly, a study on 31 SARS-CoV-2 infected patients from Berlin identified 27 potential biomarker expressions, which are connected with disease severity (Messner et al., 2020). Importantly, these biomarkers included complement components of both the classical and alternative pathways (like C1r and CFB), the coagulation system (like fibrinogen), acute-phase reactants (like CRP), and pro-inflammatory cytokine signalling (like IL-6).

COVID-19-related microangiopathy and thrombotic condition
As a part of innate immunity, MBL is a protein that has lectin domains, which can bind to some special carbohydrate groups on the surface of various microorganisms including viruses and activate the complement system. MBL belongs to the collectin protein family that also includes lung surfactant protein A (SP-A) and D (SP-D) (Turner, 2003). In a Swedish study on a cohort of 65 critically ill COVID-19 patients, it was observed that COVID-19 patients had elevated plasma MBL levels compared to healthy controls (n=72) (Eriksson et al., 2020). Furthermore, patients who developed thromboembolic complications (n=9, 14%) had significantly elevated MBL levels than patients without thrombotic problems. Interestingly, MBL was strongly correlated to plasma D-dimer levels (a marker of coagulopathy/ degradation product of blood clots in fibrinolysis), but did not exhibit any association with the degree of inflammation. On the other hand, in a study on lung tissue sections from 12 autopsies who died of the severe COVID-19 disease, the investigators documented that dilated vessels of both the venous and arterial system were mostly devoid of viable endothelium (and pneumocytes) and showed focal thrombosis (Magro et al., 2021). Additionally, immunohistochemical staining revealed endothelial and subendothelial deposition of C3d, C4d, and/or C5b-9 (MAC) in the microvasculature of all examined cases, but none of the controls.

Of note, complement component C3's final degradation product is C3d that can augment immune responses, and C4's split product is C4d (from C4b). Similar histopathological findings were also recorded in an *in vivo* experimental model (SARS-CoV-2-infected rhesus macaques). In this study, infected lung tissue sections displayed considerable macrophage infiltration, prominent changes in vascular morphology along with endothelialitis, and the presence of increased vWF (Aid et al., 2020). In addition, the investigators observed increased blood levels of several pro-inflammatory cytokines, complement components, and coagulation factors including platelet activation in infected macaques.

In a study in Spain, the investigators analysed the data from 19 COVID-19 patients admitted to ICU and observed higher levels of fibrinogen and D-dimer among patients at admission (Ibañez et al., 2021). The authors suggested that the primary source of D-dimer could be the lungs. Unlike our typical ideas about sepsis-induced coagulopathy, COVID-19-linked coagulopathy is dissimilar in many aspects. For instance, coagulation parameters such as activated partial thromboplastin time (aPTT), prothrombin time (PT), and platelet count among COVID-19 patients usually display a normal range (Hadid et al., 2021). In contrast, a majority of COVID-19 patients show higher levels of fibrinogen, which exhibit a relationship with IL-6. However, an increased level of D-dimer has been frequently linked with critical illness and mortality, i.e., prognosis (Hadid et al., 2021).

In a study wherein 400 hospitalised COVID-19 patients from the Massachusetts area were evaluated, the venous thromboembolism (VTE) rate was 4.8%, the rate of overall thrombotic complication was 9.5%, and the overall bleeding complication rate was 4.8% (Al-Samkari et al., 2020). Furthermore, a study in China analysed the data of 107 COVID-19 patients; in comparison to patients with mild infection (n=56), severe cases (n=51) had coagulation dysfunction, higher levels of fibrin degradation product and D-dimer, and severe systemic inflammation (Qi et al., 2021). In addition, the patient's D-dimer level was positively correlated with CRP and IL-6. Remarkably, in a meta-analysis, the authors reviewed 2,139 COVID-19 patients from 16 observational studies, and they noticed that coagulation dysfunction was commonly linked with severe cases, elevated mean D-dimer, and higher mortality (Xiang et al., 2021).

Pathological links between the complement and coagulation systems
Like the studies of Magro and her colleagues, which showed activation of complement components and an accompanying triggering of pro-coagulant status in severe COVID-19 disease (Magro et al., 2020, 2021), a number of literature also have suggested a connection between the complement and coagulation pathways in this disease (Chauhan et al., 2020; Ghebrehiwet and Peerschke, 2020; Lo et al., 2020). Interestingly, both complement and coagulation systems work through a common mechanism – sequential amplification of enzyme cascades as a consequence of zymogen activation; and a potential cross-talk exists between these two primitive

biological systems (Figure 1). The shared participation of both complement and coagulation systems has been noticed in diseases such as paroxysmal nocturnal haemoglobinuria (PNH), antiphospholipid syndrome, and aHUS (Dzik, 2019). It is notable that aetiologically, haemolytic-uremic syndrome (HUS) is different from aHUS. Strikingly, HUS is usually linked to Shiga toxin-producing *Escherichia coli* (O157:H7); but this aetiological factor is not associated with aHUS. The formation of thrombi in the renal blood vessels is an important feature in aHUS, along with other pathologies such as complement over-activation, thrombocytopenia, haemolytic anemia, and kidney failure.

Several reports revealed serious complications that were triggered by SARS-CoV-2 infection in patients with a history of aHUS or development of aHUS-like clinical features in COVID-19 patients (Kurian et al., 2021; Gill et al., 2022; Korotchaeva et al., 2022; Leone et al., 2022; Suzuki et al., 2022). Furthermore, the aforementioned reports generally observed a beneficial role of eculizumab, a C5-blocking monoclonal antibody, in the treatment of these patients. On the other hand, a number of reports documented antiphospholipid syndrome or the presence of antiphospholipid antibodies (aPLs) in COVID-19 patients (Yasri and Wiwanitkit, 2020; Zhang et al., 2020; Hollerbach et al., 2021). It may be worth mentioning that antiphospholipid syndrome is characterised by an increased risk of abnormal blood clot formation. Nevertheless, Zhang et al. (2020) recorded coagulopathy and aPLs in their critically ill patients. In another study, Xiao et al. (2020) detected aPLs in 47% (31/66) of critically ill COVID-19 patients' sera, whereas the said antibodies were not present in COVID-19 patients who were not in a critical state (n=13). In addition, Hollerbach et al. (2021) suggested a causative effect of aPLs in coagulopathy of COVID-19. Similarly, Hines et al. (2021) confirmed a diagnosis of PNH in acute COVID-19 infection, and they concluded that COVID-19 spike proteins could trigger the complement components of the alternative pathway, which might cause cellular injuries such as haemolysis, endothelial lesions, and end-organ damage. Moreover, a study in Italy on PNH patients at the time of COVID-19 outbreak concluded that treatment with complement inhibitors (C5 inhibitors – eculizumab, ravulizumab, and crovalimab, as well as factor B inhibitor – iptacopan) might be advantageous in the reduction of thrombo-inflammation, and overall prevention of SARS-CoV-2 infection and related disease severity (Barcellini et al., 2021).

The role of complement inhibitors
Eculizumab is one of the most commonly used complement inhibitors in the treatment of COVID-19 disease. It is a monoclonal antibody, and it inhibits the cleavage of C5 into C5a and C5b and the generation of MAC. It is reasonable to consider that preventing MAC formation could block the chain of subsequent inflammatory responses such as stimulation of inflammatory cells, cytokine storm, and coagulopathy in COVID-19 disease progression (Figure 2). In a study in Italy, 4 COVID-19 patients with severe pneumonia or ARDS were treated

with eculizumab (900 mg intravenously/I.V., up to 4 weekly infusions) along with anticoagulant enoxaparin 4,000 IU/day subcutaneously (Diurno et al., 2020). Successful recovery occurred in all patients, with a decline in inflammatory markers, including CRP level. In another study in France, 45 patients with severe COVID-19 disease received standard care, and 35 were treated with standard treatment protocol plus eculizumab in ICU. For the eculizumab group, the survival rate was 82.9% as compared to 62.2% without eculizumab (Annane et al., 2020). Clearly, a favourable health condition was recorded in patients treated with eculizumab. On the other hand, in a study wherein 8 COVID-19 patients were treated with eculizumab (1 to 3 doses of 900 mg I.V., once a week) in Brazil, and 3 COVID-19 patients with ARDS were treated with compstatin-based C3-targeted AMY-101 (5 mg/kg/daily, I.V. infusion) in Italy (Mastellos et al., 2020). Of note, by binding with C3, cyclic peptide compstatin hinders convertase formation, cleavage of C3, and complement activation. AMY-101 has been derived from Cp40, a 3rd-generation compstatin analogue. Nevertheless, the investigators noticed that both C3 and C5 inhibitors showed an anti-inflammatory response (decline in IL-6 and CRP levels) and noticeable improvement in lung function (Mastellos et al., 2020). Furthermore, a report documented marked improvement of all parameters within two days after the start of AMY-101 treatment in a patient with severe ARDS caused by SARS-CoV-2 infection (Mastaglio et al., 2020). Like eculizumab, another C5 inhibitor ravulizumab, which is used for the treatment of two complement-linked disorders – PNH and aHUS, exhibited diminished levels of serum free C5 in 22 patients with severe COVID-19 disease (McEneny-King et al., 2021). Therefore, overall, complement inhibition displayed significant clinical improvement and therapeutic benefit in COVID-19 patients with serious illnesses.

Anticoagulants in COVID-19
The state of coagulopathy, which is linked with endothelial dysfunction and diffuse microvascular thrombi formation or disseminated intravascular coagulation, displays poor prognosis in COVID-19 cases. In these patients, enoxaparin and apixaban are commonly used anticoagulants. Drugs such as enoxaparin and dalteparin belong to the group of low molecular weight heparin (LMWH), whereas apixaban inhibits free and clot-bound factor Xa and the activity of prothrombinase that catalyses the conversion of prothrombin to thrombin. Interestingly, some investigators have demonstrated that apixaban may also inhibit the activity of SARS-CoV-2 protease M^{pro}, which is associated with the viral replication and pathogenic potentiality (Chaves et al., 2022). Briefly, the results of selected clinical studies on anticoagulant therapy in COVID-19 have been discussed in Table 1.

Conclusion
The COVID-19 pandemic has increased our knowledge and seriousness about the problems of coronavirus disease and relevant pathologies, which may be

Table 1 – Selected studies on anticoagulation for COVID-19 patients

Investigators and place of study	Subjects	Findings in brief
Barco et al. (2022) (Switzerland and Germany)	Outpatients 50 years or older; enoxaparin group (n=234), no thromboprophylaxis group (n=238)	Enoxaparin did not reduce early hospitalisations and deaths
Joanico-Morales et al. (2022) (Mexico)	Patients received enoxaparin – 60 mg (n=44) and 40 mg (n=156)	60 mg dose was associated with a lower risk of death
Morici et al. (2022) (Italy)	Comparing 40 mg BID (n=91) vs. 40 mg OD (n=92) enoxaparin	OD enoxaparin was associated with higher incidence of VTE compared to BID dose. No DVT development, independently of enoxaparin dosing
Abdelwahab et al. (2021) (Egypt)	Control (no aspirin/enoxaparin, n=36), aspirin alone (n=31), enoxaparin alone (n=123), and aspirin-enoxaparin group (n=35)	Concomitant use of aspirin and enoxaparin demonstrated promising results
Albisinni et al. (2022) (Italy)	Enoxaparin was provided to 90/141 patients in either prophylactic dose (n=65) or therapeutic dose (n=25)	No significant difference between patients without anticoagulants and those on prophylactic or therapeutic dose
Assiri et al. (2021) (Saudi Arabia)	Patients were treated with various drugs such as enoxaparin (n=99), dexamethasone (n=93), favipiravir (n=67), and tocilizumab (n=37)	Enoxaparin significantly reduced the length of ICU stay and mortality in patients aged 50–75
Cardillo et al. (2021) (Italy)	Comparing the outcomes between inpatients who used enoxaparin (n=62) and fondaparinux (n=38) as thromboprophylaxis	No significant differences in clinical outcomes between these two groups
Martinelli et al. (2021) (Italy)	Patients on standard prophylaxis dosage of enoxaparin (40 mg daily, n=151) were compared with those who received high doses (1 mg/kg BID, n=127)	Patients treated with high enoxaparin dosages displayed a reduction of mortality, clinical deterioration, and VTE compared to standard dosage
Pawlowski et al. (2021) (United States)	Clinical outcomes at 28 days were compared between patients who received unfractionated heparin (n=441) and patients who received enoxaparin (n=166)	Enoxaparin was associated with lower mortality compared to unfractionated heparin
Sadeghipour et al. (2021) (Iran)	Comparison between intermediate-dose enoxaparin (1 mg/kg daily, n=276) and standard-dose (40 mg daily, n=286), among adult patients admitted to ICU	Results did not show any significant differences

Deitelzweig et al. (2022) (United States)	A total of 7,869 patients with nonvalvular atrial fibrillation and COVID-19 were included: among these patients, 6,676 continued apixaban (discontinuers = 1193)	Patients who discontinued apixaban had a higher risk of hospitalisation and thrombotic events compared to those who continued apixaban
Ananworanich et al. (2022) (United States)	Adults with mild symptoms and at high risk for disease progression – either rivaroxaban 10 mg OD (n=246) or placebo (n=251)	No impact of rivaroxaban on disease progression
Kumar et al. (2022) (India)	Hospitalised patients with mild or moderate disease received either rivaroxaban (10 mg or 15 mg OD, n=115) or enoxaparin (40 mg or 60 mg OD, n=113)	Rivaroxaban was superior to enoxaparin for prophylactic coagulopathy management
Mohamed et al. (2022) (Egypt)	Patients with moderate disease (pneumonia without hypoxia) – enoxaparin group (0.5 mg/kg BID, n=66) and rivaroxaban group (10 mg OD, n=58)	No significant differences were observed between these two groups
Ramacciotti et al. (2022) (Brazil)	Patients were randomly assigned to receive rivaroxaban (n=160) or without anticoagulation therapy (n=160). During hospitalisation, all patients received thromboprophylaxis with standard doses of heparin	Patients with rivaroxaban for 35 days improved clinical outcomes compared to non-extended thromboprophylaxis

apixaban and rivaroxaban – direct-acting oral anticoagulants (DOACs); enoxaparin – low molecular weight heparin (LMWH) and administered subcutaneously; favipiravir – an antiviral used in influenza; fondaparinux – causes antithrombin III-mediated inhibition of factor Xa; tocilizumab – monoclonal antibody against IL-6 receptor; high risk for COVID-19 – aged ≥ 65 years, and with a chronic disease, e.g., lung disease, heart disease, hypertension, cancer, and diabetes (which requires adequate daily management), or obesity; BID – two times a day; DVT – deep vein thrombosis; ICU – intensive care unit; OD – once daily; VTE – venous thromboembolism

helpful in the future as well. This multi-system disease behaves differently during its progression through different stages, viz. viral entry and replication, dissemination, widespread inflammation, and thrombotic microangiopathy/multi-organ damage. The disease processes are linked with several other health problems such as obesity and related metabolic disorders, chronic lung diseases, and immunodeficiency conditions, as well as various body systems including different components of the circulatory system such as endothelium, coagulation factors, and complement proteins. However, the precise understanding of the interplay between the complement and coagulation pathways and their status in coronavirus disease is important to interpret several issues, such as the exact nature of systemic inflammation and the pertinent roles of various cytokines. Accordingly, the favourable treatment strategies could be designed in relation to proper timings and appropriate combination of drugs in order to maximize the therapeutic efficacy.

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