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Coagulopathy in COVID-19: Focus on vascular thrombotic events

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ABSTRACT

SARS-CoV-2 causes a phenotype of pneumonia with diverse manifestation, which is termed as coronavirus disease 2019 (COVID-19). An impressive high transmission rate allows COVID-19 conferring enormous challenge for clinicians worldwide, and developing to a pandemic level. Combined with a series of complications, a part of COVID-19 patients progress into severe cases, which critically contributes to the risk of fatality. To date, coagulopathy has been found as a prominent feature of COVID-19 and severe coagulation dysfunction may be associated with poor prognosis. Coagulopathy in COVID-19 may predispose patients to hypercoagulability-related disorders including thrombosis and even fatal vascular events. Inflammatory storm, uncontrolled inflammation-mediated endothelial injury and renin angiotensin system (RAS) dysregulation are the potential mechanisms. Ongoing efforts made to develop promising therapies provide several potential strategies for hypercoagulability in COVID-19. In this review, we introduce the clinical features of coagulation and the increased vascular thrombotic risk conferred by coagulopathy according to present reports about COVID-19. The potential underlying mechanisms and emerging therapeutic avenues are discussed, emphasizing an urgent need for effective interventions.

1. Introduction

The emergence of novel coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has developed to a pandemic level, profoundly threatening the health of millions of people worldwide [1]. No effective agents against COVID-19 have been proved since the first case was reported. Although COVID-19 appears to be not that lethal than several major viral outbreaks like Severe Acute Respiratory Syndrome (SARS) in 2003 or Middle East respiratory syndrome (MERS), the characteristics of which, however, are a much higher transmission rate together with greater lethality relative to influenza [2,3]. Moreover, the latent number of asymptomatic cases combined with the estimated basic reproduction number of 2.0–2.5 emphasizes the severity of the situation [4,5].

Belonging to coronavirus family of viruses like SARS-CoV [6], SARS-CoV-2 leads to a type of pneumonia with diverse manifestations including fever (88.7%), cough (67.8%) and fatigue (38.1%) [7]. Severe patients suffer from dyspnea or hypoxemia and even experience acute respiratory distress syndrome (ARDS) or shock, which critically contribute to the increased risk of a fatality [8].

Besides the common manifestations, hypercoagulability-related thrombotic vascular events are emerging issues in COVID-19 which should be addressed [9]. In this review, we discuss a timely topic that concerns hypercoagulability involving with thrombotic events and the potential underlying mechanisms in the context of COVID-19. Several emerging therapeutic strategies associated with coagulopathy are also discussed.

2. Coagulation characteristics of COVID-19

Based on data extracted from COVID-19 patients during the first two months of viral outbreak, 59.6% severe cases showed a feature of elevated D-dimer (threshold as 0.5 mg/L) and average platelet count in severe-COVID-19 patients appeared to be lower than that in non-severe group, which attracted much attention on coagulopathy secondary to COVID-19 [7]. A retrospective cohort study enrolling 191 cases was published at March 11th, which introduced the clinical course and risk factors for adult deaths in COVID-19 patients in Wuhan, China. In this study, coagulation dysfunction was found in 27 (50%) non-survivors of COVID-19, with elevated D-dimer and prolonged PT [10]. In another study, with 183 cases enrolled and dynamic alterations in coagulation profiles recorded, Tang et al. reported a mortality of 11.5% in COVID-19 patients [11] and they found 15 (71.4%) of the deaths ascribed to COVID-19 met the diagnostic criteria of overt disseminated
intravascular coagulation (overt-DIC, ≥5 points) based on the international society on thrombosis and haemostasis (ISTH), however, only 0.6% of the survivors matched the criteria [11]. Compared with those in survivors, the levels of D-dimer and fibrin degradation product (FDP) were significantly higher while PT was longer in non-survivors [11].

Accumulating evidences suggest the novel disease trigger shows evidence of coagulopathy. Table 1 lists some reports involving the coagulation characteristics of patients with COVID-19.

As the number of PubMed citations increasing, according to the recent reports, D-dimer appears to has the potential to serve as an indicator for disease progression and severity [25-27]. Coagulation dysfunction (increased D-dimer and prothrombin time) is related to higher risk of ARDS [28]. A meta-analysis aiming for the coagulation parameters includes 9 studies and found PT and D-dimer levels were significantly higher while PLT was longer in non-survivors [11].

In the sudden outbreak of COVID-19 most of current reports are restricted to the missing coagulation data or sample size. In addition to these limitations, to avoid potential bias, multi-center studies are urgently needed to get a comprehensive understanding of the coagulation features in COVID-19 patients.

### 3. Hypercoagulative thrombotic vascular events

Although the characteristics of coagulation dysfunction in COVID-19 patients is still in study, it has been considered that elevated D-dimer level is the most typical marker and may enhance the risk of thrombotic proclivity [1,10,12]. Currently reported thrombotic vascular events by COVID-19 are reviewed as followed.

| Reference          | Sample size | Groups                                      | Coagulation parameters                  |
|--------------------|-------------|---------------------------------------------|-----------------------------------------|
| Wang et al. [1]    | 138         | ICU cases (vs. non-ICU cases)               | PT†, D-dimer*, PLT†, APTT†              |
| Zhou et al. [10]   | 191         | COVID-19 Non-survivors (vs. survivors)      | PT†, D-dimer*, PLT†                    |
| Tang et al. [11]   | 183         | COVID-19 Non-survivors (vs. survivors)      | PT†, D-dimer*, FIB†, FDP*, APTT†       |
| Huang et al. [12]  | 41          | ICU cases (vs. non-ICU cases)               | PT†, D-dimer*, PLT†, APTT†             |
| Yin et al. [13]    | 553         | COVID-19 pneumonia                          | PT†, D-dimer*, PLT†                    |
| Cheng et al. [14]  | 33          | (vs. Non-COVID-19 pneumonia)               | PLT†                                    |
| Zhang et al. [15]  | 95          | Severe COVID-19                             | D-dimer*, PLT†                          |
| Qu et al. [16]     | 30          | Severe COVID-19                             | PLT†                                    |
| Han et al. [17]    | 134         | (vs. Non-severe COVID-19)                   | PT†, D-dimer*, FIB*, FDP*, APTT†       |
| Zhang et al. [18]  | 140         | Severe COVID-19                             | D-dimer*                                |
| Chen et al. [19]   | 21          | Severe COVID-19                             | PT†, D-dimer*, PLT†, APTT†             |
| Wang et al. [20]   | 135         | (vs. moderate COVID-19)                     | PT†, D-dimer*, PLT†, APTT†             |
| Liu et al. [21]    | 30          | Severe COVID-19                             | D-dimer*                                |
| Peng et al. [22]   | 112         | (vs. Non-severe COVID-19)                   | PT†, APTT†                              |
| Mao et al. [23]    | 214         | Severe COVID-19                             | D-dimer*, PLT†                          |
| Luca Spiezia et al. | 66         | COVID-19 pneumonia (vs. healthy counterparts)| PT†, D-dimer*, FIB*, PLT†, APTT†       |

*increased, †no significance, ‡decreased.

PT, prothrombin time; APTT, activated partial thromboplastin time; FDP, fibrin degradation products; PLT, platelet; FIB, fibrinogen;
3.2. Arterial disorders

Additionally, F.A. Klok et al. reported an overall incidence of 31% of thrombotic complications (27% for VTE and 3.7% for arterial thrombotic events) in ICU patients with COVID-19 [36]. Importantly, a recent reported COVID-19 case showed a feature of aortic free-floating thrombus coupled with pulmonary embolism without aortic atherosclerosis [37], emphasizing a relatively rare but fatal emergency in arterial thrombosis with COVID-19. The novel infectious disease may predispose patients to acute myocardial infarction (AMI), especially in the patients with preexisting atherosclerosis. Most of current literatures described the cardiac involvement of COVID-19 but the incidence and pathogenesis remain unclear, possibly due to the complicated mechanisms underlying AMI under a condition of infection. Plaque instability, rupture and coronary thrombosis caused by activated macrophages or endothelial injury could be causal in the formation of coronary artery thrombus, but SARS-CoV-2 may target to myocardial angiotensin-converting enzyme 2 (ACE2) or promote the myocardial infiltration of infected immune cells, thus induce direct myocardial injury [5,38] as evidenced by myocardial localization of SARS-CoV-2 [39]. Of note, a strong association between respiratory viral infection and AMI (incidence ratio altered from 2.8 to 10.1 during 7-day infection) has been proved [40]. Recently, a case series describing 28 patients with COVID-19 and ST-segment elevated myocardial infarction (STEMI) showed that STEMI could represent the first clinical manifestation of COVID-19. Interestingly, urgent coronary angiography could not figure out the culprit plaques in about 40% of these STEMI cases [41]. Given the fact that transportation and percutaneous interventions of AMI patients with COVID-19 confer high risk, in case of facing this potential challenge, coagulation management may be of importance and established in advance.

Moreover, in a retrospective and observational case series including 214 cases, clinical data revealed that patients with severe COVID-19 had more cerebrovascular involvement (5.7% vs. 0.8%) and exacerbated consciousness (14.8% vs. 2.4%) than non-severe cases, with an elevated level of D-dimer [23]. Zhang et al. reported 7 severe COVID-19 cases with acro-ischemia in Wuhan [42]. They found hypercoagulability (elevated D-dimer and FDP) existed in these severe cases with COVID-19 [42].

3.3. Antiphospholipid antibodies in COVID-19

Finally, an alert is the situation in which three COVID-19 patients with antiphospholipid antibodies and multiple cerebral infarction were found by Zhang et al. in Wuhan, China [43]. The serological testing suggested the presence of anticardiolipin IgA, anti-β2-glycoprotein I IgA and IgG in the case series without detected Lupus anticoagulant [43]. Another study presented the results of antiphospholipid antibodies in 56 cases with confirmed or suspected COVID-19 [44]. The researchers found five of the included patients displayed abnormal antiphospholipid antibodies (anticardiolipin or anti-β2-glycoprotein I) while nearly half of the cases were positive for Lupus anticoagulant [44]. The levels of antiphospholipid antibodies may arise in presence of serious illness, syphilis, systemic lupus erythematosus, autoimmune diseases or viral infection like hepatitis B virus [45,46], and could result in recurrent thrombembolic events [47]. A special subset of antiphospholipid syndrome (APS) is characterized as triple positive antibodies: Lupus anticoagulant, anticardiolipin and anti-β2-glycoprotein, which predisposes the patients to an increased risk of thrombosis [48]. Moreover, existing antiphospholipid antibodies might interact with inflammation or complement activation, resulting in worsened coagulopathy [49,50]. However, Galeano-Valle F et al. reported antiphospholipid antibodies were not increased in patients with COVID-19 and VTE. In this study the incidence of abnormal antiphospholipid antibodies and VTE was found low [51]. The presence of antiphospholipid antibodies was considered as potential evidence for early use of anticoagulants in COVID-19 patients with coagulopathy but more data are still required [44]. Nevertheless, clinicians need to be aware of this special abnormal characteristics ascribed to potential comorbidities and maintain keen vigilance.

Interestingly, the observed coagulative profiles in COVID-19 patients appeared to reflect more of a hypercoagulability than of a consumptive coagulopathy like DIC [24]. Most of COVID-19 patients did not meet the ISTH criteria of DIC, which has been identified as critical cause of micro-circulation dysfunction and the secondary organ failure in sepsis [52]. Although recent studies found evidences of thrombotic microangiopathy (TMA) in COVID-19 patients as evidenced by the findings of thrombus deposition in the microvessels of the lungs [53,54], prominent increase in D-dimer coupled with higher PLT than would be expected in the case of TMA was presented in COVID-19 [55,56], which indicated this novel viral infection-related hypercoagulability differed from that in the classical forms. SARS-CoV-1 infection has been found accompanied by pulmonary embolism, venous thrombus, thrombosis in micro-circulation, and multiple organ infarcts [32]. Coagulative parameters changed by SARS-CoV-1 are presented similar to COVID-19 but thrombocytopenia appears to be more evident while relatively modest reduction in PLT was shown in COVID-19 [55]. Another known coronavirus, MERS-CoV, could cause multiorgan failure and DIC in fatal cases but hypercoagulability and thrombocytopenia are deemed to be unusual in this setting of infection [57]. The features of coagulopathy induced by several causes are listed in Table 2.

4. Potential mechanisms for COVID-19-associated hypercoagulability

In general, the mechanisms accounting for coagulopathy in COVID-19 patients are complicated with multiple potential risk factors. Some specific notes should be paid attention to in studying the pathogenesis of hypercoagulability conferred by COVID-19 pandemic.

4.1. Inflammation and hypercoagulability

In response to virus, innate immunity is motivated to clear the pathogen for the host but inevitable organs and tissues injuries are profound when the inflammation cascade fails to be controlled. Extensive damage to vascular endothelium and activation of platelets by cytokines storm result in coagulation dysfunction, thrombosis and thromboembolism [71]. On the other hand, over-activation of T lymphocytes accelerates the exhaustion of immune cells, decreases lymphocytes counts and confess risk of concurrent infection, thus possibly aggravating coagulation malfunction in turn [72].

The novel virus invades various kinds of cells and acute disease progression is divided into 1) early infection phase, 2) pulmonary phase, 3) hyperinflammation phase [2]. The paradigms of severe cases ultimately progress into amplified immune system with inordinate systemic inflammatory cytokine storm [73,74]. Exaggerated over-activation of inflammation is corroborated by the inflammatory hallmarks of severe cases, including cytokines like interleukin (IL-1β) and inflammatory biomarkers like C-reactive protein, procalcitonin, and ferritin [2,75]. Based on data from Tongji Hospital, Wuhan, Chen et al. found significant elevated levels of IL-6, IL-2R, IL-10 and TNF-α in severe COVID-19 patients than those in moderate cases [19]. In a meta-analysis including 21 studies, totally 3377 patients, the authors recommend the monitor of lymphocyte count, platelet count, IL-6 and ferritin to track the illness progression [76] and Gao et al. demonstrated combined detection of IL-6 and D-dimer had good specificity and sensitivity in predicting the potential worse outcomes [27].

IL-6 is one of the inflammatory cytokines featuring pleiotrophic effect [77], and mainly protects the host from infectious agents but sustained elevated level of IL-6 contributes to a series of chronic inflammatory diseases and even cancer [77-79]. Playing a critical role in acute inflammation, IL-6 induced a wide spectrum of proteins including...
Table 2

| Clinic entities | COVID-19 | SARS-CoV-1 infection | Sepsis-related DIC | TTP, thrombotic thrombocytopenia purpura | HUS, hemolytic uremic syndrome |
|-----------------|---------|---------------------|-------------------|--------------------------------|-----------------------------|
| Lab test markers | D-dimer, PLT | Creatinine, PLT, RTC, haptoglobin, ADAMTS13 panel, infection pathogen test | Microcirculation, kidney, brain | Hemorrhage, micro-thrombus, thrombocytopenia, organ injury, and/or infarcts | Microvascular injury, cerebral injury |
| Key diagnostic parameters | SARS-CoV-2 test, antibodies | SARS-CoV-1 test, antibodies | Infection pathogen test, inflammatory markers, cell counts | AngII axis is beneficial in coagulopathy | ACE2 and TMPRSS2 membrane protease |

Secondary-related DC

| SARS-CoV-2 infection | SARS-CoV-1 infection | COVID-19 | Coagulopathy, organ injury, and/or infarcts |
|----------------------|----------------------|---------|----------------------------------|
| ACE2 and TMPRSS2 | | | composed of the two proteins may underpin the tropism of SARS-CoV-2 |
| Co-expressed in tissues of lung, heart, smooth muscle, kidney, and neurons | | | Co-expression with ACE2 could rescue the platelet aggregation-induced risk of thrombosis |
| ACE2 and TMPRSS2 belong to the lineage of coronaviruses and the mechanisms behind SARS-CoV may be helpful in the understanding of COVID-19. | | |研究表明ACE2和TMPRSS2在SARS-CoV-2中的表达有助于理解COVID-19的机制。 |

4.2. ACE2 dysfunction and its thrombotic effect

SARS-CoV-2 belongs to the lineage of coronaviruses and the mechanisms behind SARS-CoV may be helpful in the understanding of COVID-19. As the internalization receptor of SARS-CoV-2 [81], in concert with TMPRSS2 membrane protease, human ACE2 allows the viral entry and the subsequent biological process [82]. Even though two viruses appear to share the same target, Spike proteins of SARS-CoV-2 shows impressive affinity for human ACE2 with over 10 fold than that of SARS-CoV [83]. ACE2 exists in a wide range of cell types [84] while even in T lymphocytes expressing less virus receptors, SARS-CoV-2 could exhibit its infectivity through Spike protein-mediated membrane fusion [85]. Importantly, Wrapp et al. found three SARS-CoV Spike protein binding antibodies failed to effect when a trial was to target the Spike protein of the novel virus, all of which indicates SARS-CoV-2 shows its own properties [85]. The unique features of this novel coronavirus may be responsible for the impressive transmission rate of COVID-19.

Due to the virus infection mediated by ACE2 and TMPRSS2, co-presence of the two proteins may underpin the tropism of SARS-CoV-2 attack. To date, ACE2 and TMPRSS2 are found co-expressed in tissues of lung, heart, smooth muscle, kidney, and neurons, where clinical complications usually occur [86]. The renin angiotensin system (RAS) is an innate hormone system that participates in regulating cardiovascular homeostasis [87]. The system of importance is mainly comprised of ACE/Angiotensin II (AngII) axis and ACE2/Ang-(1–7) axis [87]. As the key component of the former axis, AngII serves as the main effector of the RAS, which contributes critically to maintaining the homeostasis of internal environment. However, abnormal activation of ACE/AngII axis promotes various detrimental effects including oxidative stress, platelet aggregation and thrombosis [87]. In contrast to AngII signaling, Ang-(1–7) axis is beneficial in coagulopathy. ACE2 catalyzes the conversion of AngII to Ang-(1–7), which may underlie the mechanisms of cardiac dysfunction and coagulopathy in this coronavirus infection [91]. Recently a study by Li
et al. reported that SARS-CoV-2 infections, but not MERS-CoV, increased the transcriptional activity of ACE2 in primary human bronchial epithelial cells according to high-throughput RNA sequencing data [92], however, how ACE2 activity and expression are altered by SARS-CoV-2 in human tissues or serum is still unclear. To answer the question whether SARS-CoV-2 effects on coagulation by ACE2 modulation we need urgent and intense research.

Other risks for hypercoagulability include some specific preexisting disease, hypoxemia, long-term immobilization and therapy-related factors like albumin infusion [84]. Although more and more articles are published online, an in-depth understanding of how COVID-19 and coagulopathy interact is far from illuminated [93]. Of note, study by Shi et al. has proved that a baseline of cardiac injury predispenses COVID-19 patients to various complications like ARDS, acute kidney injury, accompanied with prolonged hospitalization and higher in-hospital mortality [94]. They found COVID-19 patients with preexisting coronary heart disease (CHD) and cerebrovascular disease might be more susceptible to cardiac complications than those without these characteristics (Incidence of cardiac complications: 29.3% vs. 6.0% and 15.9% vs. 2.7%, respectively). Studies involving the pathogenicity of SARS-CoV revealed that the Spike protein of SARS coronavirus could be cleaved into S1 and S2 subunits by protease factor Xa, leading to increased viral infectivity [95]. Intriguingly, an article revealed that an inserted furin site in the Spike protein of SARS-CoV-2 may be cleaved by plasminogen, resulting in increased infectivity of the novel virus, which may account for the susceptibility of patients with coronary heart disease or cerebrovascular disorders to COVID-19 [96]. Pre-existing cardiac or cerebral distress is often accompanied by endothelial injury conferring the risk of thrombotic proclivity and coagulopathy, which deteriorates vascular disturbance and allows critical SARS-CoV-2 infection leading to worse outcomes in this viral pandemic. However, patients with such chronic medial illness can also be weaker and more likely to need ICU admission. No direct evidence has been found to demonstrate hypercoagulability promotes COVID-19 infection or progression, which may be an interesting issue for future studies.

5. Promising strategies for hypercoagulability in COVID-19

First of all, sufficient support care is necessary throughout the progression of COVID-19 such as vital signs monitoring, oxygen therapy, ventilation, and extracorporeal membrane oxygenation (ECMO) in condition of critical illness [84]. The application of antibiotics tends to be beneficial in case of infection by other pathogens secondary to COVID-19. The convalescent serum containing immunoglobulin from recovered COVID-19 patients may also be a choice adjunct to cautious care and antiviral strategies, to optimize the in-hospital management.

5.1. Antiviral strategies

Direct antiviral agents are the therapeutic basis of any virus infection and viral complications including hypercoagulability. With regard to the primary cause of COVID-19, potential virally targeted pharmacologic treatments are being studied on a basis of viral structure and the known antiviral agents [97]. Currently targets that may be of use to combat SARS-CoV-2 include 3-chymotrypsin-like protease (3CLpro), Spike, RNA-dependent RNA polymerase (RdRp) and papain like protease (PLpro) [97–99]. Remdesivir is found to exhibit direct antiviral effect by inhibiting RdRp in SARS-CoV-2 with high potency [99,100]. Despite of a lack in randomized, placebo-controlled trials, remdesivir inspiredly improved clinical outcomes in the cohort of 61 severe COVID-19 patients with compassionate-use of remdesivir [101]. Moreover, by using target-based virtual ligand screening and compound database, Wu et al. screened out 78 commonly used drugs, which contains agents on the market such as nicardipine, sildenafil and telmisartan [98]. Additionally, some compounds isolated from natural products were listed as potential PLpro inhibitors by Wu et al. like (−)-Epigallocatechin gallate from Camellia sinensis [98], suggesting potent benefits of drinking tea in this pandemic.

An agent that was reported effective in mitigating SARS-CoV-2 infection in vitro is hydroxychloroquine [102]. Hydroxychloroquine has been proved beneficial in patients with antiphospholipid antibodies by attenuating endothelial dysfunction, complement and inflammation, thus reducing the risk of thrombosis [103,104]. COVID-19 patients are characterized by higher thrombosis risk and antiphospholipid antibodies test could be positive in the novel disease, which may encourage a further use of hydroxychloroquine. However, as more evidences are accumulated, adverse effects of hydroxychloroquine confer a debate in the benefits of the agent, which promotes a necessary rethinking [105]. The potential drug targets have been reviewed [106,107] and ongoing efforts will help with limiting the evolvement of COVID-19 worldwide.

5.2. Direct antithrombus treatment

To date, elevated D-dimer appears to be considered a risk factor for severe COVID-19 progression and increased incidence of thrombotic complications suggests anticoagulation strategies may benefit in SARS-CoV-2 infection. In the study by Tang et al., anticoagulant treatment by heparin (mainly low molecular weight heparin, LMWH, 40-60 mg enoxaparin/day) was proved beneficial in COVID-19 patients with coagulation dysfunction. The use of anticoagulant agents significantly improved the 28-day mortality only in severe cases (40.0% vs. 64.2%) in which sepsis-induced coagulopathy (SIC) score was over 4 points. In patients with overt elevated D-dimer (> 6 ULN or > 8 ULN, ULN: upper limit of normal, 0.5 mg/L), heparin administration significantly reduced the mortality (32.8% vs. 52.4% and 33.3% vs. 54.8%, respectively) [108].

Recently as the COVID-19 pandemic outbreaks the versatile role of heparin was proposed [109]. In this paper, Thachil J described multiple effect of heparin in COVID-19. Besides its anticoagulant property by blocking thrombin, heparin may exhibit antiinflammatory in the context of COVID-19. As Thachil J summarized, the non-anticoagulant effect may possibly involve with the suppression of neutrophil chemotaxis or leukocyte migration, inhibition of complement components like C5a, protecting microvascular endothelium from disturbance, direct binding to cytokines and even potential antiviral activity [109]. However, heparin or LMWH administration needs more consideration about the dose and coagulation features of patients because in COVID-19 patients with mild coagulopathy (4 ULN > D-dimer > 1 ULN) anticoagulant treatment showed no benefits and appeared to be even detrimental in patients without elevated D-dimer (mortality: 33.3% vs. 9.7%, P = .260) [108]. Another study found routine anticoagulative prophylaxis (5000 U subcutaneous heparin every 8 h, 40 mg enoxaparin per day or 30 mg enoxaparin twice a day) appeared to be inadequate to prevent VTE formation in the patients with severe COVID-19. Despite of anticoagulants administration, VTE still developed in 28% of the included critical ill cases (31/109), in which the levels of D-dimer were significantly elevated [110]. Additionally, heparin resistance should be noted in patients with high level of factor VII, in which the anti-Xa level might be a more suitable parameter to monitor the coagulation function with heparin treatment [111].

Besides anticoagulants, fibrinolytic and antiplatelet agents are considered for COVID-19 associated hypercoagulability. Cases were reported that treatment of tissue plasminogen activator (tPA) may improve the respiratory status [112,113], but a sustained use may be required because the observed improvement in patients lost when tPA infusion was discontinued [114]. A case control, proof of concept study aimed to examine the potential effect of enhanced platelet inhibition plus anticoagulation, which consisted of tirofiban, fondaparinux, and platelet inhibition by dual antiplatelet therapy (DAPT, including acetylsalicylic acid and clopidogrel). The researchers found this combined therapy might attenuate gas exchange deficit as evidenced by improved
A-aO₂ difference in patients with severe COVID-19 [115]. Of note, the suspicion of a protective role of DAPT arises because Rosario Rossia et al. reported that chronic direct oral anticoagulants, but not DAPT, was an independent parameter associated with better outcomes and survival in their population with COVID-19 [116]. However, a recent multicenter observational study showed negative results. 192 patients with confirmed COVID-19 were enrolled and neither antiplatelet nor anticoagulant therapy conferred benefits in the prevention of ARDS or improving survival [117]. As the protective effect of direct antithrombus treatment might be in doubt, a randomized study enrolling more patients are in need and more efforts should be made to establish the antithrombus strategy which is tailored to each subset of population.

5.3. Antiinflammatory and anticomplement therapy

Corticosteroids are widely used in the inflammatory disease including SARS and MERS, however, the results from a meta-analysis including 15 studies (5270 patients of coronavirus) questioned the effect of corticosteroids on coronavirus infection (SARS-CoV-2, SARS-CoV, and MERS). The analysis indicated that use of corticosteroids may lead to higher mortality (RR = 2.11, 95%CI = 1.13–3.94, P = .019), prolonged hospitalization (weighted mean difference [WMD] = 6.31, 95%CI = 5.26–7.37, P < .001), increased risk of concurrent bacterial infection (RR = 2.08, 95%CI = 1.54–2.81, P < .001) and hypokalemia (RR = 2.21, 95%CI = 1.07–4.55, P = .032) [118], which called for a cautious administration of corticosteroids in COVID-19. As we discussed above, IL-1 drives IL-6/STAT3 signaling to promote coagulation while IL-6 may serve as a crucial mediator in the coagulation process [77,80]. Both of the two inflammatory cytokines levels are elevated in COVID-19 patients and participate in the inflammatory cascade. Blocking inflammation with antibodies or pharmacologic agents may be beneficial in the management of COVID-19 patients. Tocilizumab and sarilumab target to IL-6 signaling, and have been approved for the treatment of rheumatoid arthritis [119]. Recently a retrospective study showed an efficient treatment of tocilizumab in 21 patients with severe COVID-19 as evidenced by improved manifestations and radiological changes in most of the cases [120]. A single-center case series describing 15 patients was published, in which Luo et al. reported the use of tocilizumab might benefit in ameliorating the cytokine storm and improving the clinical outcomes in COVID-19 patients, but the good response to tocilizumab might be partly dependent on repeated doses and severity of the illness. In this paper, the monoclonal antibody appeared to fail to rescue lives in critical severe cases, especially when a single dose was administrated [121]. In another reported clinical series, Maurizio Benucci et al. found sarilumab helped improving the outcomes of COVID-19 patients with decreased level of inflammatory parameters (C-reactive protein and serum amyloid A) [122]. Due to the small number of enrolled patients and limitations of study design, the potential effect of blocking IL-6 signaling on disease progression of COVID-19 needs data of clinical trials to elucidate. Using multiple ligand simultaneous docking (MLSD) and drug repositioning, Li et al. showed bazedoxifene and raloxifene, which are approved agents for osteoporosis in post-menopausal women with high risk of breast cancer, could inhibit IL-6/glycoprotein 130 interaction resulting in inhibited IL-6 signaling [123]. These two drugs are found to inhibit IL-6 signaling in tumor and cardiovascular disease including aortic aneurysm [124–127], which may also effect in other inflammatory settings. In a randomized, double-blind trial conducted by Ridker PM et al., antiinflammatory treatment by anti-IL-1β antibody canakinumab decreased the rate of recurrent cardiovascular events than placebo [128]. However, whether these antiinflammatory agents can succeed in COVID-19 still remains unknown.

Another approach may be the anticomplement therapy. Recently, Vijendra Ramllall et al. found that a history of macular degeneration, which is identified as a disorder with complement activation, could be associated with increased morbidity and mortality in COVID-19 pandemic [129]. A pre-print paper showed SARS-CoV-2 could interact with mannose binding lectin (MBL) to involve with complement activation. The N protein of SARS-CoV-2 activates mannose-binding protein-associated serine protease 2 (MASP-2) and promotes C4 cleavage, resulting in C4b deposition, both of which were stained positive in alveolar epithelial cells of the pulmonary tissues from the cases with COVID-19, in which the level of serum C5a was also elevated [130]. Moreover, another pre-print paper found that complement activation might play a role of importance in driving the pathogenesis of immunothrombosis in COVID-19 [131]. In atypical hemolytic uremic syndrome characterized by excessive complement activation, long-acting C5 complement inhibitor ravaluzumab can ameliorate the hematologic and renal dysfunction [132]. Complement inhibition is proved beneficial with alleviated pulmonary function in murine models that infected by SARS-CoV and MERS-CoV [133,134]. Over-activation of complement occurs in the contexts of many disorders, which may result in diffuse TMA and end organ dysfunction [135]. As Courtney M. Campbell and Rami Kahwash proposed, complement inhibition may be a new strategy combating COVID-19 [135]. As they list in this published opinion, the clinical features of severe COVID-19 are similar to the characteristics of complement dysregulation, e.g. increased levels of LDH, D-dimer, and TMA as reported.

COVID-19 patients in hyperinflammation phase may suffer from uncontrolled inflammatory cascade combined with the immune complex-triggering robust motivation of complement, with subsequent severe hypercoagulability. Diminishing the two synergistic immune reactions may aid in the management of COVID-19 patients. However, it may be in debate: if the inflammatory cytokines are protective to achieve patient clearance, or detrimental allowing the amplified inflammation and viral damage. More studies into the existing queries will be of utmost importance.

5.4. Recombinant human ACE2 and Ang-(1–7)

The interaction of SARS-CoV-2 and ACE2 provides potential targets to combat the viral entry. A systemic review introduced that cellular ACE2 may be shed into a soluble form in stress [136]. One of the strategies is recombinant human ACE2 (RhACE2) infusion, which is based on the hypothesis that this recombinant protein may serve as a decoy receptor and bind to the Spike protein of the novel coronavirus, thus diminishing the viral entry, attenuating the viral deterioration to cellular ACE2 activity and rebalancing AngII and Ang-(1–7) signaling. Recently instructive results published in Cell showed soluble RhACE2, but not recombinant mouse ACE2, could inhibit SARS-CoV-2 infection in engineered human tissues, which provide promising evidence for the aforementioned hypothesis [137]. Moreover, the antithrombotic effect of xanthenone (XNT, ACE2 activator) has been tested in hypertensive and normotensive rats [90] and its further use in coagulopathy may be discussed in future.

Another pharmacologic avenue is Ang-(1–7) administration. This therapeutic strategy has been limited to the short half-life and gut degradation before its absorption, until HPKCD/Ang-(1–7) was developed to provide the oral availability of Ang-(1–7), of which the antithrombotic properties are already verified in rats [138]. Replenishing Ang-(1–7) may help with redefining the imbalance of RAS system, serving a potential antihypertensive, antiinflammatory and antithrombotic effect in COVID-19.

6. Conclusion

An impressive high transmission rate allows COVID-19 pandemic conferring great challenge for clinicians across the world. COVID-19 can cause severe respiratory dysfunction combined with multiple complications including cardiovascular disorders, renal dysfunction, cerebral events and shock. Hypercoagulability is being discussed as a
prominent feature of COVID-19, which may affect the prognosis by promoting thrombotic vascular events, especially in severe cases. The mechanisms underlying the coagulation dysfunction may be associated with inflammatory storm, uncontrolled inflammation-mediated endothelial injury, and renin angiotensin system (RAS) dysregulation. However, more studies are needed to get a better understanding of COVID-19. To achieve tailored therapy for COVID-19, the identification of effective interventions combating the novel virus and adequate management of patients are of importance. The selected potential compounds by screening will provide more possibility for optimization of clinical work. With the ongoing efforts, we hope that the COVID-19 pandemic may be triumphed over.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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References

[1] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. Jama. (2020) 1061–1069.
[2] A. Akhmerov, E. Marban, COVID-19 and the heart, Circ. Res. (2020) 1443–1445.
[3] A.M. South, D. Diaz, M.C. Chappell, COVID-19, ACE2 and the cardiovascular consequences, Am. J. Physiol. Heart Circ. Physiol. (2020) H1084-H1090.
[4] E. Callaway, D. Trabattoni, D. Andreini, G. Ferrante, M. Ancona, et al., Acute myocardial infarction in patients with COVID-19: clinical and interventional imaging. 101 (2020) 321–322.
[5] G. Lippi, E.J. Favaloro, D-dimer is associated with severity of coronavirus disease 2019 (COVID-19) infection in critically ill patients with NCD, JTH. (2020) 1116–1120.
[6] M. Liu, P. He, H.G. Liu, X.J. Wang, F.J. Li, S. Chen, et al., Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia, Zhonghua jie he he xue za zhi 48 (2020) E004.
[7] L. Mao, H. Jin, M. Wang, Y. Hu, S. Chen, Q. He, et al., Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China, JAMA Neurology. 77 (2020) 1–9.
[8] L. Spiezia, A. Boscolo, F. Polletto, L. Cerruti, i. Campello, et al., COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. J. Intensive Care. 12 (2020) 100–109.
[9] T. Chen, D. Wu, H. Chen, W. Yan, D. Yang, G. Chen, et al., Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study, Bmj. 368 (2020) m1091.
[10] X. Li, L. Wang, S. Yan, F. Yang, L. Xiang, J. Zhu, et al., Clinical characteristics of 25 death cases with COVID-19: a retrospective review of medical records in a single medical center, Wuhan, China, Int. J. Infect. Dis. 94 (2020) 128–132.
[11] Y. Gao, T. Li, M. Han, X. Li, D. Wu, Y. Yu, et al., Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19, J. Med. Virol. 92 (2020) 791–796.
[12] C. Wu, X. Chen, Y. Cai, J. Xia, X. Zhou, S. Xu, et al., Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China, JAMA Intern. Med. (2020) https://doi.org/10.1001/jama.2020.0994.
[13] M. Xiong, X. Li, Y.D. Wei, Changes in blood coagulation in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis, Br. J. Haematol. 189 (2020) 1050–1052.
[14] G. Lippi, E.J. Favaloro, D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis, Thorabm. Haemost. 120 (2020) 876–878.
[15] G. Tavazzi, C. Pellegrini, M. Maurelli, M. Belliato, F. Sciutti, A. Bottazzi, et al., Acute myocardial infarction after laboratory-confirmed COVID-19 infection: a meta-analysis, Clinica Chimica Acta; Int. J. Clin. Chem. 506 (2020) 145–148.
[16] P.Y. Chong, P. Chui, A.E. Ling, T.J. Franks, D.Y. Tai, Y.S. Leo, et al., Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis, Arch. Pathol. Lab. Med. 128 (2004) 195–204.
[17] G.B. Danzí, M. Loffi, G. Galeazzi, E. Gherbesi, Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur. Heart J. 41 (2020) 1855.
[18] J. Poissy, J. Goutay, M. Caplan, E. Parmentier, T. Duburcq, F. Lassalle, et al., Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence, J. Thorabm. (2020). https://doi.org/10.1161/CIRCULATIONAHA.120.047430.
[19] C. Bai, S. Chen, X. Li, S. Liu, F. Wang, Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia, J. Thorabm. 18 (2020) 1421–1424.
[20] F.A. Klok, M. Krui, I.J.M. van der Meer, M.S. Arbous, D. Gommers, K.M. Kant, et al., Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thorabm. Res. 19 (2020) 145–147.
[21] A. Le Berre, V. Marteau, J. Emmerich, M. Zins, Concomitant acute aortic thrombosis and pulmonary embolism complicating COVID-19 pneumonia, Diagnostic and interventional imaging. 101 (2020) 321–322.
[22] M. Lieto, A. Marzi, V. Munster, Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses, Nat. Microbiol. 5 (2020) 562–569.
[23] G. Tavazzi, C. Pellegrini, M. Maurelli, M. Belliato, F. Sciutti, A. Bottazzi, et al., Myocardial localization of coronavirus in COVID-19 cardiogenic shock, Eur. J. Heart Fail. 22 (2020) 911–915.
[24] J.C. Kwong, K.L. Schwartz, M.A. Campitelli, H. Chung, N.S. Crowcroft, T. Karnauchow, et al., ST-elevation myocardial infarction after laboratory-confirmed influenza infection, N. Engl. J. Med. 378 (2018) 345–353.
[25] G.G. Stefanini, M. Montorfano, D. Trabattoni, D. Andreini, G. Ferrante, M. Ancona, et al., SE-elevation myocardial infarction in patients with COVID-19: clinical and angiographic outcomes, Circulation. 141 (2020) 2113–2116.
[26] Y. Zhang, W. Cao, M. Xiao, Y.J. Li, Y. Yang, J. Zhao, et al., Clinical and coagulation characteristics of 7 patients with critical COVID-19 pneumonia and acute ischemia, Zhonghua xue ye xue za zhi 41 (2020) e38.
[27] Y. Zhang, M. Xiao, S. Zhang, P. Xie, W. Cao, W. Jiang, et al., Coagulopathy and Antiphospholipid antibodies in patients with Covid-19, Journal of thrombosis and haemostasis : JTH (2020), https://doi.org/10.1111/jth.14867.
[28] L.W. Uthman, A.E. Ghavari, Viral infections and antiphospholipid antibodies, Semin. Arthritis Rheum. 31 (2002) 256–263.
[29] C. Mendoza-Pinto, M. Garcia-Carrasco, R. Cervera, Role of infectious diseases in the Antiphospholipid syndrome (including its catastrophic variant), Curr. Rheumatol. Rep. 20 (2018) 62.
[30] S. Miyakis, M.D. Lockhedin, T. Atsumi, D.W. Branch, R.L. Brey, R. Cervera, et al.,
International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS), Journal of thrombosis and haemostasis: JTH. 4 (2006) 295–306.

[48] V. Pengo, A. Ruffatti, C. Legnani, P. Gresele, D. Barcellona, N. Erba, et al., Clinical practice. Thrombotic thrombocytopenic purpura, N. Engl. J. Med. 348 (2006) 1927–1935.

[49] J. N. George, Clinical practice. Thrombotic thrombocytopenic purpura, N. Engl. J. Med. 354 (2006) 1927–1935.

[50] M. A. Bray, S. E. Sartain, J. Gollamudi, R. E. Bumpstead, Microvascular thrombosis: experimental and clinical implications, Transl. Res. (2020), https://doi.org/10.1016/j.trsl.2020.05.006.

[51] D. Giannini, I. A. Ziegas, P. Gianni, Coagulation disorders in coronavirus infected patients: COVID-19 and SARS-CoV-2, MERS-CoV and lessons from the past, J. Clin. Virol. 127 (2020) 104362.

[52] H. Wada, T. Matsumoto, Y. Yamashita, Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines, J. Intensive Care 2 (2014) 15.

[53] J. Cohen, The immunopathogenesis of sepsis, Nature. 420 (2002) 885–891.

[54] T. van der Poll, F. L. van de Veen, B. P. Scicluna, M. G. Netea, The interaction of TLRs with flagellin and high-mobility group box 1 protein: a key role in infection and inflammation, J. Exp. Med. 190 (2000) 1033–1034.

[55] B. M. Henry, M. H. S. de Oliveira, S. Benoit, M. Flechon, G. Lippi, Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis, Clin. Chem. Lab. Med. 58 (2020) 1021–1028.

[56] T. Tanaka, M. Narazaki, T. Kishimoto, Immunotherapeutic implications of IL-6 blockade for cytokine storm, Immunotherapy. 8 (2016) 959–970.

[57] J. A. Fontes, N. R. Rose, The role of hydroxychloroquine in the treatment of SARS-CoV-2: from cardiac protection to cardiac failure, Cytokine. 74 (2015) 62–68.

[58] T. Tanaka, T. Kishimoto, The biology and medical implications of interleukin-6, Cancer Immunol. Res. 2 (2014) 288–294.

[59] H. M. Kim, H. J. Ko, J. Y. Lee, S. G. Park, et al., Interleukin-1 promotes coagulation, which is necessary for protective immunity in the lung during Staphylococcus pneumoniae infection, J. Infect. Dis. 207 (2013) 50–60.

[60] A. C. Wells, Y. J. Park, M. A. Tortorici, A. T. McGuire, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein, Cell. 181 (2020) 281–92.e6.

[61] M. Hoffmann, H. Klein-Weber, S. Schroeder, N. Kruger, T. Herrler, S. Ertelchen, et al., SARS-CoV-2 cell entry factor ACE2 is blocked by a clinically proven protein inhibitor, Cell. 181 (2020) 271–80.e8.

[62] D. Wrapp, N. Wang, K. S. Corbett, J. A. Goldsmith, C. L. Hisheh, O. Abiona, et al., Cryo-EM structure of the SARS-CoV spike in the prefusion conformation, Science. 367 (2020) 1260–1264.

[63] H. Mei, Y. Hu, Characteristics, causes, diagnosis and treatment of coagulopathy dysfunction in patients with COVID-19, Zhonghua yue xue ya ye za zhi 41 (2020) 185–191.

[64] X. Wang, W. Xu, G. Hu, S. Xia, Z. Sun, Z. Liu, et al., SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion, Cell. Mol. Immunol. (2020), https://doi.org/10.1038/s41423-020-0424-9.

[65] S. Bertram, A. Heusich, H. Lavender, S. Gierer, S. Danisch, P. Perin, et al., Inflammazome and SARS-CoV-2 infection: a novel viral target, EMBO Rep. 21 (2020) 1415–1423.

[66] X. Wang, W. Xu, G. Hu, S. Xia, Z. Sun, Z. Liu, et al., SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion, Cell. Mol. Immunol. (2020), https://doi.org/10.1038/s41423-020-0424-9.

[67] S. Bertram, A. Heusich, H. Lavender, S. Gierer, S. Danisch, P. Perin, et al., Inflammazome and SARS-CoV-2 infection: a novel viral target, EMBO Rep. 21 (2020) 1415–1423.

[68] I. M. Sridharan, R. S. Go, R. S. Abraham, F. C. Fervenza, S. Sethi, S. C. Bryant, et al., Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China, JAMA Cardiol. (2020), https://doi.org/10.1001/jamacardio.2020.0950.

[69] B. D. V. Koo, Y. H. Ge, Z. Cao, W. Dong, et al., Clearance of spike protein of SARS-CoV-2 by protease factor X is associated with viral interference, Biochim. Biophys. Acta Rev. 526 (2020) 947–952.

[70] A. Angalan, M. Orhan, Exploring possible mechanisms for COVID-19 induced thrombocytopenia: unanswered questions, J. Thromb. Haemost. 18 (2020) 66–71.

[71] S. Shi, M. Qin, B. Shen, Y. Cai, T. Liu, F. Yang, et al., Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China, JAMA Cardiol. (2020), https://doi.org/10.1001/jamacardio.2020.0950.

[72] W. O. Sampaio, R. A. Souza dos Santos, R. Faria Santos, L. T. da Mata Machado, E. L. Schiffrin, R. M. Touyz, Angiotensin (1-7) through receptor Mas mediates endothelial nitric oxide synthase activation via Akt-dependent pathways, Hypertension. 49 (2007) 185–192.

[73] R. A. Fraga-Silva, S. V. Pinheiro, A. C. Goncalves, N. Alenina, M. R. Santos, The antithrombotic effect of angiotensin-(1-7) involves mas-mediated NO release from platelets, Mol. Med. 14 (2008) 28–35.

[74] R. A. Fraga-Silva, B. S. Sorg, M. Wankhede, C. Dedegu, J. Y. Jun, M. B. Raker, et al., ACE2 activation promotes antithrombotic activity, Mol. Med. 16 (2010) 210–215.

[75] H. Y. Ouditi, Z. Kasiri, C. Jiang, P. P. Liu, S. M. Poutanen, J. M. Penninger, et al., SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS, Eur. J. Clin. Investig. 39 (2009) 618–625.

[76] Y. Li, H. Li, L. Zhou, EZH2-mediated H3K27me3 inhibits ACE2 expression, Biochim. Biophys. Acta Rev. 526 (2020) 947–952.

[77] A. Angalan, M. Orhan, Exploring possible mechanisms for COVID-19 induced thrombocytopenia: unanswered questions, J. Thromb. Haemost. 18 (2020) 66–71.
of COVID-19, FASEB J. 34 (2020) 6027–6037.

[106] J.M. Sanders, M.L. Monogue, T.Z. Jodlowksi, J.B. Cutrell, Pharmacologic treat-
ments for coronavirus disease 2019 (COVID-19): a review, Jama. (2020), https://
doi.org/10.1001/jama.2020.6019.

[107] P.P. Liu, A. Blet, D. Smyth, H. Li, The science underlying COVID-19: implications for
the cardiovascular system, Circulation. (2020), https://doi.org/10.1161/
CIRCULATIONAHA.120.047499.

[108] N. Tang, H. Bai, X. Chen, J. Gong, D. Li, Z. Sun, Anticoagulant treatment is as-
sociated with decreased mortality in severe coronavirus disease 2019 patients with
cogulopathy, J. Thromb. Haemost. 18 (2020) 1094–1099.

[109] J. Thachil, The versatile heparin in COVID-19, Journal of thrombosis and hae-
motoxins: JTH. 18 (2020) 1020–1022.

[110] T.K. Maatman, F. Jalali, C. Feizpour, A. Douglas 2nd, S.P. McGuire, G. Kinnaman,
et al., Routine venous thromboembolism prophylaxis may be inadequate in the
Hypercoagulable state of severe coronavirus disease 2019, Crit. Care Med. (2020),
https://doi.org/10.1097/CCM.0000000000044666.

[111] Bean R, Kusadasi N, Sikma M, Westerink J, Huisman A. Thromboembolic events and
apparent heparin resistance in patients infected with SARS-CoV-2. Int. J. Lab.
Hematol. 2020. doi: https://doi.org/10.1111/jlh.13250.

[112] Christie DB, 3rd, Nemeck HM, Scott AM, Buchanan JT, Franklin CM, Ahmed A, et al. Early outcomes with utilization of tissue plasminogen activator in COVID-19
associated respiratory distress: a series of five cases. J. Trauma Acute Care Surg.
2020. doi: https://doi.org/10.1097/TA.0000000000002787.

[113] Barrett CD, Oren-Griengen A, Chao E, Moraco AH, Martin MJ, Reddy SH, et al. Rescue therapy for severe COVID-19 associated acute respiratory distress syn-
drome (ARDS) with tissue plasminogen activator (tPA): a case series. J. Trauma
Acute Care Surg. 2020. doi: https://doi.org/10.1097/TA.0000000000002786.

[114] Wang J, Hajizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA, et al. Tissue
plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory
distress syndrome (ARDS): a case series. Journal of thrombosis and haemostasis :
JTH. 2020. doi: https://doi.org/10.1111/jth.14828.

[115] M. Benucci, G. Giannasi, P. Cecchini, F.L. Gobbi, A. Damiani, V. Grossi, et al.,
Tocilizumab treatment in COVID-19: a single center experience, J. Med. Virol. 92 (2020) 814–818.

[116] W. Shi, et al. COVID-19 pneumonia treated with Sarilumab: a clinical series of eight patients, J. Med. Virol. (2020), https://doi.org/10.1002/jmv.26062.

[117] H. Li, H. Xiao, L. Lin, D. Jou, V. Kumari, J. Lin, et al., Drug design targeting
protein-protein interactions (PPIs) using multiple ligand simultaneous docking
(MLSD) and drug repositioning: discovery of raloxifene and bazedoxifene as novel
inhibitors of IL-6/GP130 interface, J. Med. Chem. 57 (2014) 632–641.

[118] W. Shi, H. Ma, T. Liu, D. Yan, P. Luo, M. Zhai, et al., Inhibition of Interleukin-6/ glycoprotein 130 signalling by Bazedoxifene ameliorates cardiac remodelling in
pressure overload mice, J. Cell. Mol. Med. 24 (2020) 4748–4761.

[119] H. Ma, D. Yan, Y. Wang, W. Shi, T. Liu, C. Zhao, et al., Bazedoxifene exhibits
growth suppressive activity by targeting interleukin-6/glycoprotein 130/signal
transducer and activator of transcription 3 signaling in hepatocellular carcinoma,
Cancer Sci. 110 (2019) 950–961.

[120] W. Shi, D. Yan, C. Zhao, M. Xiao, Y. Wang, H. Ma, et al., Inhibition of IL-6/STAT3
signaling in human cancer cells using Evista, Biochem. Biophys. Res. Commun.
491 (2017) 159–165.

[121] D. Yan, H. Ma, W. Shi, P. Luo, T. Liu, J. Guo, et al., Bazedoxifene attenuates ab-
dominal aortic aneurysm formation via Downregulation of Interleukin-6/glyco-
protein 130/signal transducer and activator of transcription 3 Signaling pathway
in Apolipoprotein E-knockout mice, Front. Pharmacol. 11 (2020) 392.

[122] P.M. Ridker, B.M. Everette, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne,
et al., Antiinflammatory therapy with Canakinumab for atherosclerotic disease, N.
Engl. J. Med. 377 (2017) 1119–1131.

[123] Gao T, Hu M, Zhang X, Li H, Zlu L, Liu H, et al. Highly pathogenic coronavirus N
protein aggravates lung injury by MASP-2-mediated complement over-activation. (In medRxiv. 2020).

[124] Skendros P, Mitsos A, Chrysanthopoulou A, Mastellos DC, Rafailidis P, et al. Complement and tissue factor-enriched neutrophil extracellular traps are
key drivers in COVID-19 immunothrombosis. (In medRxiv. 2020).

[125] E. Rondeau, M. Scully, G. Ariceta, T. Barbour, S. Cataland, N. Heyne, et al., The
long-acting C5 inhibitor, Ravaluzimab, is effective and safe in adult patients with
atypical hemolytic uremic syndrome naive to complement inhibitor treatment,
Kidney Int. 97 (2020) 1287–1296.

[126] H. Ma, T. Liu, D. Yan, P. Luo, Y. Wang, W. Shi, et al., Inhibition of Interleukin-6/ glycoprotein 130/signal transducer and activator of transcription 3 3 signaling
in human cancer cells using Evista, Biochem. Biophys. Res. Commun.
491 (2017) 159–165.

[127] L.E. Gralinski, T.P. Sheahan, T.E. Morrison, V.D. Menachery, K. Jensen, S.R. Leit,
et al., Complement activation contributes to severe acute respiratory syndrome
coronavirus pathogenesis, mbio. 9 (2018) (e01753-18).

[128] Y. Jiang, G. Zhao, N. Song, P. Li, Y. Chen, Y. Guo, et al., Blockade of the C5a-C5aR
axis alleviates lung damage in hDPP4-transgenic mice infected with MERS-CoV,
Emerg. Microb. & Infect. 7 (2018) 77.

[129] C.M. Campbell, R. Kahwash, Will complement inhibition be the new target in
treating COVID-19 related systemic thrombosis? Circulation. 141 (2020) 1739–1741.

[130] K.B. Pedersen, H. Chodavarapu, C. Porretta, L.K. Robinson, E. Lazartigues,
Dynamics of ADAM17-mediated shedding of ACE2 applied to pancreatic inlets of
male db/db mice, Endocrinology. 156 (2015) 4411–4425.

[131] V. Monteil, H. Kwon, P. Prado, A. Hagelkruys, R.A. Wimmer, M. Stahl, et al.,
Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-
grade soluble human ACE2, Cell. 181 (2020) 905–913.e7.

[132] Skendros P, Mitsos A, Chrysanthopoulou A, Mastellos DC, Rafailidis P, et al. Complement and tissue factor-enriched neutrophil extracellular traps are
key drivers in COVID-19 immunothrombosis. (In medRxiv. 2020).

[133] M. Benucci, G. Giannasi, P. Cecchini, F.L. Gobbi, A. Damiani, V. Grossi, et al.,
COVID-19 pneumonia treated with Sarilumab: a clinical series of eight patients, J.
Med. Virol. (2020), https://doi.org/10.1002/jmv.26062.