Review Article
COVID-19 associated thromboinflammation of renal capillary: potential mechanisms and treatment

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Abstract: Coronavirus disease 2019 (COVID-19) infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic disease with high morbidity and mortality. Inflammatory and thrombosis are its main manifestations. As an important organ of hemofiltration metabolism, the kidney is prone to blockage and destruction when filter high inflammatory and high viscous blood of COVID-19, resulting in the loss of a large amount of protein, aggravating blood concentration, and then worsening COVID-19 hypercoagulability, which may explain the phenomenon of erythrocytes aggregation blocking the capillary lumen and the main reason why the kidney has become the second largest involvement organs. Therefore, this review discusses the effects of pathophysiological mechanisms such as inflammatory storm, endothelial injury, phosphatidylserine expression, extracellular traps release on renal capillary thrombosis caused by COVID-19 infection. Meanwhile, in view of the above mechanisms, we put forward the potential targets of antithrombotic therapy, and graded management of patients, reasonable use of drugs according to the severity of the disease and the choice of time. And we support the view of prevention of thrombus before admission, continuous anticoagulation and drug choice after discharge. It is suggested that the symptomatic and supportive treatment of renal disease in critically ill patients should be combined with the concept of antithrombotic therapy. The ultimate goal is to reduce the occurrence and development of kidney disease, provide direction for the current management of COVID-19 with kidney disease, and reduce the mortality of COVID-19.

Keywords: COVID-19, inflammation, renal capillary thrombosis, antithrombotic therapy, graded management

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic disease. Approximately 66 million confirmed cases, nearly 1.52 million deaths have been reported in the world. Current review studies have reported that abnormal coagulation may be one of the most common causes of sudden death [1], associated with acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) [2, 3], while venous thromboembolism (VTE) is associated with renal dysfunction [4] and renal complications are related to higher mortality in patients with COVID-19 [5]. Histopathological analysis of autopsy patients with COVID-19 showed that SARS-CoV-2 existed in renal tissue under electron microscope, and microvascular obstruction was found by immunofluorescence staining. Fibrin thrombus appeared in partial segmental capillary lumen. The above results proved renal capillary obstruction and thrombosis [6]. Renal blockage lead to ischemia and hypoxia, then disrupt the glomerular filtration barrier and renal tubular reabsorption, accelerating protein loss, increasing blood viscosity and aggravating hypercoagulable state [7]. Therefore, explore the mechanism of renal capillary lumen thrombosis and take effective treatment measures are of great benefit to reduce renal injury, delay disease progression and decrease mortality.

Kidney plays an important role in regulating the homeostasis of the body, through filtration, reabsorption, secretion and other functions.

Under normal circumstances, soluble toxic materials in blood need to be discharged by kidney circulation every day. It is easy to block when hypercoagulable blood passes through the kidney, which may be the main reason why the kidney is the second most affected organ in COVID-19. On the other hand, the destruction of renal filtration barrier aggravates hypercoagulability, which explains the phenomenon that renal injury is related to the high mortality of COVID-19-related coagulopathy. COVID-19 patients with impaired kidney function showed not only increased risk of acute kidney injury (AKI), but also hematuria, albuminuria, elevated serum creatinine and blood urea nitrogen, decreased glomerular filtration [5, 8-10]. AKI was reported to occur in all inpatients as high as 29% [6], and up to 50% of ICU patients, with a high mortality rate [11]. The continuous renal replacement therapy (CRRT) can reduce the incidence of mortality, as a main therapy, but the therapeutic effect is not ideal [12-14]. Thus, finding other vital remedial treatment options is necessary. We further discuss the possible mechanism of coagulation disorder in renal capillary occlusion and thrombosis and put forward the view that coagulation plays a significant role in the progression of renal disease. Combined with the current clinical treatment, the key step to provide a possible clinical treatment target for delaying renal injury in the future is to explore the timing of antithrombotic therapy.

**Potential mechanisms of renal capillary thrombosis**

Whether it is COVID-19 itself or kidney disease, the mechanism of thrombosis caused by both is closely related to Virchow's Triad, showing vascular wall injury, blood viscosity increased and blood flow velocity slowed down [15]. Endothelial cell injury is the most critical factor, when subendothelial matrix (collagen, von Willebrand factor (VWF)) exposure, internal/external coagulation pathways, platelets are activated. Meanwhile, injured endothelium falls off, resulting in endothelial normal anticoagulation weakening, fibrinolysis disorder. Injury of cells in circulation promotes phosphatidylserine exposure, as an important vector of Xase-prothrombinase complex in this process, promoting thrombin generation, then slowing down blood flow, aggravating blood stasis and thrombosis [16, 17]. The above are the common me-

chanism of glomerular capillaries thrombosis (**Figure 1**). The main reason is the direct damage of endothelium caused by prerenal ischemia, stress reaction and so on, which destroys the role of endothelium in vascular homeostasis, appearing the aggregation of red blood cells, platelets, fibrin and so on.

The process of COVID-19 is inflammation-thrombus-inflammation. Mild to moderate patients showed inflammation-thrombus. Severe and critical patients showed thrombus-inflammation and renal injury mostly occurred in this process, so renal capillary thrombosis was defined as thromboinflammation. The latter was used as early as 2004 to describe the platelet-leukocyte reaction mediated by P-selectin-PSGL1 interaction in coronary stents [18]. In this review, we extend its definition to the reaction between the activation of coagulant substances and immune cells. Inflammatory indicators appeared in patients with mild to moderate COVID-19, which behave as inflammation leading to activation of coagulation. While in severe and critical patients, multiple organs involved, extensive DIC and thrombotic microangiopathy (TMA) formed, and massive inflammation broke out at this time [19]. Due to ischemia and hypoxia, endothelial injury and platelet aggregation lead to the accumulation of immune cells and aggravates the inflammatory response, which is the main cause of death in patients with COVID-19. The above results lead us to think that early prevention of thrombosis and effective anti-thrombosis therapy at moderate and severe and critical patients are of great significance to reduce renal injury, delay or stop the progression of the disease, and eventually minimize sequelae and mortality. Endothelial injury, activation of macrophages, monocytes, lymphocytes and platelets, as well as the release of inflammatory factors [20-22] are involved in the occurrence and development of coagulation disorders in COVID-19. In view of the above, we will explore their effects in renal capillary thrombosis respectively (**Figure 2**).

*Direct effect of virus and extensive endothelial dysfunction*

SARS-CoV-2, SARS-CoV-1 and MERS-CoV, belonging to the Coronaviridae, have the similar genomic structure and function [23]. A variety of coagulation mechanisms are involved in the occurrence and development of the disease
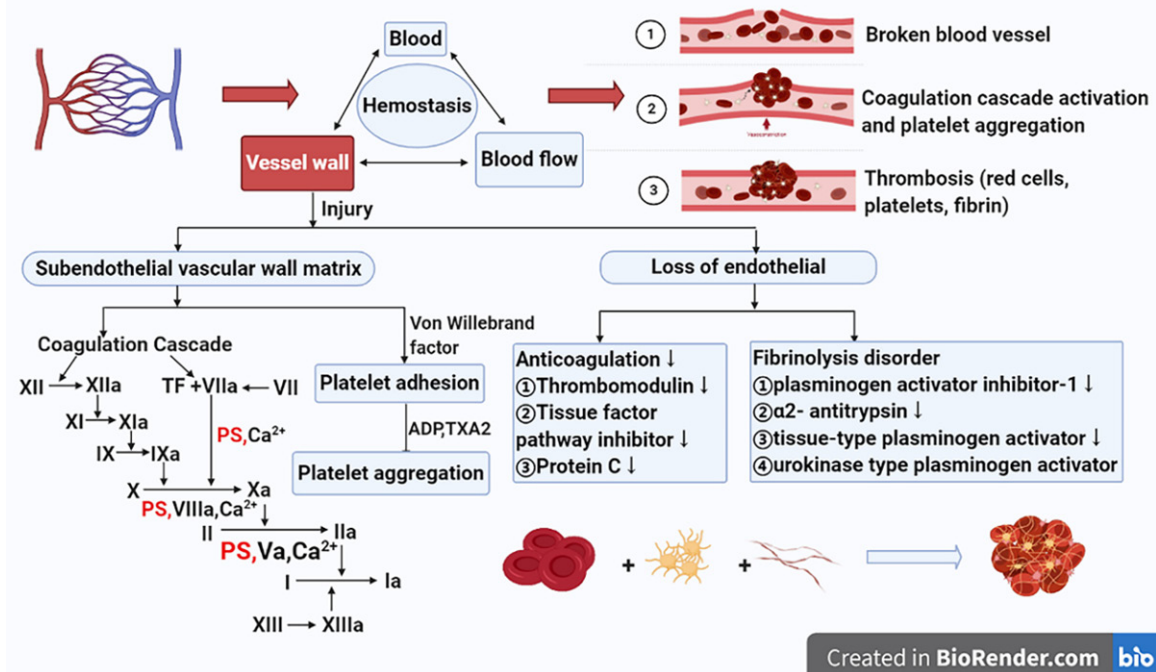
Figure 1. Cascade activation of capillary thrombosis. Blood viscosity, flow velocity and endothelial cell (EC) integrity play an important role in maintaining capillary blood homeostasis, especially EC integrity. When EC are damaged and subendothelial matrices, such as collagen and VWF, are exposed, they activate endogenous coagulation pathways and promote platelet adhesion and aggregation. Endothelial injury promotes PS exposure and TF expression, the latter activating exogenous coagulation pathway, then forming TF-VIIa complex in circulating blood, together with endogenous pathway promote Xa generation through PS, Ca^{2+} and VIIIa assistance. Xa and Va promotes IIa generation under the presence of II and Ca^{2+} on the PS, which further leads to fibrin deposition, the latter becomes dense fibrin clots under the action of XIIIa. Endothelial cells fall off in the process of injury, resulting in the weakening of their normal anticoagulation and maintenance of fibrinolysis homeostasis. When the blood passes through the damaged endothelium, it is easy to transform to procoagulation and fibrinolysis inhibition. The aggregation of red cells, platelets and fibrin in this process eventually promotes thrombosis.

infected by SARS-CoV-1 or MERS-CoV [24]. We consider that patients with COVID-19 may also have a similar coagulation disorder mechanism. As an exogenous substance, virus can induce stress response, vasoconstriction, which lead to blood stasis and thrombosis. They can bind to varieties of cell surface receptors (endothelium, bronchial epithelium, type II alveolar epithelium, renal tubular epithelium, etc.). Obvious apoptosis is caused by changes such as aggregation, cell fusion, vacuolation, syncytial formation. The translocation of vesicle and phosphatidylserine (PS) to the cell surface, nuclear concentration and fragmentation are observed, regulated by the coronavirus family member S1 protein [25]. SARS-CoV infection found that apoptotic enzymes were involved in mitochondrial metabolism [26]. Additionally, MERS-CoV study found that it could effectively infect human primary T lymphocytes and activated exogenous and endogenous apoptosis pathways [27].

We speculate that apoptosis occurs during SARS-CoV-2 invasion, accompanied by PS expose. We have confirmed that PS is involved in hypercoagulable state of renal diseases, such as diabetic kidney disease (DKD) and nephrotic syndrome [28, 29]. The histological analysis of COVID-19 infection in renal transplant patients found the accumulation of endothelium-related inflammatory cells and apoptotic bodies, then proposed apoptosis-related endothelial dysfunction [30]. Celestino Sardu et al. think that endothelium is the key target organ in COVID-19, its surface highly expresses virus-targeted receptors [31]. Endothelial dysfunction is the main determinant of microvascular dysfunction [32]. The virus attacks renal endothelium and leads to apoptosis with overexpression of PS, adhering factor VII and VIII, activating endogenous and exogenous coagulation pathways, may be one of the mechanisms of glomerular microvascular thrombosis. At the same time, the increased expression of plas-
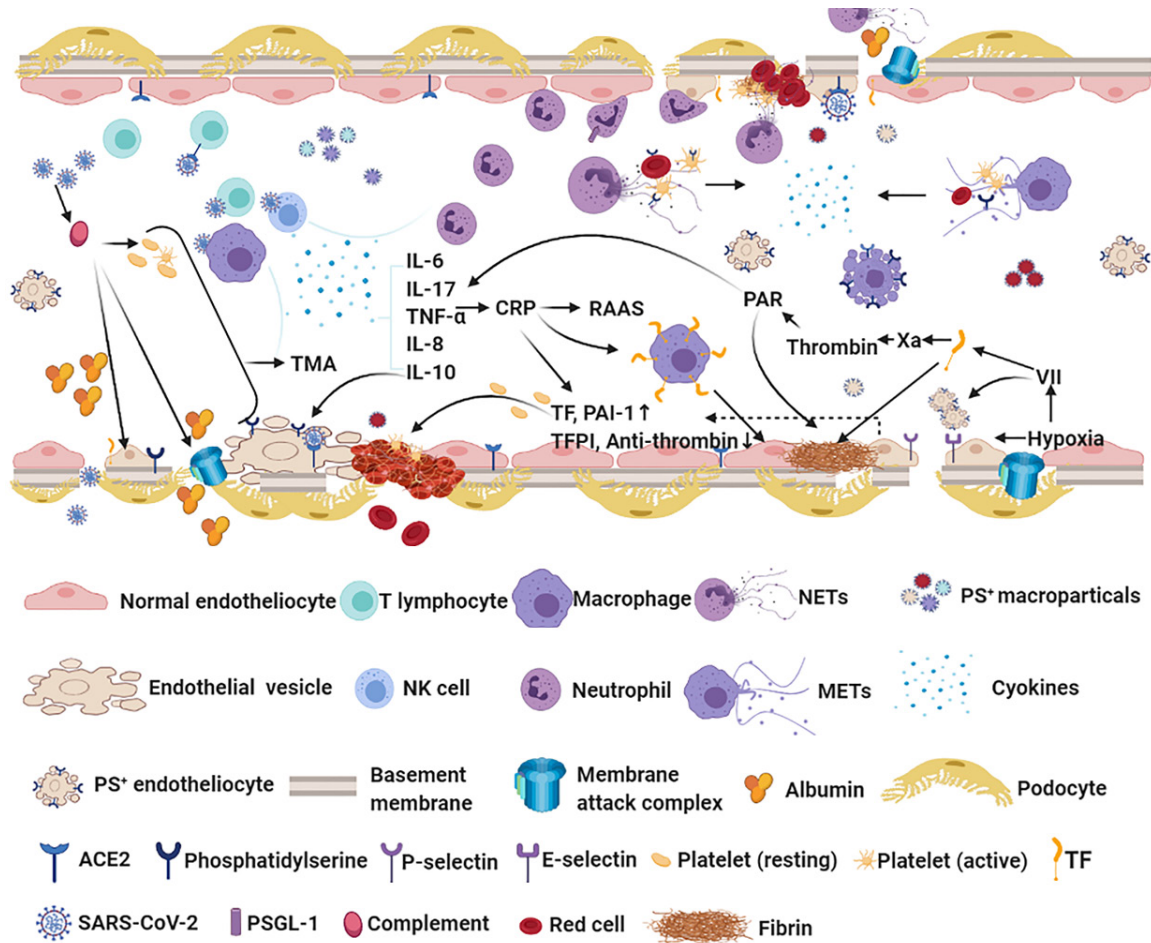
Figure 2. Possible mechanism and treatment direction of COVID-19-associated renal capillary thrombosis. Inflammatory and thrombus: SARS-CoV-2 binds to ACE2 receptors on the surface of immune cells (T cells, NK cells, macrophages), promoting the release of IL-6, IL-17, TNF-α, IL-8, IL-10, and the formation of particles, then further promotes the expression of CRP, which activates the RAAS system, increases the expression of anticoagulant and antifibrinolytic substances, promotes the expression of TF on the surface of macrophages, acting on endothelial cells and promoting PS exposure and fibrin thrombosis on it. Endothelial injury and thrombus: direct effect of virus leads to endothelial PS exposure and apoptosis; inflammatory factors cause endothelial procoagulation and antifibrinolysis; the activation of the complement system aggravates endothelial injury; hypoxia leads to endothelial ischemia and Hypoxemia. The injured endothelium formed procoagulant particles with PS and TF expression and promoted multi-site thrombosis through circulating blood; expressed E-selectin, P-selectin, enhancing platelet and neutrophil aggregation; decreased expression of TFPI, anti-thrombin, PAI-1, impairing antithrombotic ability; promoted the expression of inflammatory factors. After promoting the injury of renal endothelium, the gap increases, which leads to the leakage of plasma albumin. At the same time, viruses and immune cells also migrate to the epithelium of podocytes and renal tubules through the damaged endothelium. The increase of neutrophils produces NETs, and macrophages also express MET in oxidative stress environment. These extracellular traps lead to endothelial damage, promote the stability of thrombus and the release of inflammatory factors. Hypoxia can also activate the formation of VIIa and promote the production of thrombin, which acts on PAR and aggravates the release of inflammatory factors. The activation of complement system promotes the formation of renal membrane attack complex, aggravating oxidative stress and leads to disease progression. The expression of inflammation, endothelial injury and activation of coagulation factors in the process of thrombosis may be inhibited, which may be new methods to delay the progression of the disease.

minogen activator inhibitor-1 (PAI-1), tissue factor (TF) and down-regulation of anti-thrombin in patients with COVID-19 can not only reflect the imbalance of endothelial function, but also the reason of glomerular fibrin thrombosis [33]. In addition to PS expose in endothelial cells, it may also exist in varieties of targeted cells attacked by virus. This process may be accom-

panied by the production of microparticles with PS expose. This phenomenon still needs to be explored further.

Cytokine storm

A large number of endothelial damage and activation lead to the high expression of P-selectin, binding to P-selectin glycoprotein ligand-1 (PSGL-1), and E-selectin, which promotes the aggregation of neutrophils and macrophages, and further promotes the expression of inflammatory factors [34]. 10%-15% of COVID-19 patients progressed to ARDS triggered by cytokine storm [35], mainly in severe and critically ill patients. At present, studies have proved that inflammatory factors such as IL-6, IL-8, IL-10, IL-17, TNF-α increased in COVID-19 [36, 37]. On the 8th day with symptoms of critical patients may need to use mechanical ventilation and enter ICU treatment [36], consisted with the conclusion of Huang C et al. They found that the presence of SARS-CoV-2 in the blood and the occurrence of AKI on the 7th day [38]. While IL-6 as an early elevated cytokine could be detected on the 4th day after the onset of symptoms. We believe that "cytokine storm" plays an indispensable role in the development of the disease from mild to severe, and its excessive accumulation contributes to the deterioration of the disease. Cytokines involved in the coagulation process [39-42] have been confirmed in a variety of diseases, including coagulation abnormalities in the progression of kidney diseases [40, 43] (**Table 1**). Inflammation can regulate blood coagulation by activating C-reactive protein (CRP), increasing TF exposure on monocytes and alveolar macrophages [44, 45], and then promote thrombin production and fibrin deposition. TF, FXa, viral factor or thrombin-activated protease activate receptor (PAR) signal, promote fibrin production and enhance fibrosis [46, 47]. PAR signaling can also enhance the inflammatory response of acute lung injury (ALI) by increasing the expression of pro-inflammatory cytokines, including IL-6, IL-8 [48, 49]. The process of high inflammation can lead to the occurrence of hypoxemia [50] and the environment promotes the activation of endothelial cells and endothelial dysfunction, leading to prethrombotic state. CRP promotes the local release of PAI-1 from endothelial cells [51, 52], leading to secondary hyperfibrinolysis and promoting the occurrence of DIC. Also, bradykinin system is activated,

then the production of bradykinin increases the expression of tissue plasminogen activator (t-PA). Effectively inhibiting the production of cytokines is of great significance to delay the progression of the disease.

ACE2 receptor and RAAS system

ACE2 receptor promotes the occurrence and development of COVID-19 disease. One of the most important beneficial functions of membrane-bound and sACE2 is the degradation of angiotensin II into angiotensin. Therefore, ACE2 receptors limit several harmful effects produced by the binding of angiotensin II (Ang II) to AT1 receptors, including vasoconstriction, increased inflammation and thrombosis. The activation of ACE2-AT$_{1-7}$-Mas receptor has antithrombotic effect. Mas receptor is expressed on the surface of platelets, which increases the release of prostacyclin and NO. NO has been proved to have a nephroprotective effect and reduce the occurrence of TMA [53]. SARS-CoV-2 binds to the receptor on the surface of target cells. ACE2 receptor is down-regulated after membrane fusion, then ACE2 expression is decreased, and the antithrombotic effect of Mas receptor is weakened [54], leading to AngII accumulation, which acts on AT1 receptor, induces the expression of t-PA, PAI-1 in endothelial cells [50]. Free t-PA is neutralized by PAI-1, resulting in damage to fibrinolytic system and fibrin accumulation. The reason for the deposition of fibrin in the kidney was explained.

RAAS is of utmost importance in the pathological evolution of ARDS, and ACE2 is the main component of RAAS [50]. The RAAS system is intrinsically linked to coagulation cascades, which may aggravate the process of immune thrombosis and further drive microthrombosis in COVID-19 [50]. Severe COVID-19 often shows hypokalemia and hyperaldosteronemia, which can promote the growth of PAI-1, especially in renal tissue [55, 56]. The decrease of ACE2 can increase the level of aldosterone, promoting the expression of PAI-1, which leads to fibrinolysis inhibition and thrombosis.

Extracellular traps (ETs)

In addition to producing inflammatory factors, the extracellular traps produced by neutrophils, monocytes, macrophages and other inflammatory cells can also be used as an important

Table 1. Cytokines procoagulant coagulation mechanism of renal disease and therapeutic drugs in COVID-19

Type	Procoagulant mechanism	Expression in renal disease	Targeted therapeutic agents (97)
IL-6	1. Increased the expression of TF in endothelial cells, which promoted coagulation by triggering a molecular cascade that converts prothrombin to thrombin (39).	1. IgAN: Local deposited high-molecular polymeric IgA1 can promote mesangial cells proliferation and secretion of the pro-inflammatory cytokine. The associated cytokines (IL-6, IL-17) in serum and urine were elevated and correlated with renal pathological change (43).	Tocilizumab: IL-6R antagonist antibody, Sarilumab: IL-6R antagonist antibody Siltuximab: anti-IL-6 antibody
TNF-α	2. Through JAK-STAT signal Promoting podocyte, endothelial cells, platelet, Red cells apoptosis and induce the expression of PS, binding blood clotting factors V and FVIII (40, 97). 3. Facilitating neutrophil aggregation and inducing the formation of NETs, providing stents for thrombin, platelet aggregation and fibrin deposition (41).	2. LN: Cytokines excretion are associated with a higher activity of LN, injured endothelial cells and podocyte, Increased proteinuria and hematuria (43). 3. DKD: Chronic inflammatory process participates in the development of microvascular complications of diabetes. DKD patients showed an elevated serum level of inflammatory cytokines, which positively correlated with the extent of proteinuria (43). 4. AKI: Ischemia, nephrotoxic induced AKI can increase the expression of inflammatory factors, the latter can recruit neutrophils and activate the oxidative response, aggravating AKI (43).	Infliximab: a chimeric monoclonal anti-TNF antibody Etanercept Adalimumab: a receptor trap consisting of TNF-R2 fused to IgG1 Fc Certulizumab pegol: a human monoclonal anti-TNF antibody Golimumab: a human monoclonal anti-TNF antibody
IL-17	4. Reverse regulation of complement systems, promoting platelet activation, leukocyte recruitment, endothelial cell activation and coagulation (42).	5. CKD: Cytokines injure kidney not only by aggravating oxidative stress, chronic inflammation, and fluid overload, but also by initiating its complications, especially the chronic vascular disease (43). 6. PNS: Cytokine involve in podocyte apoptosis (40).	*Secukinumab:* a human IL-17A antagonist *Ixekizumab:* a humanized IL-17A antagonist *Brodalumab:* a human IL-17 receptor A antagonist
IL-8			None
IL-10			None

PS, phosphatidylserine; TF, tissue factor; NETs, neutrophil extracellular traps; IgAN, IgA Nephropathy; LN, Lupus Nephritis; DKD, Diabetic Kidney Disease; CKD, Chronic Kidney Disease; AKI, Acute Kidney Injury; PNS, Primary Nephrotic Syndrome.

medium to aggravate the progression of disease and promote coagulation. The autopsy report of COVID-19 showed obvious pulmonary fibrosis and neutrophil infiltration, and Yu Z et al. have been confirmed a high expression of extracellular DNA components of neutrophil extracellular traps (NETs) in COVID-19 [57]. Intravascular NETs is involved in arteriovenous thrombosis and accumulation [58]. Its histone components can activate platelets through Toll-like [59], which may explain the cause of thrombocytopenia in patients with COVID-19. NE can consume anticoagulant substances (anti-thrombin III (ATIII), tissue factor pathway inhibitor (TFPI)) [60]. Lupus nephritis, acute renal injury has confirmed that ETs is involved in the formation of renal hypercoagulable state [61, 62]. We suspect that ETs accumulation may also exist in the renal tissue of patients with COVID-19, resulting in local microthrombosis, while destroying the endothelial barrier, damaging podocytes, leading to massive production of albuminuria. When it enters the renal tubular epithelial cells, it can also lead to epithelial system disorders. As a stent, ETs can promote blood cell aggregation, fibrin deposition, strengthen the formation of clots, adhere to PS, and activate internal and external coagulation pathways. Although only NETs has been confirmed, there are lymphocytopenia, eosinopenia and macrophage activation in COVID-19, included DNA structures in the nucleus being released when it is stimulated, so there may be more than one kind of cellular DNA in COVID-19, and its reticular structure may include eosinophils, lymphocytes, macrophages and so on [63, 64]. However, these need to be further confirmed. Studies have shown that NETs ingredients have antifibrinolytic effect [65], so recombinant tissue plasminogen activator (rt-PA) therapy alone may not be sufficient to dissolve clots. NETs can also activate NF-KB to promote the expression of inflammatory factors by acting on lymphocytes through toll-like receptors. These extracellular DNA components play an essential role in thrombosis and inflammation of COVID-19, effectively prevent the formation of NETs and promote the dissolution of its components may be used as therapeutic targets for COVID-19 in the future.

Complement system

Complement system consisted of circulating proteins, a part of the innate immune system [50]. By activating platelets and endothelial cells, increasing the expression of tissue factor and VWF contribute to the formation of hypercoagulable states, then convert prothrombin into thrombin, and finally fibrinogen to fibrin. Coagulation cascade activating components in turn activate C3 and C5 [66]. There are three pathways: classical pathway, lectin pathway and alternative pathway. These three pathways are all activated in the process of COVID-19 infection. Complement can directly act on C5R receptors on the surface of macrophages and neutrophils, promoting the release of damage-associated molecular patterns (DAMPs) [67] and the outbreak of oxidative respiration [68]. They can form membrane-attacking complexes and deposit in the kidney, resulting in podocyte damage. Complement-mediated TMA leads to renal damage [42]. TMA cause hypertension, while shock caused by DIC lead to low blood pressure. COVID-19 patients are mainly characterized by hypertension, excluding underlying disease factors, and most of them are concentrated in critically ill patients, while most studies believe that DIC is more inclined to prethrombotic state. Perhaps the main mechanism of hypercoagulable phenomenon in the early stage of patients with COVID-19 is DIC. With the development of disease, a large number of complement system is activated, leading to the formation of TMA, and finally promote glomerular microthrombosis.

Hypoxia

A retrospective cohort study showed that hypoxemia as an independent factor in COVID-19 patients was associated with in-hospital mortality [69], and about 2/3 of severe and critically ill patients showed fatal injuries [70]. Hypoxia cause histanoxia formed by acid metabolite involvement, vasoconstriction, and then ischemia and hypoxia, further leading to stroke, AKI [6], tissue inflammation, extravasation, pulmonary edema and so on. Hypoxia in severe pneumonia can stimulate thrombosis not only by increasing blood viscosity, but also through hypoxia-induced transcription factor-dependent signal pathways to motivate [71]. Hypoxia can cause contraction of renal afferent arterioles, insufficient renal perfusion, increase of acidic substances, shrinkage and deformation of endothelial cells, damage of endothelial barrier function, and transformation to procoagulant and pro-inflammatory phenotype. Some studies have shown that hypoxia can

activate FVII gene to produce procoagulant microvesicle [72]. Hypoxia inhibit the expression of TFPI, up-regulate TF expression [73], and activate exogenous coagulation pathway. Therefore, multi-site microvascular thrombosis caused by hypoxia may be the cause of death in patients with respiratory failure, heart failure and renal failure in COVID-19.

Treatment

Thrombosis has a key role in the occurrence and development of disease. Effective inhibition of thrombosis is of great significance for improving renal function and reducing mortality. Currently, various drugs aimed at the mechanism of thrombosis have entered the clinical trial stage. By suppressing immunity, regulating receptors, restoring body self-balance, combined with mechanical ventilation and CR-RT treatment, the mortality rate has not been effectively reduced, but significantly ameliorated using anticoagulants, and the timing, dose and drug selection of anticoagulants are still controversial. Based on the current treatment, this paper puts forward our thoughts on antithrombotic therapy.

Anticoagulant therapy

Huan H et al. showed that PT-act were down-regulated while fibrinogen degradation product (FDP), D-dimer and fibrinogen (FIB) were higher than normal controls in patients with COVID-19. Compared with mild, severe and critically ill patients, AT and PT-act did not change significantly. D-dimer and FDP levels increased significantly in severe and critically ill patients (D-dimer increased about 40 times), while mild patients did not change significantly (D-dimer increased about 2 times) [74]. Shiyu Y et al. found that the level of D-dimer increased less than 4 times the normal upper limit (normal < 0.5 μg/mL). There was no significant difference in 28-day mortality between patients used anticoagulation and those not used anticoagulation. But reached 6 times or more of the normal value, the mortality rate of patients treated with anticoagulation significantly decreased (19.6%) [75]. The Society of Thrombosis and Hemostasis put forward the necessity of prophylactic anticoagulant therapy with low molecular weight heparin (LMWH) in all patients, but it still needs to meet the fact that the level of D-dimer is significantly increased (more

than 4 times), PT slightly prolonged (about 4 s), Platelet count < 100×10^9, FIB < 2.0 g/L [76]. For patients with different degrees of COVID-19, we consider that prophylactic anticoagulant therapy can be performed according to the level of D-dimer. Patients with an increase of less than 6 times are mainly concentrated in mild cases, the use of anticoagulants such as heparin is not considered. Because of their thrombotic tendency and the decrease of AT level, we can supplement AT or recombinant soluble thrombomodulin (rsTM), to increase physiological anticoagulant activity. Because the anticoagulant effect of AT increases significantly after binding to heparin, the risk of bleeding is lower. For severe and critically ill patients, their D-dimer levels are significantly increased, reaching the standard of preventive anticoagulation, due to the decrease of AT and the increase of fibrinogen, the therapeutic effect of anticoagulants such as heparin is not good, so the preventive dose of heparin is not enough to control the progress of the disease. Combined with the recommendations of British hospitals in the course of treatment, LMWH can be treated with half of therapeutic dose [77, 78]. In severe and critically ill patients with kidney disease, especially for dialysis patients, LMWH and fondaparin are mainly excreted through the kidney, long half-life and easy to accumulate, binding FXa, which are more likely to lead to bleeding tendency and nephrotoxicity, so unfractionated heparin (UFH) can be considered [79, 80]. The choice of treatment time can be combined with the increase of inflammatory indicators. IL-6 as the trigger point of inflammatory response can be detected on the 4th day of the disease [81], while renal injury can be detected on the 7th day [12]. Maybe we can start anticoagulant immunotherapy on the 4th day of the disease to prevent the disease from attacking the kidney and effectively inhibit thrombosis. But all the above considerations need to be further tested in randomized controlled trials.

Antiplatelet therapy

Even with prophylactic anticoagulant therapy, thrombosis is still found in 20-30% of critically ill COVID-19 patients yet. Guan et al. have shown that 36.2% COVID-19 had thrombocytopenia [82], which is mainly caused by platelet activation and involved in thrombosis [20], so to inhibit platelet activation antiplatelet th-

erapy is also essential, but it is controversial at present. It is suggested that long-acting antiplatelet drugs should usually be discontinued in most DIC patients [83]. The current expert consensus calls for positive measures to be taken for patients with platelet counts < 1000000/μl and < 50000/μl, or even to stop all antiplatelet therapy [84]. However, we believe that severe and critically ill patients with COVID-19 may be more inclined to TMA characterization. At present, there is no risk of bleeding with double antibody therapy, so antiplatelet therapy is feasible. ARDS caused by community acquired pneumonia, pre-hospital antiplatelet therapy can effectively reduce the severity of the disease and mortality. Although current studies have shown that there is no platelet aggregation in renal capillaries, platelet aggregation is mostly formed in arteries. At present, there is no study on renal arteries, which may also be related to reduce platelet consumption. Active antiplatelet therapy [85] also helps to reduce the incidence of renal damage. Studies have demonstrated that aspirin is effective on prophylaxis of venous thromboembolism [86]. Therefore, we think that the mild patients can be treated with aspirin, when the platelet count is normal or even high, early inhibition of its activity may reduce intravascular fibrin and thrombosis, severe and critical patients, 100000/μl ≤ platelet count < 150000/μl can be treated with ticagrelor, platelet count < 100000/μl can suspend treatment. Platelet activation occurs during central venous catheterization in patients with severe renal disease treated with RRT [87], which lead us to think that it is also necessary to use antiplatelet therapy besides routine anticoagulant therapy with LMWH.

Thrombolytic therapy

LMWH plays an important role in the treatment of COVID-19 patients. However, COVID-19 patients have hyperfibrinogenemia. Local fibrinolysis must be promoted in order to degrade pre-existing fibrin in the lungs. LMWH is ineffective in clearing fibrin clusters deposited in the alveolar space. At present, atomizer plasminogen activator can provide a targeted method for COVID-19 patients to degrade fibrin and improve oxygenation in critically ill patients [33]. At the same time, when critical patients need to be rescued in time, t-PA can be used as a good treatment, but the use of LMWH after t-PA treatment may increase the risk of bleeding, so UFH is recommended. Fibrin thrombosis is found in some renal capillaries, which may be treated effectively by local thrombolysis with t-PA. However, systemic or catheter-directed thrombolytic therapy also occurs a lot of bleeding events. Perhaps we can increase clot dissolution and reduce the occurrence of bleeding events by enhancing endogenous fibrinolytic substances such as TFPI, α2-antiplasmin [34].

New oral anticoagulants (NOACs)

For inpatients, prophylactic anticoagulation with intramuscular injection and intravenous injection of LMWH is feasible, but for outpatients, oral preparation is more compliant. Warfarin and NOACs are commonly used at present, but the latter is safer than the former [88]. COVID-19 affects the kidney, not only through direct damage, but also can stimulate a series of inflammation, oxidative stress, fibrosis, leading to the formation of kidney disease. Edoxaban, as one of the NOACs, a specific inhibitor of coagulation factor Xa (FXa), can improve kidney disease by inhibiting inflammation and tissue fibrosis in animal models. It is a multitarget drug as risk factors for the progression of chronic kidney disease (CKD) [89]. However, NOACs is mostly excreted through the kidney, so the use of these drugs in patients with nephropathy needs to monitor glomerular filtration rate (GFR). The NOACs recommendations of different guidelines for CKD patients and patients with VTE events [15, 90] are shown in **Table 2**, which can guide the use of drugs for COVID-19 complicated with nephropathy. Since 60% of the patients developed thrombosis within 90 days after discharge [78], it is still necessary to continue anticoagulant therapy after discharge. NOACs does not require routine blood clotting tests and has fewer drug-food interaction advantages [91]. It may be used for maintenance treatment of COVID-19 discharged patients. Studies on deep vein thrombosis have found that more than 60% of VTE occurs after discharge. Most VTE events (about 80%) occur within 6 weeks after discharge, but post-hospital thromboprophylaxis is given to less than 4% of hospitalized patients [92, 93]. Therefore, patients with COVID-19 need long-term oral anticoagulants within

Table 2. Recommendation of NOACs for COVID-19 patients with different degrees of Nephropathy

Mechanism	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
	Direct thrombin inhibitor		Direct inhibitor of activated factor X	
CrCl 30-59	PA for 5 days then 150 mg bd or 110 mg bid	10 mg bid for 7 days then 5 mg bid	15 mg bid for 3 weeks then 20 mg po	PA for 5 days then 30 mg qd
CrCl 15-29	Not recommended	10 mg bid for 7 days then 5 mg bid	15 mg bid for 3 weeks then 20 mg po	PA for 5 days then 30 mg qd
CrCl < 15	Not recommended	5 mg bid (FDA)	Limited clinicial data-15 mg qd (FDA)	Not recommended
Dialysis	Not recommended	5 mg bid (FDA)	Limited clinicial data-15 mg qd (FDA)	Not recommended

NOACs, New oral anticoagulant; CrCl, creatinine clearance; PA, Parenteral anticoagulation; bid, twice a day; FDA, Food and Drug Administration; po, per os; qd, once a day.

at least 2 months and are reviewed regularly every month to prevent disease recurrence and the formation of new complications. In addition to the direct inhibition of coagulation factors, effective targeted therapy for the causes of thrombosis is also helpful to reduce thrombosis.

Other possible therapeutic targets to thrombosis

Renal capillary thrombosis in COVID-19 includes direct action of virus, impaired endothelial function, cytokine storm, extracellular traps and hypoxia. According to the above mechanisms, there are many effective targeted therapies, containing antiviral agents [94-96], targeted receptor therapy [34, 95], anti-cytokine antibodies [97] (**Table 1**), NETs antagonists and their content inhibitors [35], complement inhibitors [98, 99] etc (**Table 3**). The current clinical trial of drugs can effectively reduce symptoms, reduce mortality, may be related to the inhibition of thrombosis during the treatment. At present, it is been suggested, in most viewpoints, continuous immunosuppressive therapy to manage patients, whether there is basic kidney disease with COVID-19, or renal disease secondary to COVID-19 [100, 101]. The dose can be reduced appropriately according to the illness. Perhaps immune-mediated thrombosis is the main reason of renal injury, which effective inhibition of inflammation and coagulation is conducive to delay the progression of the disease.

As described above, the mechanism of renal capillary thrombosis and the possible mechanism of COVID-19-related renal capillary thrombosis, from virus invasion, immunothrombosis, to the persistence of thromboinflammation, and finally multiple organ dysfunction, each stage plays an important role in the progression of the disease. It can reduce the activation of immune cells by inhibiting virus replication, such as hydroxychloroquine and antiviral agents [94-96]; block the binding of virus to body receptors, such as ACEI, ARB, but there is some controversy about them, so it is proposed that the use of recombinant human ACE2 (rhACE2) can increase the protective effect of Mas receptor and exert the effect of anti-inflammation and anticoagulation [102, 103]. Inhibition the expression of E- and P-selectin on endothelial cell reduce the aggregation of leukocytes and platelets [34]. Application of corresponding antibodies is necessary to prevent the formation of cytokine storm [97]. ETs formed by immune cells, mainly NETs, is an important bridge between thrombus and inflammation. Blocking target by directly degrading ETs or the process of its contents may be important [35]. The activation of complement system has been proved to play an essential role in COVID-19, especially as an important mediator of kidney disease. It is believed that the use of monoclonal antibodies may alleviate the disease [98, 99]. In addition to the above targets, Novel antithrombotic strategies are proposed, such as anti-XII, anti-XI, play a cascade amplification role in the coagulation process, promote thrombin generation, connect the slow peptide system with the coagulation process, and inhibit the target, which plays an important role in reducing inflammation and coagulation [34]. We believe that PS also plays an important role in the process of thrombosis. At present, a large number of studies have shown that particles and vesicles are highly produced in COVID-19 [104]. Based on our previous studies [28, 29], we consider that PS and TF expressed on the surface of particles and vesicles may be important factors of multiple organ thrombosis, so giving anti-PS, and anti-TF therapy may become one of the important treatments in future research.

Table 3. Treatment of incentives to COVID-19 associated renal capillary thrombosis

Categories	Drugs	Mechanism	Refs
Antivirals	CQ, HCQ	Effect cell membrane pH necessary for viral fusion Interfere with glycosylation of viral proteins Inhibit phospholipase activity Stabilize lysosomal membranes Block the production of pro-inflammatory cytokines Impair complement-dependent antigen-antibody reactions Decrease of the APL antibody titers	[94-96]
	Emtricitabine-tenofovir (Truvada)	The active triphosphate form of this tenofovir diphosphate inhibits activity for RdRp of virus	
Targeting receptors	ACEI, ARB, rhACE2	Upregulate ACE2 expression. ACE2 is a homologue of ACE, and functions as a negative regulator of the renin-angiotensin system	[102, 103]
Endothelial related targets	GMI-1271 Selk2	An E-selectin antagonist attenuates thrombosis and inflammatory markers without increasing bleeding A humanized monoclonal antibody binds PSGL-1 and blocks its ability to interact with selectins and chemo-kines	[34]
Cytokine inhibitors		**Table 1**	[97]
NETs inhibitors	Sivelestat, Lonodelestat Alvelestat, CHF6333	NE inhibitors, NE activates proteins essential to NET formation	[35]
	PAD4 inhibitor	PAD4 mediates histone citrullination	
	Dornase alfa	A recombinant DNase I is approved to dissolve NETs and improve symptoms	
	Anakinra Canakinumab and rilonacept	For the NET-IL-1β loop could be antagonized with approved drugs against IL-1β	
Complement pathway inhibitors	eculizumab	Anti-C5 antibody, preventing the cleavage of C5 into C5a and C5b, which are the central converging point of all pathways of complement activation	[98, 99]

NETs, neutrophil extracellular traps; CQ, chloroquine; HCQ, hydroxychloroquine; ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; rhACE2, recombinant human angiotensin-converting enzyme 2; APL, anti-phospholipid; RdRp, RNA-dependent RNA polymerase.

Conclusion and future direction

In this article, we explore the possible mechanism and therapeutic targets of renal capillary thrombosis caused by COVID-19. We consider that renal involvement and high mortality are inseparable with thrombus. So effective antithrombotic therapy may reduce the occurrence and development of renal disease. We put forward possible therapeutic targets for thrombosis in the future. At the same time, the current clinical treatment methods also show that these treatments are indeed effective, but there are few studies on the effects of blood coagulation in COVID-19. If the later randomized controlled trials can be combined with the changes of blood coagulation indexes before and after drug treatment, it is of great importance to support our conclusion. The current antithrombotic therapy lacks the choice of disease stratification and treatment time. This paper describes how to choose anticoagulants for mild, severe and critically ill patients, as well as anticoagulant intervention at the time of onset, and makes a corresponding supplement to antiplatelet and NOACs therapy, which makes up for some shortcomings of current anticoagulation therapy, but these need to be further confirmed by future clinical trials.

Acknowledgements

Disclosure of conflict of interest

None.

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