Anticoagulation therapy in COVID-19 patients with chronic kidney disease

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INTRODUCTION

Severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2) has been identified as the etiologic factor of the new emerging pandemic.¹ On March 11, 2020, after its rapid spread across the globe, the World Health Organization declared COVID-19 a pandemic disease.² During a short period after its emergence, COVID-19 has resulted in thousands of deaths worldwide.

The broad clinical manifestations and severity spectrum of COVID-19 are affected by factors such as comorbidities.³ The most common comorbidities, which increase the severity and mortality of COVID-19, are hypertension, cardiovascular diseases, diabetes, structural lung disease, chronic kidney disease (CKD), malignancy, and immunodeficiency.⁴ CKD affects 7.2% of the population aged 30 years and older worldwide, and its prevalence increases with aging.⁵ CKD increases the complications and mortality rates in COVID-19 patients, and it increases susceptibility to COVID-19 infection.⁶

One of the most frequent poor prognostic complications of COVID-19 infection is coagulopathy.⁷ Previous studies have demonstrated that 20% of COVID-19 patients with mild-to-moderate symptoms and almost all severe and critical cases developed coagulopathy.⁸ Coagulopathy in COVID-19 patients suffering from CKD (CKD/COVID-19 patients) may be augmented by

Coagulopathy and derangements in the coagulation parameters are significant features of COVID-19 infection, which increases the risk of disseminated intravascular coagulation, thrombosis, and hemorrhage in these patients, resulting in increased morbidity and mortality. In times of COVID-19, special consideration should be given to patients with concurrent chronic kidney disease (CKD) and COVID-19 (CKD/COVID-19 patients) as renal dysfunction increases their risk of thrombosis and hemorrhage, and falsely affects some of the coagulation factors, which are currently utilized to assess thrombosis risk in patients with COVID-19. Hence, we believe extra attention should be given to determining the risk of thrombosis and bleeding and optimizing the timing and dosage of anticoagulant therapy in this unique population of patients. CKD/COVID-19 patients are considered a high-risk population for thrombotic events and hemorrhage. Furthermore, effects of renal function on paraclinical and clinical data should be considered during the evaluation and interpretation of thrombosis risk stratification. Individualized evaluation of clinical status and kidney function is necessary to determine the best approach and management for anticoagulant therapy, whereas there is a lack of studies about the population of CKD/COVID-19 patients who need anticoagulant therapy now.

Key words: Anticoagulation therapy, chronic kidney disease, coagulation system, COVID-19, D-dimer

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their preexisting predisposition to thrombosis and bleeding. However, to the best of our knowledge, there are no studies that investigate the utilization of anticoagulants in the management of CKD/COVID-19 patients.

This narrative review aims to review the implications of COVID-19 in CKD patients and the current challenges associated with the management of coagulopathy in CKD/COVID-19 patients.

METHODS

For this review, a systematic literature search was conducted to investigate the coagulopathy among COVID-19 patients who suffer from CKD, using Medline, Embase, Cochrane Database of Systematic Reviews via Ovid, CINAHL via Ebsco, and PubMed, up to April 30, 2020. We were not able to find any original research or systematic reviews, specifically considering coagulopathy treatment in COVID-19 patients with CKD. Therefore, all relevant papers that investigated the coagulopathy among COVID-19 patients, as well as papers that examined coagulopathy treatment among CKD patients, were retrieved and discussed by three experts, two in the field of hematology and one in nephrology.

REVIEW

Mechanism of hypercoagulability in COVID-19

CKD increases the risk of thrombosis and bleeding due to the effects of renal failure on platelets and the coagulation cascade. The effects of SARS-CoV2 and cytokine storm aggravate this predisposition to coagulopathy in CKD patients. SARS-CoV-2 utilizes S protein to bind angiotensin-converting enzyme-2 receptor, expressed on the surface of various body cells, including the lung alveolar epithelial cells, vascular endothelium, and renal tubules.[7] The virus–receptor attachment initiates a cytokine storm from the rapidly rising pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin-1, interleukin-2, interleukin-6, and interleukin-12. This leads to systemic inflammation and further activates platelets, leukocytes, and endothelium, which subsequently causes generalized vasculitis, microangiopathy, and microthrombosis formation. In addition, direct invasion of vascular endothelium by SARS-CoV-2 (endotheliopathy) promotes tissue factor expression, coagulation pathway activation, and thrombin formation.[8]

Free thrombin circulation caused by the mechanisms mentioned above is accompanied by concurrent inhibition of anticoagulation mechanisms, such as antithrombin III, tissue factor pathway inhibitor, and proteins C and S. This procoagulant-anticoagulant imbalance results in fibrin deposition and the development of extensive microthrombosis and disseminated intravascular coagulation (DIC).[8] Notably, the aforementioned vascular injury and hypercoagulable state are two of Virchow’s triad factors that predispose patients to develop thrombosis [Figure 1]. The third factor, venous flow reduction, is also present in critical cases, since immobility, dehydration, hypotension, and sedation in these patients lead to venous stasis. The simultaneous severe hypoxia and sepsis further activate the coagulation system in COVID-19 patients.[8,9]

CLINICAL MANIFESTATIONS

Coagulation system abnormalities and direct effects of COVID-19 on kidneys are two essential aspects when analyzing clinical manifestations of CKD/COVID-19 patients [Figure 2]. Recent studies have demonstrated that kidneys are a potential target organ in COVID-19 infection. COVID-19-related kidney injury in patients with CKD worsens the kidney function and leads to rapid deterioration and even death. Kidney injury is observed in 20%–63% of hospitalized COVID-19 patients and is associated with more severe disease and higher mortality rates. Studies identified hematuria, elevated creatinine levels and blood urea nitrogen (BUN), evidence of acute tubular necrosis, and abnormalities in the renal computed tomography (CT) scan of these patients.[10,11]

The intensity and incidence of the hypercoagulability presentations are higher in CKD/COVID-19 patients. These presentations range from arterial and venous thromboembolism (VTE), such as pulmonary embolism (PE)
and renovascular thrombosis, to DIC and end-organ damage. The reported incidence of VTE varies in the previous studies, between 1.1% in patients admitted to hospital wards other than intensive care unit (ICU) and up to 36.0% in ICU patients.\[12,13]\n
DIC in COVID-19 infection is more of a prothrombotic DIC than a bleeding tendency and induces multi-organ damage [Figure 3].\[6\] Some manifestations of the end-organ injury include shock, cardiogenic-like pulmonary edema, acute kidney injury, transient myocardial ischemia with rapid left ventricular function deterioration, acute transient mesenteric ischemia, cerebral infarcts, ischemic limb, and petechial skin rash.\[8\]

**LABORATORY CHANGES**

COVID-19’s effects on the hematopoietic system and the resulting coagulopathy alter the coagulation markers. Prothrombin time (PT), partial thromboplastin time (PTT), thrombin time, fibrin degradation products (FDPs), D-dimer, fibrinogen, and platelets are mainly affected coagulation factors, which are indicators of intrinsic, extrinsic, and common coagulation pathways and secondary hyperfibrinolysis.\[14\] High von Willebrand factor (VWF) activity, factor VIII levels, and elevated antiphospholipid antibodies have also been reported in some studies, and their effects on hypercoagulability in COVID-19 is under investigation.\[9\] Kidney function affects many of the coagulation factors. The levels of markers such as VWF, fibrinogen, factor VII, factor VIII, and D-dimer are higher in CKD patients, which escalate the effects of COVID-19 on coagulation parameters.\[15\]

**DISEASE SEVERITY AND RISK ASSESSMENT**

To prevent, identify, and better manage coagulopathy, a complete individualized thrombosis and hemorrhagic risk assessment is necessary for all COVID-19 patients arriving at health-care facilities, which is done with a complete clinical and imaging evaluation to determine disease severity and the utilization of laboratory markers and assessment tools.

Older age, comorbidities such as CKD, and obesity (body mass index $\geq 30$ kg/m$^2$) are some of the predictive factors that increase the disease severity, which may increase the thrombosis risk in COVID-19 patients.\[9\]

Previous studies have shown that, in general, CKD increases the risk of outpatient and inpatient pneumonia and its associated mortality rate to up to 14–16 times.\[16\] Similarly, the presence of CKD raises COVID-19 severity and mortality rates.\[11\] Hence, it seems reasonable to consider CKD/COVID-19 patients as a high-risk group.

Padua, IMPROVE, and Caprini tools are the recommended assessment models for VTE risk stratification in routine patients.\[9\] However, more attention has been given to utilization of coagulation profile markers and their dynamic changes in thrombosis and DIC risk assessment of patients with COVID-19.

The International Society on Thrombosis and Hemostasis (ISTH) has developed sepsis-induced coagulopathy (SIC) for early recognition of sepsis associated [Table 1]. These criteria should be used in all
patients with COVID-19 infection, and a SIC ≥ 4 should be highly considered as an indicator of early DIC.[17]

The importance of D-dimer as a thrombosis assessment tool has also grown significantly. Studies have shown that higher D-dimer and FDP values in COVID-19 patients were significantly associated with higher mortality rates. According to a study, an increased level of D-dimer (>1.5 μg/mL) can predict the risk of VTE with 85% sensitivity, 88.5% specificity, and 94.7% negative predictive value.[19] In a similar study, a D-dimer value of >1 mg/L resulted in an increase in inpatient mortality.[20]

Table 1 presents the potential effect of an eGFR adjusted d-dimer cutoff value to improve the exclusion of PE reported by different studies.[20‑23]

**ANTICOAGULANT THERAPY, KIDNEY FAILURE, AND COVID-19**

Currently, there are no investigations on anticoagulant therapy, thrombosis, and bleeding risk assessment in CKD/COVID-19 patients, and all the available guidelines consider the same approach as those with no history of kidney disease. This results in ambiguity while caring for COVID-19 patients with CKD.

Many reasons make the current approach insufficient in patients with CKD. The most important is the existing effects of kidney failure on the coagulation system and alteration of the coagulation profile, which increases the risk of bleeding and thrombosis and limits the utilization of coagulation markers for risk assessment in these patients.[24] The already existing coagulopathy in CKD patients is escalated by COVID-19 infection. Hence, it is reasonable to consider individualized clinical and paraclinical DIC, thrombosis, and hemorrhage risk assessment in all CKD/COVID-19 patients who are hospitalized or isolated at home according to their eGFR.

Whether or not to start anticoagulant therapy and its optimum dosage are the main challenges that frontline physicians are tackling. As mentioned above, all patients should be evaluated individually for anticoagulant treatment as a part of initial management and daily in the course of the disease.[25] The recommendations regarding thromboprophylaxis in COVID-19 patients are diverse and evolving among the existing guidelines.

Many studies and guidelines like some Chinese guidelines currently suggest initiation of anticoagulant therapy based on thrombosis risk assessment tools, like D-dimer values, and dynamic dosage adjustment according to changes in D-dimer throughout the treatment.[21] However, ISTH recommends starting anticoagulant therapy in all hospitalized patients at the time of admission regardless of the disease severity and D-dimer value.[18] Table 3 shows current recommendations in respect to prophylactic anticoagulant therapy in COVID-19 patients.[16,7,25,26]

Currently, considering the increased mortality rates in patients with CKD and a higher risk of DIC and thrombosis in these patients, it is reasonable to consider these patients as a particularly high-risk population and administer prophylactic anticoagulant therapy in all hospitalized CKD/COVID-19 patients.

| Item | Score | ISTH overt DIC | SIC range |
|------|-------|----------------|-----------|
| Platelet count (× 10⁹/L) | 2 | <50 | <100 |
| | 1 | ≥50, <100 | ≥100, <150 |
| FDP/D-dimer | 3 | Strong increase | - |
| | 2 | Moderate increase | - |
| Prothrombin time (PT) ratio | 2 | ≥6 s | (>1.4) |
| | 1 | ≥3 s, <6 s | (>1.2, ≤1.4) |
| Fibrinogen (g/mL) | 1 | <100 | - |
| SOFA score | 2 | - | ≥2 |
| | 1 | - | 1 |
| Total score for DIC or SIC | ≥5 | ≥4 |

**Table 2**

**Table 1: International Society of Thrombosis and Hemostasis and Hemostasis sepsis-associated disseminated intravascular coagulation**

**Table 2**

**Table 3**

**Table 1** presents the potential effect of an eGFR adjusted d-dimer cutoff value to improve the exclusion of PE reported by different studies.[20‑23]
According to ISTH recommendations, a standard recommendation is that anticoagulant therapy is recommended based on thromboembolism risk. Anticoagulant therapy with LMWH/UFH can be used in patients with severe COVID-19-related coagulopathy should be assessed with ISTH DIC scores. Moderate and therapeutic doses are only advised in participants of clinical trials. Anticoagulant therapy is recommended based on thromboembolism risk. LMWH and fondaparinux are recommended anticoagulant agents, however, doses were not specified. Anticoagulant therapy with LMWH/UFH can be used in patients with severe coagulation abnormalities or signs of coagulopathy if no contraindications were given standard prophylactic dose, while 30% received intermediate dose and 10% received therapeutic dose. There is no unified recommendation on the approach regarding thromboprophylaxis dosage in hospitalized patients with COVID-19 as well as CKD/COVID-19. Bikdeli’s consensus estimated that in the time of that study, 60% of all patients receiving anticoagulant therapy around the world were given standard prophylactic dose, while 30% received moderate dose and the remaining 10% received therapeutic dose. According to ISTH recommendations, a standard weight-adjusted prophylactic dosage for VTE prophylaxis should be administered in all hospitalized patients, and the risk of heparin-induced thrombocytopenia is significantly lower in patients taking LMWH compared to those taking UFH.

The medication choice and dosage in CKD patients is highly dependent on the hospitalization status and the degree of kidney dysfunction in these patients. It seems like the preferred anticoagulant agent in patients with CKD is heparin derivatives. Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), fondaparinux, or direct oral anticoagulants (DOACs) can be used for patients with creatinine clearance (CrCl) values of more than 30 mL/min, and UFH or an adjusted dose of LMWH is recommended for those with CrCl under 30 mL/min [Table 4].

Heparin derivatives are preferred over DOACs as DOAC absorption may become affected by COVID-19-related hepatic dysfunction, low appetite, and decreased oral intake and because of the unavailability of DOACs’ antidote in health-care centers. Besides, proposed antiviral and anti-inflammatory properties of heparins may also reduce the viral invasion and break the vicious cycle of inflammation and coagulopathy in these patients [Figure 4].

LMWH seems to be preferred to UFH in noncritically ill hospitalized patients, as it has a longer half-life, which leads to less blood draws and health-care exposure. In addition, the risk of heparin-induced thrombocytopenia is significantly lower in patients taking LMWH compared to those taking UFH.

Table 2: Potential effect of an estimated glomerular filtration rate adjusted D-dimer cutoff value to improve the exclusion of pulmonary embolism reported by different studies

| Author/date | Normal (≥ 90) | Mild (60-89) | Mod (30-59) | Sever (<30) |
|-------------|--------------|--------------|-------------|-------------|
| Xin/2016 (mg/L)/medians of D-dimer | 291.5 (mg/L) | 950 (3310) | 1901.5 (3920) | 2250 (3780) |
| Vincent/2019/D-dimer (mg/L), median (IQR) | 950 (1800) | 1500 (3310) | 505±320 | 2250 (3780) |
| Meng-jie/2016 D-dimer (mg/mL) | 257±116 | 425±277 | 505±320 | 842±496 |

Table 3: Current recommendations in respect to prophylactic anticoagulant therapy in COVID-19 patients

| Study | Recommendations |
|-------|-----------------|
| ISTH[1] | All patients hospitalized with COVID-19 should receive prophylactic dose LMWH if no contraindications (active bleeding and platelet count <25×10⁹/L). Recommendation for VTE prophylaxis dosage is standard weight-adjusted dose, whereas ICU patients could receive intermediate dose. |
| American Society of Hematology (written statement updated April 17, 2020)[25] | LMWH and fondaparinux are recommended anticoagulant agents, however, doses were not specified. |
| Chinese expert consensus on diagnosis and treatment of coagulation dysfunction in COVID-19[7] | Moderate and therapeutic doses are only advised in participants of clinical trials. |
| European Society of Cardiology European Heart Journal (Atallah et al.) Published April 30, 2020[24] | COVID-19-related coagulopathy should be assessed with ISTH DIC scores. |
| | Anticoagulant therapy with LMWH/UFH can be used in patients with severe coagulation abnormalities or signs of coagulopathy if no contraindications were given standard prophylactic dose, while 30% received intermediate dose and 10% received therapeutic dose. |
| | In high-risk patients who are not admitted to ICU, enoxaparin 1 mg/kg SUBCUT BID or IV infused heparin can be utilized. |
| | In low risk patients, D-dimer values determine the dosage of anticoagulant therapy. |
| | If D-dimer >3 mcg/mL: Enoxaparin 1 mg/kg SUBCUT BID should be administered. |
| | If D-dimer 0.5 to 3 mcg/mL: Enoxaparin 40 mg SUBCUT BID should be administered. |
| | If D-dimer <0.5 mcg/mL: Then enoxaparin 40 mg SUBCUT daily should be administered. |

LMWH=Low-molecular-weight heparin; UFH=Unfractionated heparin; ISTH=International Society on Thrombosis and Hemostasis; DIC=Disseminated intravascular coagulation; CRP=C-reactive protein; ICU=Intensive care unit.
intermediate dose could be considered for ICU patients and in clinical trials.\[^6\] In addition, few guidelines recommended changing the prophylaxis dosage from the standard dose to intermediate or high dose based on D-dimer levels, SIC score, and patients’ clinical condition. The University Health Network guideline suggests high-dose prophylactic anticoagulant therapy (enoxaparin 0.5 mg/kg SC BID) in critically ill patients with D-dimer levels >2–3 μg/mL or SIC score ≥4 [Table 3].\[^{28}\]

However, there is not enough evidence to confirm the beneficence of these approaches in CKD/COVID-19 patients. Thus, it is reasonable to administer a standard prophylactic dose in CKD/COVID-19 patients; moderate- and high-dose prophylaxis could be used in clinical trials.

In addition, patients with evidence of venous or arterial thrombosis or other clinical indications for the therapeutic-dose anticoagulants, such as atrial fibrillation and valvular heart disease, should receive therapeutic dose anticoagulants if there are no contraindications [Table 4].\[^{32}\]

The DIC risk should be evaluated in all hospitalized patients with COVID-19 infection as well as CKD/COVID-19. ISTH score ≥ 5 and SIC score ≥ 4 are indicators of overt and early DIC in patients\[^{17}\] which are currently used for COVID-19 and CKD/COVID-19 patients. Unfortunately, the effect of renal impairment on the interpretation of ISTH and SIC criteria (PT, FDP, fibrinogen, D-dimer, and platelet) has not been considered but is used. After diagnosis of DIC, the initial step in the management of DIC in COVID-19 patients is addressing the underlying cause. Furthermore, heparin derivatives modify the course of prothrombotic DIC by decreasing thrombin production. If bleeding occurs, the management depends on hematologic factors. Blood products or cryoprecipitate may be used to manage bleeding in these patients.

There is no agreement on prophylaxis continual and its duration after hospitalization in CKD/COVID-19 patients. It is safe to consider the patients for postdischarge VTE prophylaxis individually, with careful assessment of thrombosis versus bleeding risk, and patients’ status at discharge. Bikdeli’s consensus group recommends extended prophylaxis with LMWH or DOACs for up to 45 days after discharge, especially in those with concurrent immobility, comorbidities such as active cancer and CKD, and elevated D-dimer, if no contraindication is present.\[^{29}\] However, regarding addressing this issue in CKD/COVID-19 patients, it is necessary to carry out specific research.

Anticoagulant therapy in patients with CKD requires strict follow-up and dose adjustment according to the anticoagulant agent and renal function. Anti-Xa levels should be ordered in patients receiving LMWH or DOACs for up to 45 days after discharge, especially in those with concurrent immobility, comorbidities such as active cancer and CKD, and elevated D-dimer, if no contraindication is present.\[^{29}\] However, regarding addressing this issue in CKD/COVID-19 patients, it is necessary to carry out specific research.

There are no specific guidelines for anticoagulant therapy in self-isolating CKD/COVID-19. There is no evidence

### Table 4: Recommended heparin dosages

| Standard prophylactic dose | Unfractionated heparin | Enoxaparin | Fondaparinux |
|---------------------------|------------------------|------------|--------------|
| 5000 units SQ q12h        | 40 mg SQ q24h          | 2.5 mg SQ q24h |
| Renal adjustment of prophylactic dose | No dose adjustment required | CrCl 15-29 mL/min: 30 mg SQ q24h | CrCl 15-29 mL/min: 1.25 mg SQ q24h |
| Standard therapeutic dose | ACS: 60 unit/kg bolus + 12 units/kg/h infusion | CrCl <15 mL/min or renal replacement therapy: Consult Pharmacy | CrCl <30 mL/min: Consult Pharmacy |
| Renal adjustment of therapeutic dose | No dose adjustment necessary | 1 mg/kg SQ q12h (for normal renal function) | Avoid use if fluctuating renal function |

ACS=Acute coronary syndrome; AFib=Arterial fibrillation; SQ=Subcutaneous route; CrCl=Creatinine Clearance; VTE=Venous thromboembolism

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**Figure 4:** Anticoagulant medication, heparin, has potential positive impacts on COVID-19. Heparin has potential antiviral capabilities as it is hypothesized that it inhibits the binding of angiotensin-converting enzyme-2 to the S1 proteins of severe acute respiratory syndrome-associated coronavirus-2. Anti-inflammatory tendency of heparin may be due to the downregulation of pro-inflammatory cytokine, interleukin-6. Further, heparin has the potential of protecting the endothelium from histones during COVID-19 infection.
that COVID-19 infection affects the kidneys in patients with mild-to-moderate illness, and the risk of thrombosis is not significantly increased in these.\textsuperscript{[11]} Hence, patients with mild-to-moderate symptoms who are self-isolating at home are mainly advised to stay active and hydrated to reduce the risk of hypercoagulability. Anticoagulant therapy is recommended if VTE risk factors are present and if no contraindications.\textsuperscript{[33]} The most-known risk factors are comorbidities such as active cancer, heart failure, and previous VTE limited mobility. If contraindications are present, intermittent pneumatic compression is a reasonable option in these patients.\textsuperscript{[32]}

Regarding previously prescribed Vitamin K antagonists (VKAs) in patients isolating at home, it is currently preferred to switch to DOACs or LMWH to limit patients’ contact with health-care workers during the procedures required for international normalized ratio monitoring in these patients.\textsuperscript{[33]} However, increasing the monitoring intervals for 8 weeks, or longer if feasible, has been proposed in stable patients on warfarin with a time-in-therapeutic range of more than 60%.

**CONCLUSIONS**

Currently, there is no approved approach to prophylaxis anticoagulant therapy in CKD/COVID-19 patients. At this moment, thrombosis, DIC risk assessment, and anticoagulation therapy approach in these patients are carried out similarly to the patients without CKD, whereas there are many challenges here. Patients with preexisting CKD should be acknowledged as a particular or high-risk population, as COVID-19 infection increases the risk of hypercoagulability and bleeding and raises the morbidity and mortality rates in these patients compared to the healthy population.

In addition, significant alteration of coagulation markers by the level of kidney dysfunction in patients with CKD sets them apart from COVID-19 patients without a preexisting history of CKD.

Hence, it is reasonable to consider the degree of remaining kidney function and its effects on the coagulation system and profile as a part of risk assessment and decision-making for anticoagulant therapy in these patients, and these are adjusted based on GFR.

Because almost all patients with the impaired renal function had elevated D-dimer and disturbance in coagulation factors irrespective of the presence of thrombosis, studies should be performed to determine the relationships among eGFR, D-dimer, and other coagulation factors, also defining the adjusted cutoffs and tools for prediction thrombosis and DIC in CKD/COVID-19 patients. Moreover, research should be specifically conducted to determine the best anticoagulant therapy approach in these special patients.

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**Conflicts of interest**

There are no conflicts of interest.

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