A review of pathophysiology, mortality, risk factors and protective measures of acute kidney injury in COVID-19 patients with underlying kidney disease and kidney transplant recipients

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ABSTRACT

Acute kidney injury (AKI) is the second prevalent organ damage among COVID-19 infected individuals, which mainly affects those with critical diseases or underlying kidney disorders. Emerging data have suggested that AKI is associated with adverse outcomes, severe COVID-19 disease, and high mortality. However, the true nature and pathophysiology of COVID-19-associated kidney injury, and its effect on patients with underlying kidney diseases and transplant recipients, still remains controversial. Accordingly, this review study aimed primarily to describe the history of AKI in COVID-19 infected patients and to achieve a robust understanding of the latest findings on the mechanism of the injury. Secondly, this systematic and precise review of the literature concerning the aspects of AKI in infected patients with chronic kidney disease and transplant recipients provided a comprehensive report of mortality in these individuals. Finally, the present research suggested the possible protective measures that physicians can take to prevent, control, and treat this condition. Our study paves the way for future works with a more robust methodology to better understand COVID-19-related kidney injury.

Implication for health policy/practice/research/medical education:
Direct viral injury of the kidney is a unique feature in the pathogenesis of COVID-19-related acute kidney injury.


Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially reported in Wuhan, Hubei province, China, in December 2019, which rapidly spread to the world with more than 207 million confirmed cases and over 4.3 million deaths globally on August 16, 2021. To date, over 4.7 billion doses of vaccine have been administered globally. However, there is still a long way to go to global vaccination and control of the virus, and concerns are rising if the current vaccines are effective against new variants of the COVID-19 virus (1).

COVID-19 most commonly presents with weakness, fever, cough, fatigue, and diarrhea; meanwhile, the presentation can range from asymptomatic infection to respiratory or multi-organ failure in critical cases. While initial reports indicated that acute kidney injury (AKI) was negligible, a growing number of studies showed that AKI is prevalent in COVID-19 patients, particularly in critical cases admitted to the intensive care unit (ICU) of hospitals. At the moment, kidney is recognized as the
second most commonly affected organ by COVID-19 after lungs. Emerging evidence has also suggested that COVID-19-related AKI is associated with adverse outcomes, including worsening comorbid disease, severe COVID-19, and mortality (2).

COVID-19 has a unique implication for patients developing AKI and chronic kidney disease (CKD) and kidney transplant recipients (KTRs). In this review, we discussed the development of AKI in COVID-19 patients, emphasizing possible pathophysiology and protective measures against the COVID-19 virus. Additionally, we provided a comprehensive overview of the effects of COVID-19 on CKD and KTRs.

**Pathophysiology**

The mechanism of renal injury by COVID-19 is described through different pathways (Figure 1). The virus might directly affect kidney tissue. SARS-COV-2 enters the host cells via two distinct receptors, namely angiotensin-converting enzyme 2 (ACE2) receptors (facilitated by TMPRSS2) or CD147 receptors (on the basolateral surface) (3). ACE2 receptors in the kidney are expressed at higher rates than the lung tissue. Moreover, in the kidney, ACE2 receptors are mainly expressed on the surface of the brush border of proximal tubules and podocytes. The NH2-terminal peptidase domain of the ACE2 receptor affects binding. TMPRSS2 is a protease on the surface of tubular cells and podocytes, which plays an important role in processing SARS-COV-2 spike proteins (Figure 2). The presence of ACE2 and TMPRSS2 can justify the findings of tubular damage in COVID-19 infection. CD147 is found to impact cytokine release and to promote renal fibrosis in animal models. A low pH-dependent endosomal cysteine protease cathepsin also facilitates the SARS-CoV entry. Chloroquine drug increases endosomal pH and may thus prevent the entry mechanism (4).

Replication of the virus in renal cells is responsible for direct injury (5). Viral particles and evidence of diffuse proximal tubular injuries, such as lumen dilation, vascular degeneration, and brush border disarrangement, can be seen in electronic microscopy. An immunohistochemistry study on tubular cells detected viral nucleocapsid fragments. Moreover, RNA and viral structures are detected through real-time polymerase chain reactions in the urine of SARS-CoV-2 infected patients. A postmortem investigation revealed an association of renal tropism in COVID-19 patients with disease severity and AKI (6). Acute tubular injury in histopathological studies in autopsies can explain the low-level hematuria and proteinuria in SARS-CoV-2. Reports of collapsing segmental glomerular sclerosis as a glomerular pathology might be attributed to higher grades of proteinuria. Proteinuria and hematuria, also in addition to leukocyturia, could be hypothetically considered as hallmarks of podocyte injury due to viral proliferation. Single-cell RNA sequencing detected viral RNA in proximal tubule cells and parietal cells (7). A recent paper showed the sedimentation of erythrocytes in renal parenchymal capillary vessels, with endothelial damage and obstruction, which could cause parenchymal cells to necrosis and subsequent fibrosis. The evidence mentioned above raises the issue of SARS-CoV-2 directly infecting and injuring renal parenchyma.

![Figure 1. Mechanism of acute kidney injury via direct and indirect pathways.](image-url)
SARS-CoV-2 could indirectly lead to kidney injury through cytokine storm, altered immune response, hypercoagulopathy, microangiopathy, rhabdomyolysis, and altered hemodynamics (8). Studies have associated SARS-CoV infection with altered coagulation as well as higher D-dimer and fibrinogen level. The hypercoagulopathy could result from several mechanisms: Angiotensin II activation, cytokine storm, macrophages and endothelium activation, along with tissue factors (9). Histopathologic findings of a study confirmed the presence of thrombi, which might be a possible cause for parenchymal infarction. An altered immune response due to viral infection could possibly contribute to kidney injury. SARS-CoV-2 can activate lymphocytes via ACE2 receptors that lead to cytokine release, activation-induced cell death, and lymphopenia (8). Infiltration of macrophages into the interstitium, complement deposits, and lymphocytes could be the leading cause of kidney tissue damage (5). After SARS-CoV-2 binding to ACE2 receptors, they are downregulated (8). Since ACE2 is counter-regulatory to ACE1, this process could increase Angiotensin II and subsequent vasoconstriction, complement activation, microangiopathy, and eventually kidney injury. Hemodynamic changes due to acute lung injury and subsequent release of cytokines and reduction in kidney perfusion can also play a role in kidney injury (10,11). Moreover, the aggressive use of diuretics in lung edema and the use of nephrotoxic drugs, such as chloroquine, can lead to AKI (12,13). In addition, SARS-CoV-2-associated cardiomyopathy, as an indirect factor, could yield hemodynamic instability, insufficient renal perfusion, and acute renal injury (11,14). A postmortem study showed that rhabdomyolysis associated with SARS-CoV-2 infection could cause cast deposits and increased creatine kinase in the kidneys. Severe SARS-CoV-2 is correlated with high cytokine and pro-inflammatory factors (15). Cytokine storm, which is known for the release of cytokines like IL-6, IL-2, IL-7, IL-10, and TNF-alpha, is associated with SARS-CoV-2 infection. Cytokine release could be responsible for microvascular dysfunction, changes in vascular permeability, and dysfunction of microcirculation, and kidney injury (11,16).
AKI in infected patients with chronic kidney disease

Generally, patients with underlying kidney disorders, such as CKD, are at a higher risk of infection. Due to immune system dysregulation, patients with CKD and, more specifically, end-stage renal disease (ESRD) are at a higher risk of developing severe COVID-19 disease with increased mortality (17-21). Additionally, CKD is associated with a more severe SARS-CoV-2 infection (22). Radiologic evaluations in CKD patients with COVID-19 disease illustrated an influx in the incidence of abnormal findings (23). Regardless of CKD itself, hypertension and diabetes are known as comorbidities of SARS-CoV-2 infection, which are more common in CKD patients (22, 24). Each of these comorbidities is an independent risk factor of severe SARS-CoV-2 conditions (25). Compared to the other underlying conditions, such as cardiovascular diseases or diabetes, CKD accounts for an increased rate of ICU admission. It has been reported that pneumonia-related death is 15 times higher in CKD than that in the general population. Thus, respiratory manifestations of SARS-CoV-2 in CKD patients can be more detrimental.

In COVID-19 infection, CKD is a predisposing factor for the severe form of AKI. Even patients who survive AKI might be at a higher risk of long-term complications, such as CKD. Laboratory and clinical findings have demonstrated that CKD patients with SARS-CoV-2 infection are at a higher risk of AKI if they have increased serum creatinine (26). Selby et al suggested monitoring patients with SARS-CoV-2-associated AKI injury for further development to CKD. Moreover, Cheng et al. proposed urinary micro-albumin, β-2 microglobulin, KIM-1 (kidney injury molecule-1), NGAL (Neutrophil gelatinase-associated lipocalin), [TIMP-1]•[IGFBP7] ([tissue inhibitor of metalloproteinase]• [insulin-like growth factor-binding protein 7]), serum cysteine, and renal biopsy as complementary evaluation tests for CKD prediction (22).

In view of the downregulation of ACE-2 in SARS-CoV-2 infection, CKD patients show a pro-inflammatory state resulted from higher angiotensin II (Ang II) and cytokines, a finding that was previously suggested in previous investigations (22-27). In their work, certain markers, such as CD147 and transforming growth factor-beta as fibrosis markers, were reported to be high in CKD patients (27). Thus, they are at a higher risk of fibrosis and AKI. Furthermore, patients with a more severe form of CKD and more elevated serum creatinine are likely to have an increased count of lymphocytes. Regarding the changes in the immune cells, these patients may show a more severe form of systematic inflammatory response that may lead to a worse scenario for multi-organ damage (26). Hospital transmission of SARS-CoV-2 was suggested to be the most common pathway for infection. We know that renal replacement therapy (RRT)-receiving patients who need regular hospital visits are at risk. As immunocompromised patients, they are also in regular contact with health care providers and other patients, and have a higher chance of COVID-19 infection. Due to the possible activation of unfavorable pathways in ACE-2 binding of novel COVID-19 virus, there are concerns about the regular treatment of CKD patients with ACE inhibitors. Regarding the isolation protocols and limited continuous renal replacement therapy (CRRT) facilities, patients with ESRD face limitations and hardships for their regular RRT. The need for post-RRT even aggravates these limitations in new cases of severe SARS-CoV-2-associated AKI (23-28). Lockdowns in cities may also affect the regular treatment plan in patients with ESRD. Eventually, patients with predisposing renal conditions, such as CKD, are further threatened by more severe infection due to COVID-19. Special care and considerations are needed for these populations.

AKI in infected kidney transplant recipients

The rate of infection with SARS-CoV-2 in KTRs is higher than that in the general population. Immunosuppression and the relevant comorbidities make KTRs susceptible to acute SARS-CoV-2 infection. Some of the most prevalent comorbidities among KTRs are hypertension, obesity, lung disease, diabetes, and underlying heart conditions. These comorbidities are counted as independent risk factors for severe COVID-19 infection and multi-organ failure and death. We assume that the concomitance of immunodeficiency with underlying comorbidities can face the organ recipients at significant risk of mortality. In the literature, the mortality rate of KTRs with SARS-CoV-2 infection is reported high, 18% to 32% (29-33)— among all the causes of death— compared to 1% to 5% in the average population (29). In a single-center study, Alberici et al reported that in the first week of hospitalization, over 75% of KTRs with COVID-19-associated pneumonia experienced a fast deterioration of conditions, 25% of whom died (34). Patients who need ICU admission may face a higher mortality rate of up to 52% (30, 31). COVID-19-associated mortality in KTRs is reported to be even higher than that among the elderly without a kidney transplant. Therefore, being a KTR could be a more fatal risk factor compared with old age (29).

Although a number of researchers may advise that KTRs who get infected with SARS-CoV-2 need to decrease or stop receiving immunosuppressive treatment, Cravedi et al (33) showed that immunosuppression withdrawal is not associated with survival. Husain et al, also stated that tapering immunosuppressive drugs does not lead to mortality in outpatients (35).

On the other hand, in a study by Akalin et al,
stopping immunosuppressive drugs, besides the use of anti-inflammatory drugs, did improve the outcome of hospitalized patients in terms of mortality (29). In conclusion, it is yet to be investigated that how immunosuppression can affect the survival of KTRs.

Due to the lack of immune response, KTRs are expected to show a more subtle form of symptoms, particularly in the early days of infection (30). Hence, physicians should be more sensitive concerning diagnostic tests utilization, such as RNA polymerase chain reaction, for detecting SARS-CoV-2 infections in these patients. In the study by Huang et al on KTRs with new COVID-19 disease, fever was not a prominent initial symptom (15). In contrast, Cravedi et al demonstrated that fever, dyspnea, myalgia, and diarrhea are the main symptoms on admission to the hospital (33). These findings are comparable to a study by Husain et al, which found fever, cough, and dyspnea as initial symptoms in KTRs with SARS-CoV-2 infection (35).

Even though there is no evidence that the mechanism of COVID-19-associated AKI in KTRs differs from that in normal populations, the extent of injury seems to be more comprehensive. Serum levels of inflammatory factors, such as procalcitonin and IL-6, have been observed to be higher in KTRs who failed to survive. The known mechanism of cytokine storm—initiated by COVID-19 and release of cytokines—seems to play a role in the end-organ damage and worsening of conditions and mortality in KTRs. Tocilizumab is an IL-6 antagonist suggested to affect the prevention of cytokine storm. Laboratory findings have confirmed that T-cells, including CD8 and CD4, are decreased in KTRs with novel SARS-CoV-2 infection. Thus, their impaired immune system might show a weaker response to the virus replication and subsequently yield a faster disease progression and organ dysfunction. The baseline level of lymphocytes was reported to be higher in KTRs who survived SARS-CoV-2 infection compared to that in non-survivors. It could be therefore concluded that the count of lymphocytes is a prognostic factor in the severity and mortality of SARS-CoV-2 in KTRs. The novel COVID-19 virus is included in pathways of lymphocyte cell death through binding to ACE2 receptors. Both the predisposing immune system susceptibility in KTRs and the effect of the virus on T-cells can simultaneously lead to a more prominent altered state in lymphocytes and thus weaker immune response in the host.

Other potential factors, like social and economic status (for example, poverty and low educational level) may play a role in the severity and rate of death in both general population and KTRs (36). KTRs should have medical visits regularly. Given the COVID-19 pandemic, regular contact with health facilities by this immunosuppressed and high-risk population may be irrational. Furthermore, these follow-ups are essential for detecting possible signs of rejection or infections and adjusting the dose of drugs. The best solution to this dilemma is teleconsultation, which can minimize the risk of transmission by reducing unnecessary hospital visits. It also helps us identify KTRs with symptomatic COVID-19 and help them with other problems related to their transplantation (37). Other solutions discussed before are preparing places and settings with a low probability of contamination, social distancing, and monitoring other comorbidities. One remarkable point to consider is the procedure of transplantation, which is too risky to be conducted during this pandemic (especially in patients with comorbidities) due to the two following reasons: the donor with positive COVID-19 can transmit the infection to the recipient; in the first few months after transplantation, the recipients should administer high doses of immunosuppressive drugs which make them susceptible to severe infections, including COVID-19 in KTR (38). We concluded that KTRs, as a highly susceptible population to COVID-19 infection, need specific considerations with regards to the risks they are facing during the pandemic.

Mortality

SARS-CoV-2 patients with kidney disease have a higher risk of mortality. More severe kidney injury is accompanied by more severe COVID-19 general conditions and the association between AKI and mortality increases with illness severity. The high number of patients with SARS-CoV-2 infection in ICUs, who receive RRT, confirms this finding. However, in AKI patients with COVID-19 disease, serum creatinine, blood urea nitrogen, proteinuria, hematuria, and stages of AKI could independently predict the mortality in the hospital. Higher stages of AKI lead to a higher rate of death. For note, factors such as higher age, diabetes, and hypertension yield higher rates of AKI. Likewise, patients with normal creatinine levels experience a better prognosis (28). CKD in COVID-19 infection has been associated with a poorer prognosis and might be a predisposing factor for higher mortality. Patients with CKD and those who receive RRT during their SARS-CoV-2 infection tend to have an increased rate of mortality. CKD patients who develop new AKI are less likely to survive. Compared to the general population, ESRD patients are at a higher risk of mortality due to SARS-CoV-2 infection. In the elderly and ICU-added patients, sepsis has been closely associated with AKI. In severe SARS-CoV-2 cases, with both sepsis and AKI, mortality rates were reported to increase. Previous investigators showed that, AKI in elderly patients puts them at higher risk of death compared to younger individuals; they therefore need special attention and further investigation (35-39).
The mortality rate of AKI in patients with COVID-19 was reported to be 93%, 35% (40), 11% (41), 90% (42), 52% (43), and 96% (44) in different studies. It should be noted that higher rates of AKI-associated mortality might arise from the biased selection of patients with higher disease severity (40-44). In a review study by Hansrivijit et al, the pooled estimated mortality in COVID-19 patients with AKI was 13%. Meta-analysis studies have indicated that pooled risk ratio of death is 4.6-15.27 in SARS-CoV-2-associated AKI compared to that in non-AKI patients. Previous research has mainly reported in-hospital death rates. Thus, limited data exist on post-discharge death rates of SARS-CoV-2-associated kidney injury. Moreover, the controversy in death rates suggests that other possible factors could affect the association between SARS-CoV-2 infection, kidney injury, and death. Patients with underlying kidney diseases or new-onset kidney injuries have a limited treatment choice and less chance to get included in new treatment trials (since they are often excluded) (43-45). Accordingly, the burden of high mortality rates in these patients seems to be harder to overcome. We concluded that the mortality of SARS-CoV-2-induced AKI is not distinctive from deaths caused by respiratory failure; in fact, there is sufficient evidence to confirm the impact of AKI as an independent factor on the mortality of COVID-19 patients (42-45).

**Protective measures**

Protective measures against kidney injury (Figure 3) associated with SARS-CoV-2 infection fit in three primary subscales: first, to prevent the possible direct/indirect causes of AKI; second, to improve the prognosis and outcomes of patients with AKI; third, to reduce the long-term sequel of AKI. We aimed to suggest and discuss the available methods to reduce the incidence of COVID-19-associated kidney injury since it can lead to limiting the burden of COVID-19, for instance, decrease disease severity, ICU admission, morbidity and mortality rates, and healthcare costs. To achieve these goals, we need to clearly understand the underlying causes, detect and monitor high-risk patients, know the benefits and risks of drugs, estimate the severity of patient’s conditions, and perform a well-timed and accurate intervention (45-47).

To prevent AKI, we should identify the well-known risk factors of developing AKI in COVID-19 infected patients. Most AKI risk factors are shared with non-COVID-19 patients with severe diseases, like hypertension, diabetes, cardiovascular diseases, previous kidney disease, liver dysfunction, and dehydration. Moreover, several possible preventable factors are mentioned in the pathophysiology section, including direct or indirect kidney injury associated with the SARS-CoV-2 virus. To the best of our knowledge, ACE-2 and CD147 receptors are the main binding sites for the entry of the virus. Thus, using the recombinant soluble form of ACE-2 can possibly limit virus entry and lower viral load by neutralizing viral spike proteins. Since ACE-2 receptors are highly expressed in the kidney cell, it could be assumed that the kidney benefits the most from this possible treatment. An in vitro study also showed potential benefits of CD147 inhibitor for preventing virus entry (3). Inhibition of TMPRSS2 might also weaken the viral entry because this protease facilitates the ACE-2 pathway. The virus endosomal entry relies on a low PH-dependent

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**Figure 3.** Protective measures against the AKI in hospitalized patients (illustration created with biorender.com).
protease called cathepsin in the host cells. Changes in cell PH with a particular drug, like chloroquine (which changes the cell pH), can hypothetically disrupt the entry and replication of the virus. We concluded that, the other suggested anti-viral therapies for COVID-19, which inhibit or disrupt viral replication assembly and release are not suitable in the presence of kidney injury (46,47).

Similar to direct mechanisms of kidney injury, it is possible to prevent or control indirect kidney injury in SARS-CoV-2 infection. As the main pathway for kidney injury, the cytokine storm is known through releasing various pro-inflammatory factors. Hypothetically, preventing the release or inhibiting the receptors of cytokines, besides anti-inflammatory drugs, would result in less severe inflammation and organ damage. Tocilizumab and sarilumab, as monoclonal antibodies against IL-6 receptors, can help to reduce the effect of IL-6 and control the subsequent damage to the kidney. It has been discussed that patients can potentially benefit from anti-TNF therapies, such as infliximab or adalimumab. Potentially, dysregulation of the immune system and activation of complements are controllable by preventing cytokine release. Hemodynamic instability can lead to kidney injury through the reduction in kidney perfusion. Activation of RAAS, cytokine storm, systemic inflammation, and changes in hemodynamics are the main elements of reduced kidney perfusion (11). Thus, precise monitoring and controlling of hemodynamics are highly conducive. Controlling cardiac ejection fraction with echocardiography, tight control of blood pressure, and proper fluid balance might help to prevent kidney injury, particularly in severe SARS-CoV-2 infection. Rhabdomyolysis, as a possible mechanism in indirect kidney injury, is preventable by adequate and well-timed fluid administration. Regarding the evidence of hypercoagulability and microangiopathy in the kidney, administration of a prophylactic or therapeutic dose of anticoagulants, notably when D-dimer levels increased, could help the prognosis and outcome of the patients. Adequate knowledge of pathophysiologic mechanisms and risk factors of kidney injury in SARS-CoV-2 infection can help us to manage and prevent the complications and consequences.

Underlying kidney diseases and AKI while infected with COVID-19 are followed by various comorbidities that increase the risk of morbidity and mortality. Therefore, a precise initial assessment and correct history taking and examination of these patients are of great necessity. While trying to employ the most beneficial therapy in SARS-CoV-2 infection, we need to consider the possible adverse effects of the treatments. Cautious use of nephrotoxic drugs, monitoring serum levels, avoiding overzealous diuretics therapy, proper fluid balance, monitoring urinary output (insertion of urinary catheters), and checking markers of kidney injury, such as plasma creatinine could help to limit the in-hospital kidney injury.

Patients who develop a SARS-CoV-2-associated AKI are at risk of subsequent CKD. We could suggest regular follow-up, examination, and assessment of these patients after discharge with regards to possible chronic complications. A variety of laboratory tests are available that can potentially predict CKD in this population (22). Patients with pre-existing CKD or ESRD are at a higher risk of infection; thus, we should limit their contact with other patients and healthcare staff and provide them with separate facilities for regular visits apart from COVID-19 centers. New developments in dialysis units (like extension lines in CRRT machines and remote patient monitoring) provides treatment with less contact and lower chance of infection (48).

Moreover, patients with CKD infected with COVID-19 are at a higher risk of mortality. Attentive monitoring of serum creatinine, discreet treatment choice, and avoiding overtreatment are steps toward maintaining renal health in patients with CKD. We should be aware that patients with pre-existing CKD are at risk of higher stages of the disease (ESRD). Due to the pandemic and the urgent need for RRT in severe SARS-CoV-2 infection, the resources have faced shortage. Limited healthcare staff and facilities as well as constant contact with infected patients put the patients with underlying kidney diseases in grave danger. Hence, they need special observation and care.

Based on the obtained results herein, it is essential to conduct proper treatments according to the causes of kidney injury. Further evidence is needed concerning the possible effective treatments. Furthermore, COVID-19 patients at a higher risk need special attention therefore the occurrence of kidney injury could be prevented. Patients with underlying CKD or new-onset kidney injuries need proper and precise evaluation and treatment; their prognosis should be improved, as a result of which mortality could decrease. Eventually, evaluations should not be limited to the hospitalization period, but be pursued by regular assessments of kidney function.

**Conclusion**

COVID-19-induced AKI shares numerous similarities, as described in the indirect viral injury of the kidney, with AKI arising from other causes, including sepsis or cardiac surgery. Yet, direct viral injury of the kidney is a unique feature in the pathogenesis of COVID-19-related AKI. The outcome of COVID-19 invasion concerning the kidney appears similar to the other forms of sepsis. Accordingly, we strongly recommend therapies to prevent COVID-19-induced AKI and improve COVID-19 outcome in general. While several therapies are proposed
for COVID-19-related AKI, testing their potential efficacy is encouraged. Large-scale clinical trials or more data on retrospective clinical experience are required to assess the efficiency of therapies on patients with CKD or end-stage renal disease and KTRs.

**Authors’ contribution**

AP, HK, SM, KH, BA and AN were the principal investigators of the study. LM and JB were included in preparing the concept and design. MM revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

**Ethical considerations**

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

**Conflicts of interest**

The authors declare that they have no competing interests.

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