**Review Article**

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# Continuous Renal Replacement Therapy (CRRT) in Patients with COVID-19 Infection

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## Abstract

COVID-19, a pandemic caused by a novel coronavirus, in severe cases, it may involve multiple organs including the kidneys. Kidney involvement has been reported in many cases and the most common presentation is with acute kidney injury (AKI) proteinuria and hematuria. The pathogenic mechanism of renal involvement in coronavirus disease 19 (COVID-19) is still unclear. It is supposed to result from a combination of several contributing factors, such as dehydration, acute tubular necrosis, toxic tubular damage, cytokine storm or rhabdomyolysis. CRRT can use in multiorgan failure and associated by reduce mortality.

**Keywords:** COVID-19; Corona virus disease 2019; CRRT; Child.

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## Introduction

Continuous renal replacement therapy (CRRT) was first introduced by Kramer in 1977 (1), and pediatric CRRT was first used in 1985 by Ronco et al (2). CRRT is known for the most important renal replacement modality in critically ill patient with acute kidney injury (AKI) (3, 4). Even though hemodialysis (HD) and peritoneal dialysis (PD) are recognized interventions for patients who necessitate renal replacement, CRRT is identified to be a more proficient therapy for stabilizing circulatory, acid-base, and electrolyte balance for unstable patients (5). CRRT provides a slow and gentle fluid removal from body and remove inflammatory mediators of sepsis such as interleukin, TNF-alpha, and complement (6). Indeed, early intervention with CRRT may inhibit the cytokine cascade/ systematic inflammatory response and the associated inflammatory injury (7). In addition, CRRT has been effectively utilized for quick clearance of both exogenous and endogenous (e.g., ammonia) toxins without the concentration rebound that characterizes toxin elimination by intermittent hemodialysis, and in severe sepsis with multiorgan dysfunction syndrome (MODS) (8, 9). Using the high-permeability of membranes may assist to improve the anti-inflammatory cytokine to proinflammatory cytokine ratio, down-regulate the body's inflammatory response, and ameliorate the systemic inflammatory response (10).

Yizhi Peng and his colleagues evaluated the effect of veno-venous continuous renal replacement therapy on the plasma levels of endotoxin and cytokines in severely burned patients with sepsis. Their study showed the Plasma endotoxins and cytokines (TNF-alpha, IL-1 beta, IL-6 and IL-8) can be removed effectively with CRRT (11).

Determining the therapeutic dose for continuous veno-venous hemofiltration in seriously ill children depends the situation. Individual doses should be determined according to the disease situation, metabolic state, fluid volume, and duration of dialysis (12).

## Kidney compromise in patients with COVID-19

New data on coronavirus disease indicates that kidney involvement appears to be an important issue in these patients. New coronavirus disease (COVID-19) is a newly discovered contagious disease caused by the acute respiratory syndrome virus (SARS) Coronavirus (CoV) -2, which mainly manifests itself as acute respiratory disease with interstitial and alveolar pneumonia, but which can affect several organs such as the kidney, heart, digestive tract, blood and nervous system (13). In previous SARS and MERS CoV reports infections, acute kidney injury (ARI) developed in 5% to 15% of the cases and had a high mortality rate (60% - 90%). Early reports indicated a lower incidence (3% –9%) of ARI in patients with COVID-19 infection (14). However, recent reports have shown a higher incidence of kidney abnormalities. A study of 59 patients with COVID-19 found that 34% of patients developed massive albuminuria on the first day. At admission, 63% developed proteinuria during their hospital stay (15). Cheng et al.13 recently reported that out of 710 consecutive hospital patients with COVID-19, 44% had proteinuria and hematuria and 26.7% had hematuria on admission. The prevalence of increased serum creatinine and blood urea nitrogen was 15.5% and 14.1%, respectively. ARF was an independent risk factor for hospital mortality in these patients (16). The exact mechanism of kidney involvement is unclear: postulated mechanisms include sepsis, which leads to cytokine storm syndrome or direct cell damage due to the virus. Angiotensin converting enzyme and dipeptidyl peptidase-4, both expressed in renal tubule cells, were identified as binding partners for SARS-CoV and MERS-CoV, respectively (17). Recent studies have shown the presence of viral RNA in the urine and kidney tissue of this infection, suggesting that the kidney system is also a target of COVID-19 infection and that direct viral invasion into the tubule and the interstitial is possible. This condition can be referred to as COVID-19 nephropathy. In addition, sepsis-related cytokine storm syndrome due to COVID-19 infection could lead to indirect kidney cell damage and acute renal dysfunction (18)

## COVID-19 and cytokine release syndrome

COVID-19 disease caused by Coronavirus can induce rapid activation of innate immune cells, especially in patients with severe disease. There is a higher circulating neutrophil numbers in COVID-19 survivors than non-survivors, and the infection also induces lymphocytopenia, which mainly affects the CD4 + T cell subset, including effector, memory, and regulatory T cells. According to the innate immune activation, the levels of many inflammatory effector cytokines such as TNF, IL-1β, IL-6, IL-8, G-CSF and GM-CSF as well as chemokines such as MCP1, IP10 and MIP1α are increased in patients with COVID-19 critically ill patients are higher. In addition, the levels of some T cell-derived cytokines such as IL-17 are associated with SARS-CoV-2 infection (19). Some patients with COVID-19 develop a cytokine storm that resembles secondary hemophagocytic lymphohistiocytosis, a hyperinflammatory condition caused by viral infections (20). Huang et al. reported the clinical properties and cytokine profile of critically ill patients with COVID-19 in Wuhan, China, and suggested a cytokine storm (i.e. higher concentrations of granulocyte colony-stimulating factor, gamma interferon-induced protein 10, protein) monocyte chemoattractant 1, Macrophage inflammatory protein 1α and tumor necrosis factor α) may be associated with the severity of the disease (19). Another study by Chen L from China reported that increased expression of interleukin (IL) serum 2R and IL-6 can be a predictive indicator of the severity and outcome in patients with COVID-19. (21) In addition, cytometric analysis of peripheral blood flow showed that T cell hyperactivation partially explained severe immune damage in this patient. Therefore, cytokine storms should be considered in the treatment of COVID-19 and should not be neglected (22). To date, the therapeutic options for severe COVID-19 are limited. Various antiviral drugs such as lopinavir / ritonavir have shown no benefit compared to standard treatment. In addition to antiviral therapy alone, a new treatment strategy should have a significant impact on the clinical outcome. Immunomodulatory therapy to downregulate the cytokine storm can provide more information on the treatment of COVID-19. Combined use of an immunomodulatory agent for the reduction of cytokine storm and an antiviral agent may give doctors more time to support patients with COVID-19. Corticosteroids are one of the most commonly used drugs for immunomodulatory therapy for infectious diseases. Based on treatment experience in China,

conservative use of corticosteroids is only recommended in certain critical patients (e.g., patients with hypoxemia) in low to moderate doses (no more than 1 to 2 mg /kg/day methylprednisolone or equivalent) for a short duration (3-5 days) as described in the novel protocol for the diagnosis and treatment of coronavirus pneumonia (study version 7) issued by the Chinese National Health Commission (23). Chloroquine and its hydroxychloroquine derivative are also used in the treatment of COVID-19. Both chloroquine and hydroxychloroquine are weak bases and can accumulate in acidic cellular organelles (e.g. lysosomes). In this way, they can increase endosomal / lysosomal pH and inhibit virus replication (24). In addition to antimalarial and antiviral effects, they have anti-inflammatory effects that is the basics of them in treatment of autoimmune diseases such as rheumatoid arthritis and lupus erythematosus. Therefore, chloroquine and hydroxychloroquine can reduce the production of various pro-inflammatory cytokines such as IL-1, IL-6, interferon-α and tumor necrosis factor that are involved in the cytokine storm (25).

Tocilizumab is a good therapeutic choice for cytokine release syndrome, in T- cell immunotherapy with chimeric antigen receptors. However, clinical experience with tocilizumab in viral diseases is too limited (26). Yi Yang's retrospective cohort study included all COVID 19 patients who underwent invasive mechanical ventilation in Wuhan from February 12 to March 2, 2020. All patients were followed until death or all survivors were followed up for at least a week. Results: The average age of 36 hospitalized patients with COVID-19 with invasive mechanical ventilation was 69.4 (SD 1.8) years and 30 (83.3%) men. 22 (61.1%) patients received CRRT (CRRT group) and 14 cases (38.9%) were treated in a conventional strategy (non-CRRT group). There were no substantial differences in age, gender, comorbidities, complications, treatments, and most laboratory findings, except for patients in the CRRT group with higher aspartate aminotransferase and serum creatinine levels. During the average follow-up of 10.4 days, 12 out of 22 (54.5%) patients in the CRRT group and 11 out of 14 (78.6%) patients in the group without CRRT died. Kaplan-Meier analysis showed longer survival in patients in the CRRT group than in the group without CRRT (P = 0.032). The relationship between CRRT treatment and reduced mortality risk remained significant after adjustment for confounding factors in seven different models with an adjusted risk ratio (aHR) between 0.283 and 0.424. Older age, higher levels of IL1b, IL2 receptor, hs cTnI and NT proBNP were independently associated with an increased risk of mortality in patients treated with CRRT (27). With adsorption technology, hemoperfusion can remove excess inflammation mediators released by abnormal inflammatory reactions to maintain immune imbalance.

## Conclusion

CRRT can be beneficial for the treatment of patients with COVID 19 with intensive mechanical ventilation. In patients infected by COVID-19 and multiorgan failure using of CCRT would reduce mortality rate**.**

## Conflict of Interest

The authors declare no conflicts of interest.

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