COVID and Kidney: The Struggle So Far

Introduction

Severe acute respiratory syndrome coronavirus disease-2 pandemic (SARS-COVID-19) posed a global health challenge, including many special concerns for patients with kidney diseases. As the pandemic began, the nephrology fraternity worldwide geared up for rapid reconfiguration of services to address the unprecedented increased demand for acute renal replacement therapy (RRT) in COVID critical care units. Strategies were devised to address the safety concerns of patients of incenter maintenance hemodialysis due to their inability to adhere to lockdown, social distancing, and home isolation norms given the compulsion to attend treatment. Concerns also existed about feasibility and rationale of kidney transplantation in pandemic scenario, as it might increase the risk of postoperative death in new recipients. Despite the rapid development of vaccines and identification of effective treatments for severe disease, many of these challenges persisted with the continuing emergence of novel SARS-CoV-2 variants. Numerous studies were published over the course of time addressing the above concerns. However, the ability to draw meaningful conclusions from these studies had been another challenge owing to various limitations such as different methodologies and lack of standardization in treatment. Now with COVID in hiatus, it is time to assimilate the lessons learned from the published literature in the past 2 years.

Acute Kidney Injury in COVID-19

Acute kidney injury (AKI) was frequently reported in COVID patients, especially in severe disease. The incidence varied from 5% to 10.5% in China to 22%–36% in the United States, depending on the testing and admission policies, level of severity, and comorbid illnesses, with a higher incidence and greater need of RRT in critically ill patients.[1,2] Pathophysiology of AKI in COVID was multifactorial. Acute factors such as sepsis, cytokine storm, direct viral cytopathic effect, organ crosstalk, role of angiotensin converting enzyme inhibitor 2 receptor (ACE 2), and hypovolemia were postulated. The predictors for AKI included old age, male gender, increased requirement of vasopressor medications, and need of respiratory support, especially mechanical ventilation. Underlying comorbid illnesses such as diabetes, hypertension, cardiovascular disease, and prior chronic kidney disease (CKD) further exacerbated the acute insult.[3,4] The overall outcome of COVID with AKI was poor, with up to 67% mortality, which was 13 times higher than patients without AKI.[1]

The management of AKI, as in non-COVID scenarios, was largely supportive, including fluid and hemodynamic assessment, avoidance of nephrotoxic drugs, and management of electrolyte and acid-base abnormalities. Renal replacement with intermittent hemodialysis and continuous RRT (CRRT) depended on the hemodynamic status of the patient and availability of resources. No significant difference was reported among various modalities of CRRT: Continuous venovenous Hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), continuous venovenous hemodiafiltration, or hybrid hemodialysis therapies, such as prolonged intermittent RRT or sustained low-efficiency dialysis in critically ill patients. Extracorporeal therapies such as hemoperfusion and hemoadsorption were initially postulated to be of potential benefit in view of their ability to remove cytokines; however, evidence supporting this hypothesis was not very robust.

Chronic Kidney Disease and COVID-19

Estimating the incidence of COVID-19 in patients with CKD was difficult, as the "denominator population," that is the total number of individuals with CKD is typically unknown. However, patients with underlying CKD were more likely to develop severe COVID, superimposed AKI, and had a greater than threefold increased need of acute RRT. After adjustment of all other risk factors, CKD patients were found to have the highest mortality in COVID. The mortality was to the tune of 33% in people with glomerular filtration rate (GFR) of ≤60 ml/min/m^2 (i.e., CKD 3, 4, 5). The risk of death was more than double in advanced CKD (CKD Stage 4, 5; GFR ≤30 ml/min/m^2) compared to those with normal kidney function.[5,6] This higher risk of COVID-19-related death among patients with CKD may in part reflect the unprecedented increased demand for critical care resources during the early peak of pandemic, which resulted in reduced access for patients who were considered to be at the highest risk of poor outcomes. To our knowledge, no studies have evaluated the risk of requiring chronic RRT in patients with CKD after surviving COVID.

Patients on maintenance hemodialysis (CKD Stage 5 on dialysis) with relatively immunosuppressed state, other associated comorbidities, and repetitive unavoidable exposure to hospital environment were particularly vulnerable to COVID, besides increased risk to develop severe infection compared to the general population. Patients were educated to adhere to COVID appropriate behavior, and those with signs and symptoms of illness were tested, and the confirmed cases were isolated from the COVID-negative patients. Dialyzing COVID patients was a real struggle, and strategies varied from place to place and evolved with time. Some places had separate designated

COVID facilities, whereas some institutes had separate areas. A few units arranged different shifts; however, another few could only make corner beds available.

COVID-19 and De Novo Immune-Mediated Kidney Diseases

There were reports of de novo immune-mediated kidney diseases with COVID-19, such as immunoglobulin A nephropathy, vasculitis, membranous nephropathy, minimal change disease, and collapsing focal segmental glomerulosclerosis. Whether the association is incidental or temporal is unknown. Quantifying the extent of associations can only be done by comparing the incidence of specific kidney diseases before and after the pandemic within histopathology registries. However, patients were less likely to undergo biopsy during the COVID-19 pandemic, and therefore, data may be unrepresentative. Another approach would be to compare individuals with and without COVID for development of de novo immune-mediated kidney disease within a comparative cohort study with protocoled follow-up. Routine data are likely to be confounded by the fact that post-COVID patients are more likely to receive follow-up investigations (such as serum creatinine and urinary indices), and therefore, more likely to be diagnosed than COVID-naive people leading to overestimation of the association.[2,7]

COVID-19 and Pharmacoepidemiology in Kidney Diseases

Safety of existing drugs in COVID-19

Early in the pandemic, the potential safety concerns were raised about the use of ACE inhibitors, which are considered a standard of care for many patients with hypertension, CKD, ischemic heart disease, and heart failure. These concerns arose from the finding that SARS-CoV-2 enters cells through the functional receptor, ACE2, and some suggestions that ACE2 expression might be upregulated by ACE inhibitors. However, various observational studies consistently suggested that no association exists between ACE inhibitor use and the incidence and/or progression of COVID-19. This finding has since been confirmed by two randomized controlled trials that demonstrated no difference in outcomes, such as COVID progression and death, among hospitalized patients, regardless of whether they continued or discontinued ACE inhibitor treatment.[8,9]

COVID-19 therapies

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial demonstrated the benefits of dexamethasone, tocilizumab, and baricitinib in reducing mortality in hospitalized patients with COVID-19. The study found no benefit of other therapies that were used widely in patients with kidney disease early in the pandemic, including lopinavir–ritonavir, hydroxychloroquine, and azithromycin. Dexamethasone reduced the requirement for RRT by 39% and tocilizumab by 28%.[10] The combination of casirivimab–imdevimab monoclonal antibody therapy was also found to reduce mortality in seronegative patients hospitalized with COVID-19; participants included those on dialysis and kidney transplant recipients.[11]

COVID-19 vaccines in kidney disease

A number of studies have evaluated the efficacy and safety of COVID-19 vaccines in patients with kidney diseases, including those on dialysis and kidney transplant recipients. The available evidence indicates that kidney transplant recipients and patients on dialysis have an impaired response to vaccines compared with that in the general population. In a study of over 9000 patients on dialysis, 87% and 96% of the patients had developed a seroresponse to the BNT162b2 Pfizer and mRNA-1273 Moderna mRNA vaccines, respectively, but only 37% had developed a seroresponse to Ad26.COV2.S Janssen adenoviral vector vaccine 14–74 days after completion of the vaccination schedule.[12] However, the longer term follow-up demonstrated that antibody responses to the mRNA vaccines declined within 6 months.[13] A more recent study found that the third dose of BNT162b2 Pfizer vaccine improved humoral immune responses in kidney transplant recipients; however, the effectiveness of this approach on clinical outcomes such as death and hospitalization remains unknown.[14] An analysis of the National Transplant Registry data from England found that fewer deaths occurred among transplant recipients vaccinated with ChAdOx1-S Oxford–AstraZeneca vaccine than among unvaccinated transplant recipients following SARS-CoV-2 infection, whereas there was no survival benefit associated with the BNT162b2 Pfizer vaccine.[15] A REnal Patients COVID-19 VACcination Immune Response study, which includes patients with CKD not on dialysis, is presently ongoing.[16]

COVID-19 and Kidney Transplant

Kidney transplant patients on immunosuppressive drugs were at increased risk of contracting infection and developing complications related to illness.

The three main issues pertaining to renal transplant were:

1. The potential risk of transmission of infection in peritransplant period
2. Management of immunosuppression during the pandemic
3. Type of clinical presentation, disease course, or outcomes of infection in immunosuppressed transplant recipients.

Management of the immunosuppression in COVID patients was akin to treading a tight rope, with target to control infection without compromising graft function. The overall consensus was to discontinue antimetabolites and decrease the dose of calcineurin inhibitors (CNIs) by 50%, with steroids to continue unchanged, as in management of other viral infections, such as cytomegalovirus and BK virus.

The important aspect was adequate knowledge of drug interactions between immunosuppressants and potential COVID therapies, like usage of protease inhibitors which increase the serum levels of CNIs.

The European registries show overall 25% mortality in postrenal transplant patients diagnosed with COVID-19, with 3% deaths in mild disease, 24% in those requiring hospital admission, and 45% in those requiring intensive care unit care.[17,18]

Transplant activity during COVID-19

The pandemic had a significant impact on organ transplant program, with worldwide statistics showing a significant decline, kidney transplant being the worst affected than any other organ transplants. Data showed a significant decrease in deceased donor kidney transplants in France and the United States (90.6% and 51.1%, respectively),[19] with similar trends reported from India.[20] Later, the World Health Organization issued guidelines that transplantation activity can be restarted maintaining proper precautions.

Long COVID and Kidney

A growing number of studies are now focusing on post-COVID complications, including renal outcomes. Individuals who have survived COVID-19 exhibit an increased risk of AKI and major adverse kidney events, such as decline in estimated GFR of ≥50%, end-stage renal disease (ESRD), or all-cause mortality. Overall, the rate of ESRD is almost threefold higher in survivors than in individuals without known infection. The pathophysiological processes by which COVID-19 might lead to a decline in kidney function remain unknown. Autopsy studies of patients who have died with COVID-19 suggest that SARS-CoV-2 could directly infect the kidney, causing upregulation of profibrotic cell signaling pathways, although large immunohistochemistry series of kidney biopsies have not found evidence of SARS-CoV-2 expression.

Conclusions

The pandemic significantly impacted the kidney disease patients and their outcomes. The global medical fraternity worldwide needs to be applauded for the timely scientific inputs that guided in the rational management of renal issues of COVID-19. However, some questions that still remain unanswered include identification of approaches to improve outcomes in patients with kidney disease and quantifying the long-term impacts of COVID on the kidney leading to development and progression of CKD.

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Submitted: 28-Oct-2022
Revised: 27-Dec-2022
Accepted: 02-Jan-2023
Published: 27-Mar-2023

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Quick Response Code:

Website: www.ijabmr.org

DOI: 10.4103/ijabmr.ijabmr_571_22

How to cite this article: Kaur S, Mehta S. COVID and kidney: The struggle so far. Int J App Basic Med Res 2023;13:1-4.