Clinical Kidney Journal

Clinical Kidney Journal, 2022, vol. 15, no. 9, 1639–1642

https://doi.org/10.1093/ckj/sfac122
Advance Access Publication Date: 2 May 2022
Editorial Comment

EDITORIAL COMMENT

Kidney replacement therapy patients with COVID-19 in the vaccine era: what do we need to know?

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ABSTRACT

Kidney disease is one of the most important factors affecting the prognosis of patients with coronavirus disease 2019 (COVID-19). Patients on kidney replacement therapy (KRT; dialysis and kidney transplant recipients) are vulnerable to severe complications of COVID-19. As the pandemic evolves and preventive strategies, availability of healthcare facilities, treatment approaches and vaccination strategies change, studies are needed on COVID-19 epidemiology and outcomes in KRT patients that contribute to vaccination regimens, treatment protocols and immunosuppressive therapies of KRT patients with COVID-19. In their registry-based study, Quiroga *et al.* analyzed COVID-19 KRT patients in Spain across six pandemic waves in order to evaluate dynamic treatment approaches and outcomes as well as the efficacy of vaccination.

Keywords: COVID-19, dialysis, immunosuppression, kidney replacement therapy, SARS-Cov-2 vaccination

Patients with solid organ transplants and dialysis patients are at the highest risk of coronavirus disease 2019 (COVID-19) death according to reports from the first pandemic waves [1]. Quiroga *et al.* [2] conducted a prospective registry-based cohort study of dialysis and kidney transplant (KT) patients who developed a confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In this cohort study of six pandemic waves in Spain, the aim was to analyze the changes over time in healthcare measures, including vaccination, affecting SARS-CoV-2 infection in patients on kidney replacement therapy (KRT). The authors collected data on epidemiological details, KRT characteristics and modalities, treatment details, immunosuppressive therapy and adjustments, symptoms on diagnosis, medications for SARS-CoV-2 and mechanical ventilation needs. They report that KT patients and the first wave were independent predictors of hospital admission, while older age, disease severity and intensive care unit (ICU) rejection were predictors of mortality. In later pandemic waves, COVID-19 was mainly observed in vaccinated KT patients and in unvaccinated dialysis patients. The authors report that, overall, later in the pandemic the mortality decreased and ICU admissions increased [2].

At the start of the COVID-19 pandemic, both Spain and the UK reported a higher incidence of COVID-19 in dialysis patients compared with transplant patients, possibly due to the limited self-isolation capacity of dialysis patients [3, 4]. Patients with kidney failure requiring in-center hemodialysis (HD) should be prioritized for vaccination. HD itself is a risk factor for possible COVID-19 exposure, as there is close interaction with healthcare providers and other dialysis patients [5]. Widespread transitioning of HD patients from in-center to home is not feasible, and dialysis and transplantation were the leading global risk factors for COVID-19 mortality in the prevaccine era [5]. Patients on dialysis had mortality rates similar to those of kidney transplant recipients [6], but they were infected twice as frequently due to the infeasibility of shielding [7].

COVID-19 had a similar clinical course in transplant and dialysis patients and this was worse than in the general population [6]. Quiroga *et al.* [2] found similar fatality rates among

Received: 23.4.2022; Editorial decision: 28.4.2022

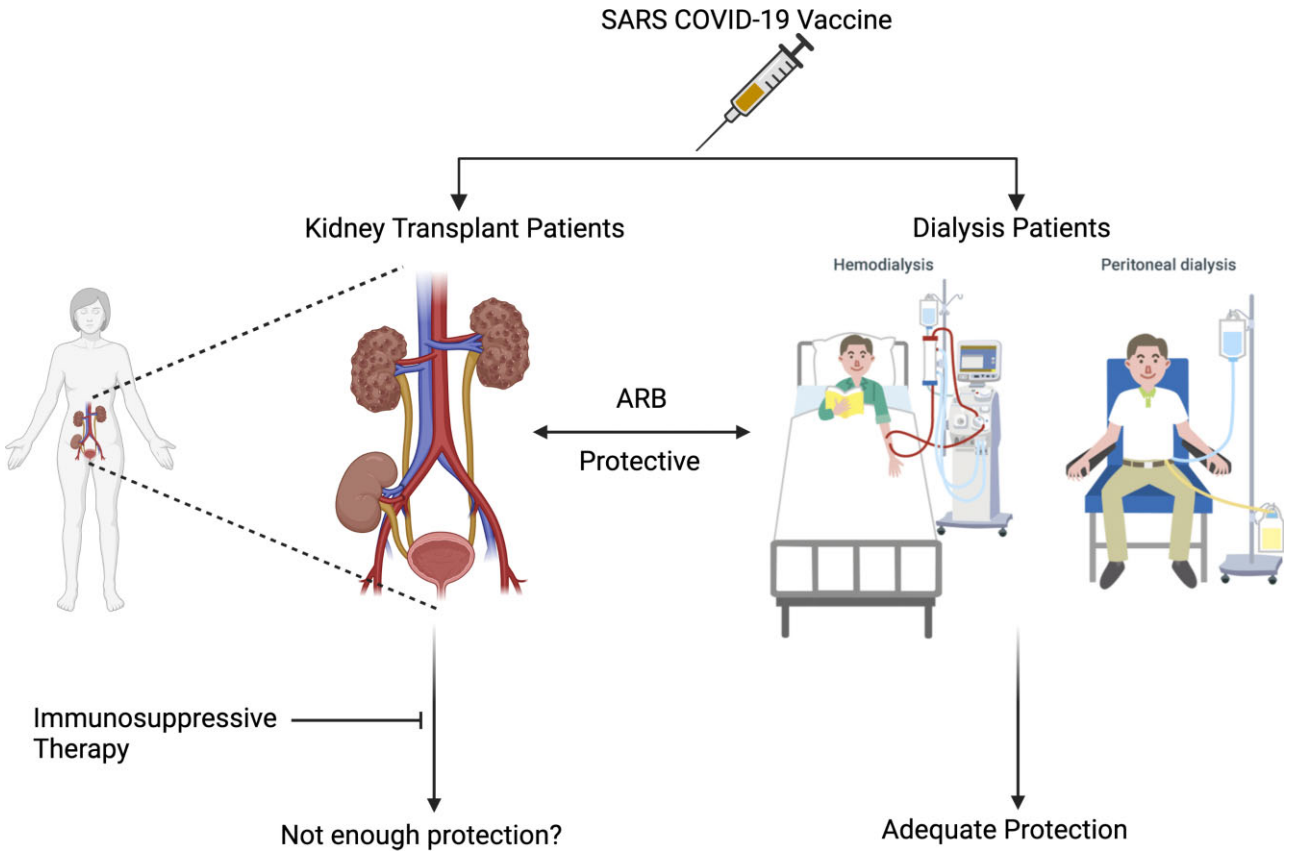

FIGURE 1: Factors influencing SARS-CoV-2 vaccine protection in patients on KRT. ARB: angiotensin receptor blocker.

vaccinated KT and dialysis patients with COVID-19; however, due to the lower protective effect of vaccination in KT patients compared with dialysis patients, there were 8.5 more deaths among vaccinated KT patients than among vaccinated dialysis patients. They also observed a shift in COVID-19 epidemiology among patients on KRT over time, as the majority of SARS-CoV-2 cases among KRT patients occurred in the in-center HD group in the initial wave, while it was in the KT recipient group since the fourth wave. While vaccinated KT patients comprised the majority of COVID-19 cases in the fifth and sixth waves, unvaccinated HD patients were infected at a higher rate in the sixth wave, after the administration of a booster dose of vaccine. The authors report that KT and peritoneal dialysis patients were less likely to be asymptomatic and that mortality decreased in KRT patients after the start of vaccination. The analysis of the Spanish KRT registry demonstrated that as SARS-CoV-2 vaccination prevalence progressed starting from the fourth to the sixth waves (20%, 84% and 79%, respectively), the mortality rates among COVID-19 KRT patients decreased from 28% (the first-wave mortality rate) to 17%, 22% and 19% for the fourth to the sixth waves, respectively. Among vaccinated patients, mortality was highest in the fifth wave, prior to the booster dose (21%), than in the third/fourth wave (12%), when the initial vaccination was recent, and the sixth wave (15%), when the booster dose had been recently administered [2]. Of note, these analyses preceded the arrival of the SARS-CoV-2 omicron variant to Spain.

Patients on HD have reduced innate and adaptive immune responses [8], which may cause relative hyporesponsiveness to vaccines [5]. This does not preclude the use of vaccines in the standard of care of dialysis patients [9]. However, Quiroga *et al.* [2] identified the vaccinated KT population as the key KRT population in whom hyporesponsiveness to vaccines might lead to more SARS-CoV-2 infections. However, a systematic review reported that both KT and dialysis patients experience lower seroconversion rates after a series of messenger RNA COVID-19 vaccines than the general population and therefore suggested that nonseroconverted KRT patients or those with early loss of anti-Spike antibodies should be considered for a third dose [10]. Health authorities in many countries opted to offer the third dose to the entire population, as was done in Spain. In this regard, the study by Quiroga *et al.* [2] also reports the efficacy of a booster vaccine in the HD population, evident by the fact that almost half and most of the HD patients infected in the fifth and sixth waves, respectively, were unvaccinated. However, it is also important to acknowledge that mortality from COVID-19 in HD patients is not limited to the initial hospitalization period, as an increased risk may extend for up to 1 year after the infection, with the highest risk observed in the first 3 months [11, 12]. Considering the increasing number of KRT patients worldwide, vaccination is a key element for protection against COVID-19, as the availability of vaccines decreased the number of COVID-19 cases dramatically in this population [2].

Quiroga *et al.* [2] report that calcineurin inhibitor–free and mammalian target of rapamycin (mTOR) inhibitor–free immunosuppressive regimens in KT patients were associated with higher mortality, in contrast to steroid-free regimens, which were associated with lower mortality, lower ICU and hospital admissions. Similarly, Johnson *et al.* [13] recommend

steroid-sparing modifications to the immunosuppression of KT patients with COVID-19, with the rationale being that corticosteroids may increase viral shedding, inhibit immune response and reduce pathogen clearance. It is important to emphasize that this refers to chronic therapy with corticosteroids for immunosuppression, not to the de novo prescription of high-dose corticosteroids during the cytokine storm phase of severe COVID-19. In a meta-analysis conducted regarding immunosuppression management in KT patients with COVID-19 infection, the most frequently used approach was the discontinuation of antimetabolite drugs and mTOR inhibitors, while calcineurin inhibitors were withdrawn only in symptomatic patients. The authors of the meta-analysis mentioned that certain antiviral drugs used in COVID-19 infection might cause increased serum levels of calcineurin inhibitors and mTOR inhibitors due to drug–drug interactions [14]. An individualized approach to immunosuppressive therapy modifications is needed along with more data.

In this regard, an Italian study from the early stages of the pandemic indicated that when immunosuppression was maintained (or shifted from mycophenolate mofetil to high-dose steroids), all KT recipients with concomitant COVID-19 survived [15]. This observation is in the line with the decreased mortality observed in the Randomised Evaluation of COVID-19 Therapy clinical trial in patients in the general population with severe COVID-19 randomized to dexamethasone [16]. Immunosuppression-free regimens reported high rejection rates [17]. The British Transplantation Society guideline on KT patients with COVID-19 recommends total discontinuation of antiproliferative agents and minimization of calcineurin inhibitors. The guideline mentions that steroids could be counterproductive in early disease but may be considered in the case of acute respiratory distress syndrome [18].

Interestingly, baseline renin–angiotensin system (RAS) blocker use was found to be protective [2]. The main mechanism was suggested to be the blocking of the active role of angiotensin receptor-1 on SARS-CoV-2 entry into cells by soluble angiotensin-converting enzyme 2 [19]. Supporting the results, initiation or continuation of RAS blocker reduced the death risk, whereas discontinuation increased the risk [20]. A recent meta-analysis indicated no significant benefit or harm from RAS blocker use for either susceptibility, illness severity or mortality of COVID-19 infection [21]. Furthermore, RAS blocker use, other than decreasing the peak viral load, was found to increase T cell counts in peripheral blood compared with other antihypertensive drugs, suggesting another mechanism of benefit in COVID-19 infection [22].

Limitations of the study include the lack of information on the duration of immunosuppressive treatment and details on the immunosuppressive drug adjustment during the COVID-19 episode. This information is important to understand the influence of chronic immunosuppressive regimens on vaccination status and vaccination efficacy. Another limitation worth mentioning is the need for polymerase chain reaction testing for all possible asymptomatic KRT patients as the gold standard to diagnose COVID-19. This will eliminate the selection bias, as asymptomatic COVID-19 patients would be missed in the analysis, masking the possible vaccination protection in KRT patients.

In conclusion, Quiroga *et al.* [2], in their registry analysis, demonstrate the changing patterns of the COVID-19 pandemic in Spain in the context of KRT patients. While a reduction of COVID-19 cases was observed with the widespread administration of vaccines, there is a need to optimize vaccination regimens in KT recipients, who remain the most vulnerable KRT population.

FUNDING

None.

CONFLICT OF INTEREST STATEMENT

M.K. is a member of the *CKJ* editorial board. The authors declare no other conflicts of interest.

(See related article by Quiroga et al. Evolving spectrum but persistent high mortality of COVID-19 among patients on kidney replacement therapy in the vaccine era: the Spanish COVID-19 KRT Registry. *Clin Kidney J* (2022) 15: 1685–1697.)

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