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REVIEW ARTICLE

COVID-19 Pandemic – Nephrologist's Perspective

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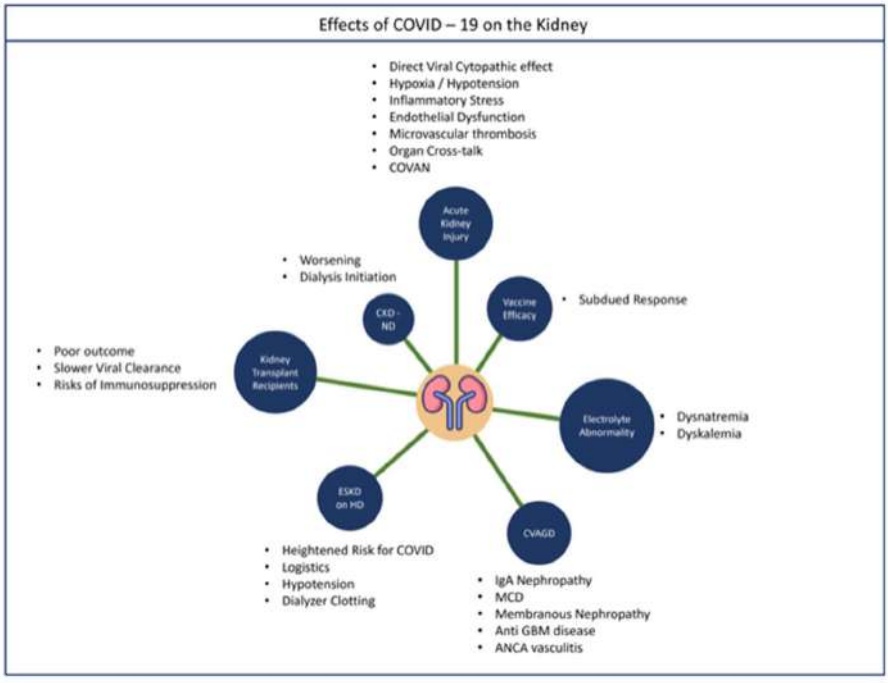
Abstract
Nephrology services across the world, already struggling to cope up with chronic kidney disease (CKD) of epidemic proportions, faced enormous challenges during the COVID pandemic. SARS CoV -2 virus affects kidney directly and indirectly through systemic effects. Also, the pandemic impacted almost all aspects of renal care services in several ways. This review article aims to discuss the impact of COVID on kidney and renal care services under the following headings.

Keywords: COVID 19, Coronavirus pandemic, Kidney

Graphical Abstract



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Introduction

Coronavirus pandemic, has in fact, proved to be a 'war in disguise'. The hither-to unexperienced medical, administrative, financial and emotional challenges posed by the pandemic provided an opportunity for introspection on the adequacy of health care delivery system and on the resilience of health sector to face unexpected challenges.

Though lung is the primary organ affected by the coronavirus, other organ systems including kidney also are affected in several ways.

Acute Kidney Injury

There has been a wide discrepancy in the incidence of acute kidney injury (AKI) in patients with COVID, ranging from 5% to 60%. The reasons for the wide variations in AKI incidence could be the different definitions of AKI used and the varying degrees of severity of COVID in the study population. Incidence of AKI increases with increasing severity of COVID. Patients requiring mechanical ventilation are at higher risk for AKI. In a study of 154 patients with COVID associated AKI, the mortality was 38% and old age, severe CT severity, higher CRP and requirements of inotropes were independent predictors of mortality [1].

The patho-mechanisms of COVID-related AKI are multi-factorial, including systemic effects, possible direct viral cytopathic effect and the host's immune responses to COVID. Renal tubular epithelial cells and podocytes express ACE II receptors. Hence, it is possible that there can be direct viral cytopathic effect. Following factors, in varying degrees and combination contribute for AKI (Table 1).

Table 1. Mechanism of Acute Kidney Injury

1	Hypoxia
2	Hypotension
3	Macrophage activation
4	Inflammatory stress (Hyper-ferritenemia is a surrogate)
5	Activation of coagulation
6	Microvascular thrombosis
7	Endothelial dysfunction
8	Cytokine storm – IL-1, IL-6, TNF alpha
9	Oxidative stress
10	Complement activation
11	Organ 'cross-talk'
12	Rhabdomyolysis

1. COVID – related acute kidney injury (AKI)
2. Impact of COVID on patients with non-dialysis requiring CKD
3. COVID in patients on maintenance hemodialysis
4. COVID in kidney transplant recipients (KTR)
5. COVID vaccination in patients on Renal Replacement Therapy
6. COVID vaccine – associated glomerular diseases (CVAGD)
7. Dyselectrolytemia in CCOVID
8. Kidney in Long-COVID

Kidney Pathology in COVID

Acute tubular necrosis and acute interstitial nephritis are the commonly reported pathological lesions. Rhabdomyolysis induced by COVID may result in myoglobin pigment cast nephropathy. Severe endothelial dysfunction/injury ensues in thrombotic microangiopathy (TMA). Renal artery occlusion resulting in renal infarction has been reported.

An exciting pathology, 'collapsing glomerulopathy' has been encountered in COVID. Collapsing glomerulopathy is characterised by glomerular tuft collapse and proliferation of visceral epithelial cells. This pathology is referred to as COVAN (COVID – Associated Nephropathy). It is debated whether COVAN is induced by direct viral invasion of the glomerular epithelial cells or mediated by heightened gamma interferon activity in COVID. Collapsing glomerulopathy was classically described in patients with Human immunodeficiency virus, of African ancestry, and referred to as HIVAN – HIV-Associated Nephropathy. Most of the patients with HIVAN possess specific APOL 1 (apolipoprotein 1) gene polymorphisms which confer protection against trypanosomiasis. The same phenomenon of presence of nephropathic APOL 1 gene alleles has been observed in most of the patients with COVAN also [2].

Management

Milder forms of AKI can be managed conservatively. Renal replacement therapy is required for severe AKI. Mode and form of dialysis have to be decided by the

hemodynamic status of the patient. For hypotensive and hypoxemic patients, acute peritoneal dialysis, continuous renal replacement therapy (CRRT) or sustained low-efficiency dialysis (SLED) would be preferable. In critically-ill ICU patients who are hemodynamically unstable to tolerate hemodialysis, acute intermittent peritoneal dialysis was shown to be effective in resource-limited settings in a retrospective cohort of 91 patients [3]. A meta-analysis of 6 studies done in pre-COVID era, showed no difference in mortality and rate of complications in patients with acute kidney injury who underwent acute intermittent peritoneal dialysis to those who received extra-corporeal dialysis therapy [4]. The mortality risk in such sick patients was governed by the presence of comorbidities and severity of COVID pneumonia and not the modality of renal replacement therapy. There is evidence that peritoneal dialysis has added advantage of clearance of inflammatory cytokines like TNF-∞ and IL-6 [5,6].

In a South Indian study of COVID patients with AKI age above 70 years and the need for mechanical ventilation were associated with increased mortality [7].

It is commonly observed that AKI worsens prognosis in COVID patients. Collapsing glomerulopathy has a poor renal outcome.

It is a matter of concern that COVID-related AKI may predispose to progression to chronic kidney disease. In an observational study of 313 patients with severe COVID warranting intensive care unit admission, 240 patients developed AKI. There was a mortality of 34% and among the survivors, 16% of patients progressed to CKD at 3 months [8].

Impact of COVID on patients with non-dialysis requiring Chronic Kidney Disease (CKD-ND) (Figure 1)

Patients with CKD-ND are at a higher risk for contracting COVID as compared to general population. Most of the patients with CKD-ND experience worsening of kidney function, even necessitating initiation of dialysis in some patients. Inflammation, microvascular thrombosis and oxidative stress are the possible mechanisms. COVID induces a hypercoagulable state. Macrophage activation, release of 'death-associated molecular patterns' and 'pathogen-associated molecular patterns' result in release of tissue factor resulting in activation of coagulation. There is evidence for complement activation in severe COVID. Complement activation and hypercoagulable state mutually enhance each other [9].

COVID in patients End Stage Kidney Disease (ESKD) on maintenance dialysis

Patients with ESKD undergoing maintenance haemodialysis are a heightened risk for getting COVID in view of the compromised immunological status and the frequent visits to hospital for getting dialysis. These patients and the health care delivery system faced several challenges

a) Reaching the dialysis centre was difficult during complete lockdown for many patients. A survey was conducted to study the impact of complete lockdown on haemodialysis services after 3 weeks of lockdown implementation [10]. The survey included 19 major hospitals across the country (8 public and 11 private hospitals). There was a decrease in the number of patients from 2517 to 2,404. 28.2 % patients had missed one or more dialysis sessions, 2.74% required emergency dialysis session and 4.13% patients stopped reporting for dialysis.
b) Need for establishing a dedicated dialysis facility for COVID patients with dedicated medical and paramedical staff
c) Higher incidence of hypotension during haemodialysis due to hypoxemia
d) Increased incidence of clotting of dialyzers due to hypercoagulability.

Patients on continuous ambulatory peritoneal dialysis (CAPD) did not encounter significant challenges. This advantage realised during COVID pandemic has prompted policy makers to promote CAPD in some parts of the country. There was also resurgence of urgent start CAPD during the pandemic [11,12].

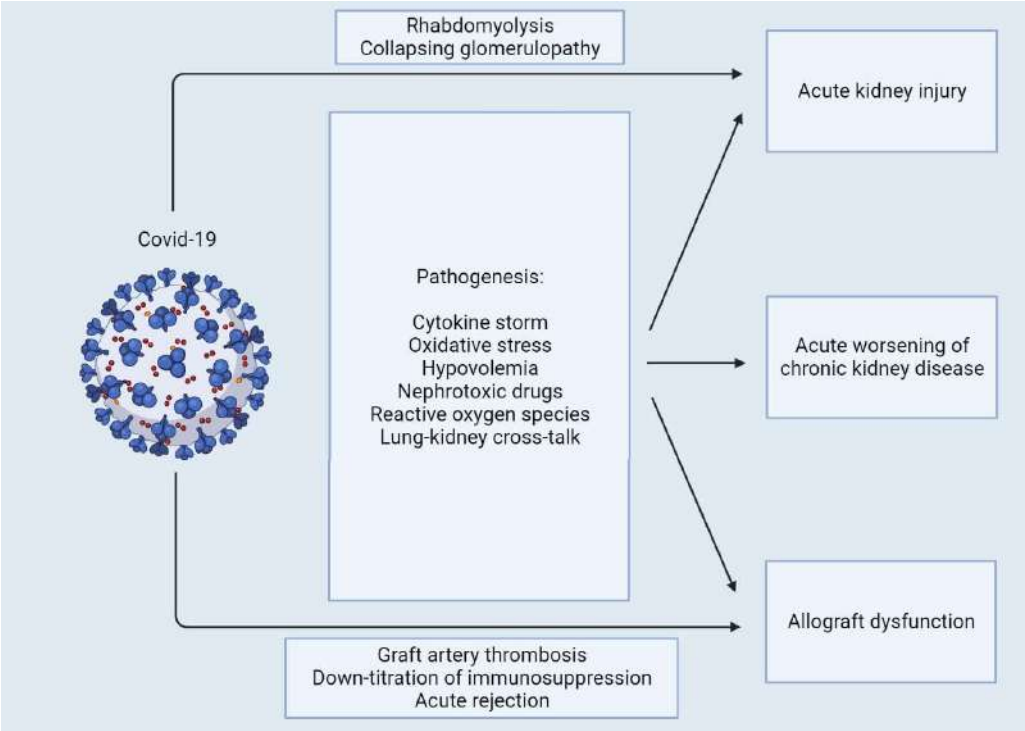

Fig. 1. Impact of COVID on Kidney - Pathomechanisms

The subset of patients requiring initiation of renal replacement therapy due to worsening of their kidney function during COVID infection had worse prognosis than those already on maintenance hemodialysis. A study of 109 patients who required initiation of hemodialysis during COVID infection showed a higher mortality rate of 44% with older age and presence of diabetes as independent predictors of poor outcome [13].

Initially, there was hesitancy to use remdesivir in patients with kidney failure due to uncertainty on safety and tolerance. Aiswarya et al. [2], in a prospective, observational study of 48 COVID patients with ESKD and on regular haemodialysis, administered remdesivir in a modified dose (100 mg intravenous infusion on alternate days, four hours prior to haemodialysis session) and found to be safe and well tolerated. Though remdesivir did not confer mortality benefit, early administration (<48 hours of hospitalisation) of remdesivir resulted in a significant decrease in duration of hospitalisation.

Nithya et al. [3], in an observational study of 483 COVID patients who required dialysis, noted a mortality of 18.8%. Old age and acute -on-chronic kidney failure were the significant predictors of mortality. Report from another cohort of patients from South India reported a higher mortality rate of 27.5% in patients with end-stage renal disease. Patients with comorbidities like hypertension, diabetes and pre-existing pulmonary disease had a poor prognosis [16].

Patients with end-stage kidney failure on maintenance hemodialysis are less likely to mount an adequate immune response against SARS CoV due to low immune status. Hence, it was hypothesised that passive immunisation with convalescent plasma (CP) would be beneficial. But, in an Indian study on the safety and efficacy of CP, there was no mortality benefit in 37 patients who received CP, as compared to 31 patients in the control group [4].

COVID in Kidney transplant recipients

COVID in kidney transplant recipients (KTRs) poses additional challenges. Being on anti-rejection immunosuppressive drugs, KTRs, are at a higher risk for contracting COVID and a poor outcome. A higher mortality has been documented among KTRs afflicted

with COVID. As per a study based on United Network for Organ Sharing (UNOS) database [18], direct COVID death and all-cause mortality were seen in 28.7% KTRs.

Another study using data of ERACODA [19] (European Renal Association Covid 19 Database) reported a 28-day probability of death of 21.3% in 305 KTRs. Advanced age was significant determinant of mortality in KTRs.

An Indian study of 129 KTRs affected with COVID, reported mortality of 20.1% and graft dysfunction in 68.9% [20]. It was also observed that the mortality rate and severity if COVID infection were the highest during the second wave (delta variant) of COVID-19 infection compared to other waves. Kidney pathology in those who survived COVID infection and had acute allograft dysfunction showed varied pathologies like acute cellular rejection, antibody mediated rejection and graft pyelonephritis, although evidence for COVID per se as a risk factor for acute rejection is lacking [21]. The possible reason for acute rejection could be down-titration of immunosuppression. It is rather a difficult decision to down-titrate immune suppressants to facilitate recovery since it would increase risk of allograft rejection. The situation was more complicated during the second wave by the concurrent/succeeding occurrence of invasive mucormycosis in some patients [22].

Though there are no definite guidelines, it is a widely accepted practice to discontinue anti-metabolites (mycophenolate mofetil / azathioprine) and reduce the dose of calcineurin inhibitors (tacrolimus / cyclosporine) in the hospitalised patients with COVID. It remains uncertain as to when to restore original dosage of immune suppressives, whether only after complete recovery or early in the recovery phase itself. KTRs are particularly vulnerable to secondary bacterial infections with a significant negative impact on the outcome.

There is no evidence for COVID per se, being a trigger for acute rejection.

In general, viral clearance takes a longer time in KTRs and patients with end stage kidney failure.

Kidney Transplantation services during COVID pandemic

Kidney transplantation services were suspended in most centres across the globe during COVID pandemic, since the KTRs have to be on intensive immunosuppression during the initial post-transplant period, making them more susceptible to COVID.

Guidelines were subsequently issued by NOTTO (National Organ and Tissue Transplantation Organisation), governing kidney transplantation. It is mandatory to rule out Covid infection in recipients and donors. Failure to identify asymptomatic COVID infection in either the recipient or the donor would result in disastrous consequences for the recipient.

1. COVID Vaccination in patients on Renal Replacement Therapy

There has been subdued response to vaccination in patients with end stage kidney failure on dialysis and in KTRs due to the impaired immunity.

The possible causes for impaired immune response include, reduced expression of co-stimulatory molecules and Toll-like receptors on immune -reactive cells, decreased production of T cell cytokines with resultant impaired activation and proliferation of T cells and reduced number of naïve and memory B cells [23].

KTRs, being on triple immune suppressants (steroids, calcineurin inhibitor and mycophenolate mofetil) are particularly vulnerable for failure of seroconversion following vaccination.

In a meta-analysis of 27 studies [24] involving 4,264 patients on renal replacement therapy (dialysis or KTRs), humoral response after two doses of vaccination for SARS CoV was 44% lower than in the general population. Seropositivity rates among KTRs, patients on peritoneal dialysis and haemodialysis were 26.1%, 92.4% and 84.3% respectively. Compared to general population, KTRs were 80% less likely to mount humoral response after COVID vaccination. Use of mycophenolate mofetil (MMF) has been found to be a significant contributory factor for blunted immune response.

Strategies to improve seroconversion rates include administration of additional doses of vaccine, heterologous additional dose, intradermal administration and use of adjuvants.

Kamar et al. [25], observed an increase in seropositivity rate from 40% to 68% in KTRs after a third dose of vaccine.

A study involving infection -naïve KTRs , showed lack of humoral response to 3rd and 4th doses of vaccine in 24% and 19% respectively [26]. The authors concluded that there was no additional benefit of fourth dose of vaccine due to poor T cell responses..

COVID Vaccine – Associated Glomerular Disease (CVAGD)

Glomerular diseases have been reported [27] in close temporal association with administration of COVID vaccination. The most common glomerular diseases associated with COVID vaccine are IgA nephropathy and minimal change disease. Other reported glomerulopathies include membranous nephropathy, anti-glomerular basement membrane disease and anti-neutrophil cytoplasmic antibody vasculitis.

Also, there have been anecdotal reports of recurrence of IgA Nephropathy, minimal change disease and membranous nephropathy following COVID vaccination.

Both mRNA and adenoviral vaccines have been associated with CVAGD.

The putative patho-mechanisms of CVAGD include molecular mimicry of the spike protein with host peptides.

Dyselectrolytemia

Dysnatremia and dyskalemia are common in patients with COVID. Dyselectrolytemias contribute for added morbidity and mortality. Hyponatremia is the most common dyselectrolytemia observed. The most common cause for hyponatremia is hypovolemia. There are anecdotal reports of 'syndrome of inappropriate anti-diuresis' associated with COVID resulting in severe hyponatremia [28,29].

Hypernatremia due to poor intake of water, particularly in the elderly is common in the severely ill patients. Hypernatremia has to be managed with administration of water and hypotonic solutions viz., 0.45% saline and 5% Dextrose solution.

Causes for hypokalemia include poor oral intake, insulin administered for hyperglycemia and diarrhoeal illness observed in about 10% of patients with COVID.

Hyperkalemia was observed in COVID patients who developed rhabdomyolysis as a rare complication of the disease and in those who developed renal failure.

Kidney in 'Long COVID'

There is emerging evidence that some COVID survivors develop post-acute phase sequelae involving pulmonary and extra-pulmonary organ systems including the kidneys. A cohort study [30] involving 1,81,384 COVID survivors treated at Veterans Health Administration Healthcare system revealed a higher risk for AKI, eGFR decline, end-stage kidney failure and major adverse kidney outcomes (MAKE). The kidney disease risk correlated with severity of COVID illness. This study has highlighted the potential long-term adverse renal consequences of COVID. It is imperative that post-COVID follow-up care should include kidney care component also.

Conclusion

The clinical spectrum of COVID includes kidney also. Kidney disease and COVID exert a mutually negative impact on each other. Management of Kidney disease in COVID is fraught with challenges.

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Conflicts of interest

The authors declares that they do not have conflict of interest.

References

1. Murugesan V, Devaraju PK, Balasubramanian CM, Senthilkumaran G, Vs J, Rajarathinam VD, et al. POS-023 Clinical Profile and Predictors of Mortality in Patients with Covid 19 - Related Acute Kidney Injury A Single Centre Experience. Kidney Int Rep. 2022; 7(9): S472.
2. Velez JCQ, Caza T, Larsen CP. COVAN is the new HIVAN: the re-emergence of collapsing glomerulopathy with COVID-19. Nat Rev Nephrol. 2020; 16(10): 565–7.

3. Varghese B, Rajagopalan A, Arunachalam J, Prasath A, Durai R. Acute Intermittent Peritoneal Dialysis in Critically Ill COVID-19 Patients with Renal Failure: Saviour or Succourer. Open Urol Nephrol J. 2022; 15(1). https://openurologyandnephrologyjournal.com/VOLUME/15/ELOCATOR/e1874303X2203290/FULLTEXT/
4. Liu L, Zhang L, Liu GJ, Fu P. Peritoneal dialysis for acute kidney injury. Cochrane Database Syst Rev. 2017;(12). https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011457.pub2/full
5. Zhao WX, Liu XM, Yu CM, Xu H, Dai JR, Chen HY. Peritoneal dialysis effectively removes toxic substances and improves liver functions of liver failure patients. Eur Rev Med Pharmacol Sci. 2018; 22(8): 2432–8.
6. Altmann C, Ahuja N, Kiekhaefer CM, Andres Hernando A, Okamura K, Bhargava R. Early peritoneal dialysis reduces lung inflammation in mice with ischemic acute kidney injury. Kidney Int. 2017; 92(2): 365–76.
7. Sindhu C, Prasad P, Elumalai R, Matcha J. Clinical profile and outcomes of COVID-19 patients with acute kidney injury: a tertiary centre experience from South India. Clin Exp Nephrol. 2022; 26(1): 36–44.
8. Lumlertgul N, Pirondini L, Cooney E, Kok W, Gregson J, Camporota L. Acute kidney injury prevalence, progression and long-term outcomes in critically ill patients with COVID-19: a cohort study. Ann Intensive Care. 2021; 11(1): 123.
9. Batlle D, Soler MJ, Sparks MA, Hiremath S, South AM, Welling PA. Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology. J Am Soc Nephrol. 2020; 31(7): 1380–3.
10. The Adverse Effect of COVID Pandemic on the Care of Patients With Kidney Diseases in India PubMed. 2022. https://pubmed.ncbi.nlm.nih.gov/32838077/
11. Shamy OE, Patel N, Abdelbaset MH, Chenet L, Tokita J, Lookstein R. Acute Start Peritoneal Dialysis during the COVID-19 Pandemic: Outcomes and Experiences. J Am Soc Nephrol. 2020; 31(8): 1680–2.
12. Sourial MY, Sourial MH, Dalsan R, Graham J, Ross M, Chen W. Urgent Peritoneal Dialysis in Patients With COVID-19 and Acute Kidney Injury: A Single-Center Experience in a Time of Crisis in the United States. Am J Kidney Dis. 2020; 76(3): 401–6.
13. Arumugam V, Lamech TM, Govindasamy N, Sastry BV, Dhanapalan A, Thanikachalam DK., POS-558 Clinical characteristics and outcomes of patients with COVID-19 and renal failure requiring initiation of hemodialysis. Kidney Int Rep. 2021; 6(4): S245.
14. Use of Remdesivir in Patients With COVID-19 on Hemodialysis: A Study of Safety and Tolerance – PubMed. 2022. https://pubmed.ncbi.nlm.nih.gov/33354635/
15. Nithya G, Lamech TM, Arumugam V, Dineshkumar T, Gopalakrishnan N, Aiswarya D, et al. A clinical study on the changing dynamics of disease severity, management strategies and outcomes of COVID-19 in patients requiring haemodialysis. J Nephrol. 2021; 34(4): 999–1006.
16. Clinical Characteristics and Short-Term Outcomes of ESKD Patients Undergoing Hemodialysis with COVID-19 Infection in Madurai, South India. 2022. http://turkjnephrol.org/en/clinical-characteristics-and-short-term-outcomes-of-eskd-patients-undergoing-hemodialysis-with-covid-19-infection-in-madurai-south-india-136996
17. Sajmi S, Goutham K, Arumugam V, Gopalakrishnan N, Lamech TM, Aiswarya D. Efficacy and safety of convalescent plasma therapy in SARS-CoV2 patients on hemodialysis. Hemodial Int. 2021; 25(4): 515–22.
18. Okumura K, Nishida S, Dhand A. Trends in COVID-19 Mortality Among Solid Organ Transplant Recipients: Implications for Prevention. Transplantation. 2022; 106(8): e380–1.
19. Hilbrands LB, Duivenvoorden R, Vart P, Franssen CFM, Hemmelder MH, Jager KJ. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. Nephrol Dial Transplant. 2020; 35(11): 1973–83.
20. Arumugam V, Sastry BVRH, Solomon DJ, Gopalakrishnan N, Kannan BS, Shankar P. Clinical characteristics and outcome of novel coronavirus disease in kidney transplant recipients: A single-center prospective observational study. Indian J Transplant. 2021; 15(3): 189.
21. Shaji S, Ravindran K, Paulpandian V, Kamalakannan G, Solomon D, Kannan BS. POS-959 Clinical profile and outcome of SARS-COV2 infection in renal transplant recipients - a single centre experience. Kidney Int Rep. 2022; 7(2): S418.
22. P V, Ravindran K, Solomon D, Shaji S, Kamalakannan G, Kannan BS. POS-801 COVID associated mucormycosis in kidney transplant recipients- A case series. Kidney Int. Rep. 2022; 7(2): S343–4.
23. Betjes MGH. Immune cell dysfunction and inflammation in end-stage renal disease. Nat Rev Nephrol. 2013; 9(5): 255–65.
24. Ma BM, Tam AR, Chan KW, Ma MKM, Hung IFN, Yap DYH. Immunogenicity and Safety of

COVID-19 Vaccines in Patients Receiving Renal Replacement Therapy: A Systematic Review and Meta-Analysis. Front Med. 2022; 9: 827859.

25. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. N Engl J Med. 2021; 385(7): 661–2.
26. Thomson T, Prendecki M, Gleeson S, Martin P, Spensley K, De Aguiar RC. Immune responses following 3rd and 4th doses of heterologous and homologous COVID-19 vaccines in kidney transplant recipients. E Clin Med. 2022; 53: 101642.
27. Tiffany N Caza, Clarissa A Cassol, Nidia Messias, Andrew Hannoudi, Randy S Haun, Patrick D Walker, Rebecca M May. Glomerular Disease in Temporal Association with SARS-CoV-2 Vaccination: A Series of 29 Cases. Kidney360. 2021; 2(11): 1770-1780.
28. Ho KS, Narasimhan B, Kumar A, Flynn E, Salonia J, El-Hachem K, et al. Syndrome of inappropriate antidiuretic hormone as the initial presentation of COVID-19: A novel case report. Nefrologia 2021;41(2):219–20.
29. Yousaf Z, Al-Shokri SD, Al-Soub H, Mohamed MFH. COVID-19-associated SIADH: a clue in the times of pandemic! Am J Physiol Endocrinol Metab 2020;318(6):E882–5.
30. Kidney Outcomes in Long COVID. American Society of Nephrology. https://jasn.asnjournals.org/content/32/11/2851