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## On the occasion of world kidney day 2023; renal impacts of COVID-19

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### ABSTRACT

World kidney day is an international campaign focused on bringing awareness to kidney health throughout the world and reducing the incidence of renal disease and its related medical complications. This mini-review sought to take a short look on the renal impact of SARS-CoV-2, with a particular focus on post-COVID-19 nephropathy as a new dilemma in the era of nephrology, which can be a new concern for nephrologists that requires more attention and particular strategies. *Keywords:* SARS-CoV-2 vaccine, Glomerulonephritis, Acute kidney injury, World kidney day, SARS-CoV-2, COVID-19-related nephropathy, APOL1 gene, Collapsing glomerulopathy, Podocyte

### *Implication for health policy/practice/research/medical education:*

Nephrologists should consider the possible emergence of renal diseases following COVID-19 disease and vaccination in individuals without prior kidney issues.

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### Introduction

The coronavirus disease 2019 (COVID-19) pandemic has caused an extraordinary hindrance for health and health care delivery across the world (1). This disease spectrum has a morbidity and mortality not only due to its lung involvement but also due to its other organ derangements involving the kidney or heart (2), causing it to be regarded as a leading global health threat (3).

The international world kidney day campaign is an opportunity to bring attention to the significance of the kidney health throughout the world, and to reduce the incidence of renal disease along with its medical, social, and economic impacts. Each year there is a theme for world kidney day, with the theme for 2023 being "Kidney Health for All".

Following the introduction of COVID-19 vaccinations, several, albeit rare, cases of renal dysfunction have been reported. Furthermore, there are some cases of kidney dysfunction after six-to-twelve-month evaluation even in persons without prior kidney disease.

The medical and economic impact of COVID-19 pandemic has stretched resources for medical care of other even unrelated acute and chronic diseases even in richer nations, affecting kidney care in other areas.

We are learning more about the disease spectrum and renal manifestations of COVID-19, and a particular focus on post-COVID-19 nephropathy is necessary (3). Here we take a short look at this topic as a new dilemma in the era of nephrology, along with the presentation of the aims and strategies of "world kidney day" for this year.

### Materials and Methods

In this mini-review, we searched Google Scholar, Scopus, PubMed, EMBASE, EBSCO and Web of Science, using the following keywords: SARS-CoV-2 vaccine, glomerulonephritis, acute kidney injury, world kidney day, SARS-CoV-2, COVID-19-related nephropathy, APOL1 gene, collapsing glomerulopathy, podocyte, thrombotic microangiopathy, focal segmental glomerulosclerosis and COVID-19 vaccination. This study was conducted

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through searching through relevant articles published during the period of 2015 to 2022.

### An overview of COVID-19-related nephropathy

A short glance at some of the latest published articles in 2022 reveals that the renal system is the second most important organ system affected by this disease following the respiratory system, since a clear renal viral tropism has been detected (4).

Irrespective of the baseline renal condition, acute kidney injury (AKI) is a common occurrence following severe instances of the COVID-19 disease, which, in turn, significantly increases morbidity and death among patients. Acute renal tubular necrosis is the underlying pathology in most of these AKI cases, though, there have also been several case reports of collapsing glomerulopathy as well as other morphologic lesions.

AKI following COVID-19 is usually multi-factorial in pathogenesis. Hemodynamic instability, cytokine-mediated damage, hypoxic injury, along with direct viral invasion and its cytopathic effect are usually implicated (3). Even a mild kidney dysfunction worsens the prognosis and increases the hospitalization rate and risk of death in those effected (4).

It seems that renal tropism of SARS-CoV-2 plays a trivial role for a significant renal involvement (5), since the morphological features inflammatory response accompanied by severe SARS-CoV-2 are more common. Therefore, hemodynamic variability due to sepsis or multi-organ dysfunction and the resultant pre-renal state are the main factors in COVID-19 renal involvement (3).

As a lung-kidney crosstalk, conditions such as acute respiratory distress syndrome (ARDS) or invasive ventilation following COVID-19 have a detrimental effect on the development of AKI (5). It is plausible that, high ventilation pressures affect kidney perfusion and, consequently prompt the development of sudden renal disturbance. Accordingly, inflammatory reaction associated with ARDS is another factor for lung-kidney crosstalk. The endothelial cell dysfunction, characteristic of COVID-19, as well as the COVID-19-induced hypercoagulability state are additional factors (5). In fact, the pathologic findings of thrombotic microangiopathy have been well described in occasional cases (3).

Collapsing focal segmental glomerulosclerosis (FSGS), the most commonly detected glomerulopathy following COVID-19, is the result of podocyte injury. It is well known that collapsing glomerulopathy is related to APOL1 gene polymorphisms, notably in cases of patients with African ancestry. The APOL1 gene encodes apol1 (apolipoprotein-1), as a part of high-density lipoprotein compound (6).

Upregulation of the APOL1 gene through the viral

infection leads to initiation of toll-like and interferon receptors, hence causing dysregulation of podocytes in the glomeruli (7,8). These genetic variants are common in people of western African origin (6), and several case reports of collapsing glomerulopathy following COVID-19 were in individuals of African descent (9). Importantly, the carriers of APOL1 variants were found to be at greater risk of chronic renal disease, with a risk of FSGS found to be 17 times greater than that of the general population (6). Following endothelial damage and local inflammation due to COVID-19, the cascade of immune cell infiltration and microvascular thrombi will supervene (10).

Rare cases of minimal change disease, anti-glomerular basement membrane disease, immunoglobulin A nephropathy, anti-neutrophilic cytoplasmic antibody-associated vasculitis and other variants of FSGS following COVID-19 have also been reported (3).

### COVID-19 and chronic kidney disease

Chronic kidney disease (CKD) seems to be an independent risk factor for poor outcomes in cases of COVID-19. Even in adjusting for the other comorbidities, such as hypertension, diabetes, and vascular disease, present in patients with CKD, that are also risk factors for poor outcomes (11). In a midsize US dialysis provider from February to June of 2020, patients on dialysis who developed COVID-19 disease, had a mortality rate of 24.9%, about 7-times higher than similar group of patients who were not diagnosed with COVID-19 (12). While this data is mostly from the period that COVID-19 vaccines were just introduced and most patients were not vaccinated, it emphasizes the importance of prevention and treatment in this group. Diabetes mellitus, hypertension, advanced age and cardiovascular disease are more represented in dialysis patients and, apart from kidney disease, are all strong risk factors for COVID-19 morbidity and mortality.

While the immunogenicity rate after vaccination is lower in patients receiving dialysis, especially those with diabetes (13), vaccination still has a reasonable protective effect against severe forms of COVID-19 in dialysis patients (14). In dialysis patients after COVID-19 vaccination, the protective antibody titers are diminished faster than in the general population, but booster doses significantly increase antibody levels and should be emphasized accordingly (15).

#### Post-COVID 19-vaccination renal dysfunction

Vaccination is by far the most effective strategy to prevent or decrease the severity of COVID-19 disease and related death and morbidities (1), with SARS-CoV-2 vaccines being a crucial point of control over the COVID-19 pandemic. Covid vaccines are mostly effective

and safe. With billions of doses globally administered, certain side effects have understandably emerged. Post vaccination kidney related injuries are well-described (16). Not surprisingly, various autoimmune disorders following COVID-19 vaccination have also been described (1). The pathologic features and clinical consequences are diverse (17). Diminished appetite and poor oral intake, nausea and vomiting, shortly after vaccination can lead to a pre-renal state. Tubular cell dysfunction, interstitial inflammation and glomerular lesions, and vasculopathy/vasculitis are among other pathologic lesions. IgA nephropathy with painless gross hematuria, minimal change glomerulopathy with nephrotic syndrome, thrombotic microangiopathy, and acute tubulointerstitial nephritis have been reported (17); all these patients had normal baseline renal function before vaccination.

Recently, Luo et al examined the incidence of post-vaccine renal injury by Moderna, Pfizer-BNT, and Janssen. They identified 1331 cases of AKI from December 2020 to June 2021 from the database of the Vaccine Adverse Event Reporting System (VAERS) (18). They found that Pfizer-BNT had a stronger association with AKI than Moderna and Janssen, with the majority of AKI patients being elderly. The etiology of post-vaccine AKI mostly was volume depletion, followed by sepsis. This study showed cases who injected Pfizer-BNT and developed AKI had the highest mortality (19.78%) compared to those who received Moderna (17.78%), or Janssen (12.36%).

### Conclusion

The COVID-19 pandemic has had direct and indirect detrimental effects on global healthcare and the global economy, respectively. Not only have patients with CKD and end stage kidney disease been disproportionately affected, but even patients with no underlying kidney disease have been shown to develop AKI that significantly worsened outcomes. While vaccination in patients with CKD and ESRD has an attenuated and shortened immunogenic response, it is still the most effective way of preventing severe forms of disease in this population. Vaccination has so far been carried out at billions of doses and unsurprisingly, side effects including cases of different types of renal injury can occur, creating more challenge for the world of nephrology.

### Authors' contribution

Conceptualization: SVT and AP.

Methodology: SVT.

Validation: SVT.

Investigation: SVT and AP.

Resources: AP.

Data curation: KR.

Writing—original draft preparation: SVT, AP.

Writing—review and editing: KR and AP.

Visualization: SVT.

Supervision: AP.

Project administration: AP.

### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical issues

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

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