COVID-19 AND KIDNEY DISEASE: WHERE WE ARE AND WHERE DO WE GO FROM HERE

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ABSTRACT

SARS-CoV-2/COVID-19 pandemic has been challenging for the healthcare system worldwide by simulating tremendous **efforts** to develop therapeutic strategies that target all the patients. Currently, more than 6.6 million deaths have been reported worldwide. As the extent of the clinical implications of COVID-19 infection began to unfold, health professionals realized that COVID-19 was not an isolated respiratory disease alone, but rather a systemic one, affecting multiple organs. The pandemic was particularly demanding for nephrology specialists as kidneys were among the most affected organs. They were simultaneously forced to provide treatment and follow-up to their chronic kidney disease patients, a highly vulnerable and high-risk population. Kidney involvement was wide-ranging and included acute kidney injury, de-novo glomerular and chronic kidney disease, progression of pre-existing chronic kidney disease, and the impact in kidney transplants and vaccination. The present paper makes a comprehensive assessment of the kidney involvement during COVID-19 pandemic, based on biennial follow-ups, studies and a literature review.

Keywords: Covid-19, kidney disease, nephrology

1. INTRODUCTION

The COVID-19 pandemic has claimed the last two years more than 6.6 million lives globally, placing an enormous strain on societies and healthcare systems around the world (WHO 2022). At the beginning of the pandemic, efforts were made to prevent infection from spreading, by early recognition and prompt isolation of infected patients, and rigorous contact tracing

(Thomas Craig *et al*., 2021). However, as containment of the infection became unpredictable and challenging, the focus shifted in mitigating the effects of the disease. The pandemic proved the critical role of health system resiliency in providing essential health services and maintaining health systems functioning. Therefore, the cornerstone of health system resiliency is keeping health workers, patients and visitors safe through a series of measures (WHO 2022), including infection prevention and control best practices such as intermittent quarantine, mandatory use of face masks and protective equipment, social distancing, restrictions in private and public gatherings, and domestic and international travel to minimize transmission and stop the outbreaks and protect vulnerable and at-risk populations as stated in (Haiqian *et al*., 2021; Dadras *et al*., 2021).

Patients with chronic kidney disease (CKD) are particularly susceptible to developing severe infection due to their immunocompromised status and the presence of preexisting comorbidities associated with worse outcomes and higher mortality. Patients receiving long-term renal replacement therapy (RRT) are among these vulnerable populations. Renal replacement therapies encompass in-center hemodialysis, home hemodialysis, peritoneal dialysis, and renal transplantation. End-stage renal disease (ESRD) patients, unlike the general population, cannot adhere to social distancing measures, as the overwhelming majority undergo in-center hemodialysis in specific dialysis units, increasing their risk of infectious interactions with infected patients or healthcare workers (Fox and Poulikakos 2021). Renal transplant patients represent another distinctly susceptible population.

Health statistics in Albania show that about 10% of the population is affected by chronic kidney disease (CKD), including end-stage-kidney disease (ESKD). Around 1,500 patients diagnosed with ESKD are treated with hemodialysis and about 300 patients have undergone a successful renal transplant procedure (Institute of Public Health Albania 2018 and FSDKSH). Current data worldwide has shown that the estimated mortality rate in these two subgroups is at about 20%, significantly higher compared to that of the general population (Ibernon *et al*., 2021). These findings suggest that these patients, specifically, require broader testing, priority in vaccination and more complex management in case of infection, to ensure better outcomes.

2. MATERIALS AND METHODS

The present paper is an observational, retrospective, cohort study overviewing the involvement of kidney during COVID-19 infection. Patients suffering from acute kidney injury (AKI) to patients undergoing development or progression of chronic kidney disease (CKD) are here involved. In addition, the impact the COVID-19 pandemic on renal transplant patients is

investigated. Here, the data of chronic maintenance hemodialysis patients collected from the electronic medical records of a single dialysis center at Hygeia International Hospital Tirana, Albania between June 2020 and January 2022 were used. The total number of patients involved is 170. The presence of COVID-19 infection was confirmed through RT-qPCR test in pharyngeal swabs. We obtained baseline patient characteristics including demographic, clinical, laboratory data and past medical history, which were statistically analyzed using the IBM SPSS Statistics 26.

In addition to the biennial follow-up (June 2020 and January 2022) and long experience, a wide literature was used for a better understanding of the renal implications caused by COVID-19 infection among chronic kidney disease patients, and previously healthy adults.

3. RESULTS

The present study was carried out between June 2020 and January 2022, and 170 chronic hemodialysis patients were involved. Results showed that 52 out of 170 chronic hemodialysis patients were diagnosed with COVID-19 infection. The mean age was 61.5±12.3 years, and 65.4% of the patients were men. We found that elevated C reactive protein, high RDW, low lymphocyte and eosinophil counts were risk factors for severe COVID-19 disease. The mortality rate among **vaccine** recipients was 8%, and among unvaccinated patients 66.7% (Table 1-2). Lymphopenia and eosinopenia were the strongest predictors of mortality. Moreover, mortality was noted to be higher in patients with diabetic nephropathy and peripheral vascular disease (Rista *et al*., 2022).

Between March 2021 and April 2021, 80.6% of the patients underwent full vaccination process (2 doses of Pfizer-BioNTech vaccine), whereas 19.4% of them refused vaccination. Following the vaccination campaign, mortality among vaccinated patients was estimated at 8%, as opposed to 66.7% in unvaccinated patients. Logistic regression analysis showed that even after adjusting for age, gender and dialysis vintage, vaccination status was statistically significant on mortality rate ($p<0.001$). Moreover, our data showed that among vaccinated patients who subsequently contracted Covid-19, 72% developed a mild infection, 24% a moderate infection and 4% developed severe disease. On the contrary, in the unvaccinated group 5.3% and 14.3% developed a mild and moderate infection, respectively, with the remaining 80% of patients developing severe disease. After adjusting for age, gender and dialysis vintage, age ($p<0.021$) and vaccination status ($p<0.005$) were significant predictors of disease severity (Rista *et al*., 2022).

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[b]	Age	.229	.146	2.454	1	.117	1.257	.944	1.675
	Sex(1)	-23.371	11909.204	.000	1	.998	.000	0.000	
	Vacination	-4.432	2.161	4.206	1	.040	.012	.000	.822
	YearsinHD	-.091	.342	.071	1	.789	.913	.466	1.785
	Constant	-13.637	9.905	1.896	1	.169	.000		

Table 1. Variables in the Equation[a].

Table 2. Vacination statis * Severity Crosstabulation[a].

			Severity			Total
			Mild	Moderate	Severe	
Vacination statis	no	Count	1	1	4	6
		% within Vacination statis	16.7%	16.7%	66.7%	100.0%
		% within Severity	5.3%	14.3%	80.0%	19.4%
	yes	Count	18	6	1	25
		% within Vacination statis	72.0%	24.0%	4.0%	100.0%
		% within Severity	94.7%	85.7%	20.0%	80.6%
Total		Count	19	7	5	31
		% within Vacination statis	61.3%	22.6%	16.1%	100.0%
		% within Severity	100.0%	100.0%	100.0%	100.0%

a. Vaccine = yes

4. DISCUSSION

Renal involvement during the COVID-19 pandemic was heterogeneous, but classifiable into the following six major categories: i) previously healthy patients who developed acute kidney injury (AKI), ii) COVID-19 associated and vaccine-induced glomerular disease, iii) chronic kidney disease patients infected with COVID-19, iv) chronic hemodialysis patients infected with COVID-19, v) renal transplant patients infected with COVID-19, and vi) patients with kidney involvement undergoing vaccination.

Potential mechanisms of kidney injury during COVID-19 infection

Several mechanisms have been proposed to explain kidney injury during COVID-19 infection. Hypovolemia originating from fluid loss due to fever or gastrointestinal symptoms, leads to intravascular volume depletion and AKI (Ng *et al*., 2020). Acute tubular injury develops due to ischemic, toxic factors, or a combination of both, along with coagulation and endothelial dysfunction in the setting of sepsis (Mohamed *et al*., 2020; Ng *et al*., 2020).

Acute tubular injury occurs in the context a hyperinflammatory syndrome associated with an extensive release of pro-inflammatory cytokines, the so-called “cytokine storm” that may induce rhabdomyolysis and granular cast nephropathy, kidney-lung crosstalk leading to bidirectional damage to both organs, widespread thrombotic microangiopathy due to coagulation dysregulation and disseminated intravascular coagulation (DIC) (Mohamed *et al*., 2020; Ng *et al*., 2020; Tang *et al*., 2020; Ye *et al*., 2020). Some studies suggest that collapsing glomerulopathy, a severe form of glomerular disease observed in some patients, develops due to this hyperinflammation, as well (Ng *et al*., 2020). The pathogenesis of other glomerular diseases associated with COVID-19 infection is less well-defined.

Nephrotoxic medications are important contributors to kidney injury, having been widely used during the pandemic. Antiviral agents and antibiotics due to concerns for secondary bacterial infections predisposing for tubulointerstitial diseases, diuretics and anti-inflammatory drugs to modulate inflammation and persistent fever can also be an important source of acute kidney injury (Binois *et al*., 2020; Ng *et al*., 2020).

COVID-19 and acute kidney injury (AKI)

SARS-CoV-2 causes acute kidney injury (AKI) with direct and indirect mechanisms. Direct injury occurs due to endothelial damage from viral entry, complement activation, local inflammation and collapsing glomerulopathy (Ng *et al*., 2020). Indirect effects on the kidney include the development of sepsis, use of nephrotoxic medications, systemic inflammation,

hypercoagulability, and thromboembolic disease and can be more prevalent (Mohamed *et al*., 2020; Ng *et al*., 2020; Tang *et al*., 2020; Ye *et al*., 2020). Clinical manifestations of COVID-19-induced AKI included proteinuria, hematuria, elevated creatinine, elevated urea, as well as hyperkalemia and acidosis.

The prevalence of AKI among COVID-19 patients was first estimated to be around 3-9% in the first studies emerging from China at the beginning of the pandemic (Chan *et al*., 2021). Further studies then showed that the prevalence of AKI among hospitalized patients ranged between 28-43%, with half of them showing mild disease with a 1.5-2-fold increase of serum creatinine and the remaining half developing moderate and severe disease with more than doubling of serum creatinine (Chan *et al*., 2021b; Samuel *et al*., 2021). AKI was present in 61-79% of severely ill patients, with the need for renal replacement therapy (RRT) in 19% of hospitalized patients and 34-73% of ICU patients (Chan *et al*., 2021b).

A study comparing the development of AKI in hospitalized patients with and without COVID-19 revealed the incidence of AKI was higher among the 2600 patients who had COVID-19 compared with over 19,500 patients who were hospitalized for other reasons (31 versus 18 percent), which could not be explained by differences in the traditional risk factors for AKI between the two groups (Fisher *et al*., 2020; Moledina *et al*., 2021). When comparing mortality rates between COVID-19 and influenza, the 90-day mortality was higher among patients who had COVID-19 compared to those who had influenza (35 versus 9 percent) (Strohbehn *et. al*., 2021).

AKI in the setting of COVID-19 is associated with poor outcomes and high mortality rates. One retrospective study of nearly 10,000 patients showed that in-hospital mortality progressively increased from patients without AKI at 7%, to those with AKI not requiring renal replacement therapy (RRT) at 46%, to 79% in patients with AKI requiring acute RRT (Dwyer *et al*., 2022). Different studies found that mortality of AKI requiring renal replacement therapy varied from 35-90% (Dwyer *et al*., 2022; Roushani *et al*., 2022).

COVID-19 associated and Vaccine-induced glomerular disease

A minority of patients developed nephrotic-range proteinuria, with or without AKI. Multiple reports of collapsing focal segmental glomerulosclerosis (FSGS), presenting with high-grade proteinuria and AKI, emerged during the pandemic, and were commonly associated with high-risk APOL-1 genotypes (Akilesh *et al*., 2021; Shetty *et al*., 2021). Other glomerular diseases have been reported including IgA nephropathy, anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, anti-GBM (Goodpasture's) disease (Huang *et al*., 2020; Prendecki *et. al*., 2020; Uppal *et al*., 2020).

Vaccination with messenger RNA (mRNA) vaccines (Pfizer-BioNTech) has been associated with the development of glomerular diseases or relapses in pre-existing glomerular diseases (Klomjit *et al*., 2021). The most commonly reported de-novo glomerular diseases following vaccination include IgA nephropathy, anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, minimal change disease, anti-GBM (Goodpasture's) disease (Anderegg *et al*., 2021; Klomjit *et al*., 2021; Lebedev *et al*., 2021; Tan *et al*., 2021).

COVID-19 and chronic kidney disease (CKD)

Kilis-Pstrusinska *et al*., (2021) said that many studies confirmed a decline in renal function following COVID-19 infection, with elevated serum creatinine levels (≥ 30%) at discharge in 7.4% of patients, and persistent altered renal function in about 7-8% of patients. This deterioration was more significant in patients that develop AKI, with COVID-19-induced AKI promoting a more rapid renal decline in eGFR by 11.3 mL/min/1.73 m2/year, as opposed to those with AKI of other origins (Dwyer *et al*., 2022).

25% of the patients that developed AKI had a reduced renal function at discharge, and 31% patients with AKI requiring renal replacement therapy (RRT) continued dialysis (Kilis-Pstrusinska *et al*., 2021; Dwyer *et al*., 2022).

COVID-19 in chronic hemodialysis patients in Albania

Chronic hemodialysis patients have a higher risk for developing severe COVID-19 because of multiple co-morbid conditions, and impaired immune system compared to the general population. Chronic hemodialysis patients are more susceptible to severe COVID-19 infection, primarily due to pre-existing concomitant diseases and immune system dysfunction. Higher morbidity and mortality rates have been documented, as opposed to the general population. A significant difference in mortality rates was observed even among dialysis and non-dialysis CKD patients, with estimated mortality rates four times higher in the dialysis population, compared to non-dialysis CKD patients (Kocak *et al*., 2021)

This increased susceptibility to adverse outcomes has been attributed to several risk factors including demographic factors and older age, underlying comorbidities, impaired and suboptimal immune response and socioeconomic factors. Consequently, these past two years, a lot of effort was put into determining robust predictors of disease severity and mortality in this population, to ensure an early and aggressive treatment of high-risk patients and ultimately improve the prognosis among these vulnerable patients.

Our study found that elevated C reactive protein, high RDW, low lymphocyte and eosinophil counts were risk factors for severe COVID-19 disease, whereas lymphopenia and eosinopenia were the strongest predictors

of mortality (Rista *et al.*, 2022). These findings are consistent with larger studies that have revealed lymphopenia and eosinopenia to be the most important predictors of severity and mortality in COVID-19 infection (Ghizlane *et al*., 2021; Yan *et al*., 2021).

Kidney transplantation

Many studies have shown the last two years that kidney transplant recipients are more susceptible to severe health conditions and fatality, in addition to the impact on kidney transplantation surgery due to the COVID-19 pandemic (Akalin *et al*., 2020; Pinchera *et al*., 2022). Moreover, all the medical resources were allocated to providing treatment for COVID-19 infection making surgery procedures kidney transplant recipient an elective procedure. Consequently, the number of patients receiving kidney transplants decreased considerably.

As kidney transplant patients undergo immunosuppressive therapy and some of them have underlying comorbidities as well, they are more prone to developing severe forms of the infection.

Early in the pandemic, several studies reported significantly higher mortality rates among kidney transplant patients, compared to those in the general population. Estimated mortality ranged from 13% to 28% in kidney transplant recipients (Akalin *et al*., 2020). Optimal tailoring and stopping of the immunosuppressive regimes, while maintaining low-dose steroids and providing adequate supportive care during the infection was exceptionally challenging. Nevertheless, as treatment of COVID-19 infection was standardized, modifying the intensity of the immunosuppressive therapy during active infection coupled with early use of antiviral agents, supportive measures and vaccination led to reductions in mortality rates in this population (Akalin *et al*., 2020; Pinchera *et al*., 2022). Organ rejection following COVID-19 infection has been reported to be around 1.9% (Pinchera *et al*., 2022).

Vaccination

Given their immunocompromised status and underlying comorbidities, the CKD patients would be considered a particularly vulnerable population and prioritized in vaccination programs, making them one of the first groups to undergo full vaccination. ESRD patients have a suppressed immune response due to the accumulation of uremic toxins, accelerated aging, increased oxidative stress and chronic inflammation, associated metabolic disorders (impairment in the synthesis of vitamin D and erythropoietin) and potential immunosuppressive therapies.

Vaccination efficacy in non-dialysis dependent CKD patients

Vaccination among non-dialysis dependent CKD patients was highly effective in preventing symptomatic infection, hospital admissions and fatality. A large, observational study in British Columbia, Canada comprising 18,850 patients with CKD found that after receiving two or three doses the risk of infection was less than 71% and 78%, respectively (Atiquzzaman *et al*., 2022). In this same group, the risk of COVID-19 related admissions and death was less than 84% and 90%, respectively. (Atiquzzaman *et al*., 2022).

Vaccination efficacy in dialysis dependent CKD patients

The studies subsequently carried out to assess the efficacy of vaccines in these patients found an impressive rate of seroconversion with detectable S-protein-reactive T cell immunity in 59-97% of patients (Babel *et al*., 2022). Despite the suboptimal humoral response that was observed, vaccination against COVID-19 among dialysis patients was found to be safe and adequate, with no significant differences as opposed to the general population (Babel *et al*., 2022).

Several studies have been conducted to assess the efficacy of vaccination in preventing symptomatic infection, COVID-19-related hospitalizations and death in dialysis patients. They found that full vaccination with two doses prevented symptomatic infections and death in 18.1% and in 66.0 % of patients, respectively (Torres *et al*., 2022). Moreover, after adjusting for other risk factors, full vaccination in dialysis patients was associated with a 75% lower risk of admission and 88% lower risk of death (Ashby *et al*., 2022).

These findings underscore the significant impact vaccination has had in preventing severe diseases, minimizing hospitalization rates and preventing deaths, among patients on chronic hemodialysis.

Vaccination efficacy in renal transplant patients

Many studies involving cohorts of renal transplant recipients have confirmed a low immunogenicity of COVID-19 vaccination (Babel *et al*., 2022). When comparing renal transplant patients with dialysis patients, a significantly lower seropositivity rate was noted among renal transplant patients at 26.1%, as opposed to those of 84.3% and 92.4% observed among hemodialysis and peritoneal dialysis, respectively (Babel *et al*., 2022). Nevertheless, a robust S-protein-specific CD4+ T cell response has been observed, leading to the hypothesis that renal transplant patients may develop a sufficient cell-mediated immunity that confers some protection, despite an inadequate humoral response (Babel *et al*., 2022).

Further studies evaluating the type of vaccine and the need of additional boosters are necessary to develop a vaccination program tailored to the specifics of this population.

5. CONCLUSIONS

As evidence shows that COVID-19 infection, despite its severity, affects renal function, history of COVID-19 infection should be considered a risk factor for kidney disease. Implementing screening programs to detect declining renal function following COVID-19 infection of high-risk patients may be beneficial to an early detection of kidney disease.

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