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Coronavirus Pandemic

Sequels of COVID-19 in nephrology. Chronic kidney patients are more prone to hemodialysis need and mortality

Erjola Bolleku[1], Ermal Likaj[2], Larisa Shehaj[3], Ilir Akshija[4], Edmond Puca[5], Entela Puca[6,7], Xhesi Baci[1], Alma Idrizi[1]

[1] *Nephrology Department, UHC Mother Tereza, Tirane, Albania*
[2] *Cardiac Surgery Department, UHC Mother Tereza, Tirane, Albania*
[3] *Nephrology Department, Salus Hospital, Tirane, Albania*
[4] *Statistics Service, UHC Mother Tereza, Tirane, Albania*
[5] *Service of Infection Disease, UHC Mother Tereza, Tirane, Albania*
[6] *American Hospital, Tirane, Albania*
[7] *Western Balkans University, Tirane, Albania*

Abstract

Introduction: Acute kidney injury involves inflammation and intrinsic renal damage, and is a common complication of severe coronavirus disease 2019 (COVID-19). Baseline chronic kidney disease (CKD) confers an increased mortality risk. We determined the renal long-term outcomes of COVID-19 in patients with baseline CKD, and the risk factors prompting renal replacement therapy (RRT) initiation and mortality.
Methodology: We included 77 patients (median age was 67.1 ± 13.7 years) with a history of renal failure at baseline and recovery from COVID-19 at our institution, in a retrospective analysis from December 2020 to May 2021. Demographic, clinical, and laboratory data were compared between patients requiring RRT and those who did not. A correlogram analysis determined the risk factors for RRT. Survival analysis using the Kaplan-Meier method and Cox regression statistics assessed in-hospital mortality.
Results: 70.1% of the patients had CKD. RRT initiation was higher in patients with known CKD (46.4%) than in those with no known CKD (28.5%). Those with diabetic nephropathy had a higher predisposition for RRT initiation compared to other CKD etiologies. Diabetics (42.3%) and hypertensive nephropathy (33%) were the most common etiologies in the general population. Blood urea nitrogen (BUN), creatinine, phosphorus, lactate dehydrogenase, and proteinuria were significantly higher; and platelets and calcium levels were lower; in patients requiring RRT. Decreased lymphocyte count negatively correlated with BUN levels.
Conclusions: Known CKD patients had a higher initiation rate of RRT, and laboratory features suggestive of kidney damage. However, RRT patients did not have an increased risk of mortality.

Key words: COVID-19; chronic kidney disease; renal replacement therapy.

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Introduction

The majority of coronavirus disease 2019 (COVID-19) patients experienced moderate symptoms, although a few went on to experience multiorgan failure and severe respiratory distress syndrome. The kidneys are among the organs that are most prone to injury or failure as a result of COVID-19. According to some studies, organ transplantation and an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m^2 were associated with a significant risk of mortality in COVID-19 patients with chronic kidney disease (CKD) [1–3]. Early data revealed acute kidney injury (AKI) as a substantial complication of severe COVID-19, in addition to CKD being a risk factor for poor outcomes among patients with COVID-19. The causes of COVID-19-related AKI are likely multifactorial; and include viral septicemia, pneumonia, aggravated inflammatory response, endothelial damage, hypercoagulability, myocardial dysfunction, drug nephrotoxicity, and the effects of general hypoxia and dehydration on renal perfusion. Additionally, COVID-19 worsens AKI, necessitates more renal replacement therapy, and slows full renal recovery before discharge [4–8]. These elements raise the possibility of developing CKD incidentally, or progression of preexisting CKD. The development and persistence of inflammation, renal fibrosis, aberrant kidney gene expression patterns, and functional deficits after ischemic kidney damage may prevent a full recovery of kidney function in many individuals with AKI, even if serum creatinine (SCr) often returns to normal levels after the condition. These underlying

pathophysiological pathways may be amplified in COVID-19 along with deteriorating diabetes or hypertension control. Novel kidney-specific plasma and urine biomarkers may be able to identify the primary underlying causes and identify the patients who are most at risk of developing CKD during COVID-19 hospitalization [9–11]. Patients with COVID-19 at the acute phase have detailed epidemiological and clinical characteristics, pathophysiology, and complications described, but the long-term effects of the condition are still completely unknown. The purpose of this study was to describe the long-term effects of COVID-19 on kidney function and to define any potential mortality and renal replacement therapy (RRT) risk factors.

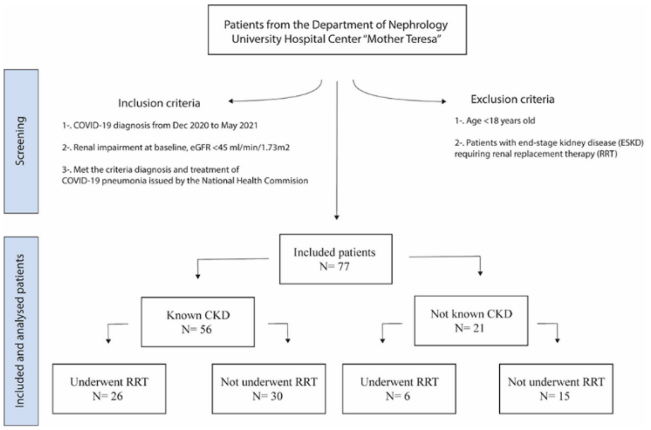
Methodology

Study design and populations

This was a retrospective study conducted at Mother Teresa Hospital, the main tertiary teaching hospital in Tirana, Albania, which was assigned the responsibility for the treatment of severe COVID-19 patients by the local government. Patients were enrolled if they met all of the following eligibility criteria: 1) age 18 years or older; 2) diagnosed with COVID-19 infection and admitted in the hospital at any time between December 2020 and May 2021; 3) had renal impairment at baseline, which was defined as eGFR < 60 mL/min/1.73m^2, persisting for 3 months or more; 4) met the uniform recovery criteria issued by the Committee of Technical Experts in Albania for the diagnosis and treatment of COVID-19 pneumonia.

We excluded those who were younger than 18 years old and those who had end-stage kidney disease (ESKD) requiring RRT. Given the retrospective nature of the analysis of electronic medical records, individual-level informed consent was not obtained.

Figure 1. Patients classified by chronic kidney disease (CKD) and renal replacement therapy (RRT).



Study outcomes

The primary outcome was the incidence of RRT in patients with COVID-19 infection with renal impairment at the presentation. The secondary outcomes were mortality rate and risk factors related to RRT.

Data collection

The demographic characteristics, clinical symptoms, and laboratory data were extracted from electronic medical records. All the comorbidities were reported by patients or family members. During the hospitalization, the patients were followed up with laboratory exams, including serum creatinine, blood urea nitrogen (BUN), hemoglobin, leukocyte, lymphocyte, platelet count, D-dimer, high-sensitivity C-reactive protein (CRP), cholesterol, phosphorus, glucose, ferritin, and lactate dehydrogenase (LDH). A urine dipstick test to assess proteinuria was performed in all patients. The eGFR was calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) method. Data of patients who had been supported by RRT and had died were also extracted.

Statistical analysis

The variables were classified as demographics, laboratory findings including inflammation markers, and dialysis status, at the first admission after a COVID-19 episode. Categorical variables were presented by frequencies and percentages; continuous variables were presented as means and standard deviations. A value of $p < 0.05$ was considered significant during comparison procedures. Survival analysis and Cox regression statistical procedure were used to evaluate mortality in the hospital. Statistical analysis was realized through the IBM SPSS Statistics 26.0 software (IBM Corp, Armonk, NY, USA).

Results

Among the 77 patients who participated in this study, 56 (72.7%) were known to have underlying CKD. A total of 32 patients underwent RRT during the study period; 26 of those patients had CKD (Figure 1). Therefore, the incidence of RRT in COVID-19 patients who had renal insufficiency at the first presentation was 41.6%. Moreover, 46.4% of patients with identified CKD required dialysis, compared to 28% of patients with unknown CKD status. Thus, patients who were known to have CKD had a higher probability of ending up with RRT ($p = 0.045$).

Overall, nearly 60% of patients were male and the median age was 67.1 ± 13.7 years. Nearly 90% of the

Table 1. Baseline patient characteristics.

Clinical Characteristic	Overall (N = 77)	Patients who underwent RRT (N = 32)	Patients who did not undergo RRT (N = 45)	*p* value
Age (years)	67.1± 13.8	66.2 ± 14.0	67.7 ± 13.9	0.630
Male gender (%)	58.4%	68.8%	51.1%	0.773
Known comorbidity	87.0%	90.6%	84.4%	0.596
Known diabetes mellitus	50.7%	50.0%	53.3%	0.773
Time of hospitalization, days	56.0 ± 50.7	50.7 ± 53.5	59.6 ± 49.1	0.494
Hemoglobin, g/dL	10.5 ± 2.2	9.6 ± 2.0	11.1 ± 2.1	0.002
White blood cells, 1000/mm^3	10.8 ± 4.4	10.6 ± 4.5	11.0 ± 4.4	0.682
Lymphocyte, %	13.9 ± 8.1	13.0 ± 8.6	14.5 ± 7.9	0.417
Platelet, 1000/mm^3	248.7 ± 130.6	242.3 ± 108.1	253.2 ± 145.6	0.719
Blood urea nitrogen, mg/dL	207.1 ± 118.2	248.2 ± 120.6	177.3 ± 108.2	0.009
Serum creatinine, mg/dL	6.1± 4.3	8.6 ± 5.0	4.2 ± 2.3	0.000
Albumin, g/dL	3.2 ± 0.7	3.2 ± 0.6	3.2 ± 0.8	0.944
Potassium, mmol/L	5.0 ± 1.4	5.1 ± 1.6	4.9 ± 1.3	0.433
Sodium, mmol/L	137.2 ± 6.6	136.7 ± 4.3	137.6 ± 7.9	0.518
Magnesium, mEq/L	1.8 ± 0.4	1.9 ± 0.4	1.8 ± 0.4	0.699
Calcium, mg/dL	6.4 ± 3.4	5.5 ± 3.4	7.2 ± 3.3	0.037
Phosphorus, mg/dL	5.2 ± 1.7	6.1 ± 1.8	4.5 ± 1.2	0.001
Uric acid, mg/dL	7.7 ± 2.5	7.5 ± 2.0	7.9 ± 2.9	0.558
Glucose, mg/dL	159.7 ± 114.5	150.1 ± 77.7	166.4 ± 134.6	0.547
C-reactive protein, mg/dL	6.9 ± 8.0	5.6 ± 4.8	7.8 ± 9.7	0.232
D-dimer, µg/mL	3,551.2 ± 4,926.0	4,537.8 ± 5,544.1	2,811.3 ± 4,350.7	0.197
Lactate dehydrogenase, U/L	312.6 ± 229.7	419.0 ± 310.8	234.2 ± 85.3	0.005
Aspartate aminotransferase, U/L	31.2 ± 34.0	36.9 ± 46.9	27.3 ± 21.0	0.296
Alanine transaminase, U/L	40.7 ± 75.4	56.5 ± 113.3	30.0 ± 27.8	0.227
Ferritin, ng/mL	634.3 ± 814.4	502.7 ± 347.9	765.8 ± 1,108.1	0.441
Proteinuria	91.9%	100%	86.1%	0.048
Hematuria	90.3%	92%	89.2%	0.999

RRT: renal replacement therapy.

patients had at least one comorbidity including CKD and diabetes mellitus (DM). Notably, those who underwent RRT had significantly more underlying CKD than those who did not. The average time of hospitalization from the moment of recovery from COVID-19 was 56 ± 50 days. All individuals who participated in this study had high SCr at the first presentation. During hospitalization, the mean peak SCr was 6.1± 4.3 mg/dL and the mean peak BUN was 207.1 ± 118.2 mg/dL. Patients who required RRT were found to have significantly greater peak SCr and BUN levels than those who did not. In addition, patients who underwent RRT had significantly lower hemoglobin, lower serum calcium, higher phosphorus, and higher serum LDH than those who did not. All of the patients showed elevated levels of high-sensitivity CRP, and coagulopathies were prominent, with a mean D-dimer concentration of 3,551.2 ± 4,926.0 g/mL. Moreover, the urine dipstick test showed that most patients had proteinuria and hematuria. In addition, proteinuria was found as a major predictor of the initiation of RRT (p = 0.048) (Table 1)

Seventy percent of patients had a history of kidney disease, with the following causes: 32.5% diabetic nephropathy, 26% hypertensive nephrosclerosis, 9.1% autosomal dominant polycystic kidney disease (ADPKD), 7.8% glomerular diseases (GD), and 1.3% chronic allograft nephropathy (CAN). Regarding the etiology of patients known for CKD, it was observed that those who were diagnosed with diabetic nephropathy had a high predisposition to start RRT (p = 0.037) (Table 2).

Pearson correlation analysis indicated that age had a negative correlation with platelet levels (p = 0.008) and a positive correlation with BUN (p = 0.017) and D-dimer (p = 0.007) levels. The older patients (> 65 years old) had higher BUN and D-dimer values. In addition, patients whose hospitalization time for COVID-19 recovery was longer had lower BUN levels (p = 0.017) and higher albumin levels (p = 0.007). When the

Table 2. Causes of chronic kidney disease (CKD).

Etiology of CKD	Total (N =77)	Patients who underwent RRT (N =32)	Patients who did not undergo RRT (N =45)
Diabetic nephropathy	25 (32.5%)	12 (15.6%)	13 (16.9%)
Hypertensive nephrosclerosis	20 (26.0%)	9 (11.7%)	11 (14.3%)
ADPKD	7 (9.1%)	3 (3.9%)	4 (5.2%)
Glomerular diseases	6 (7.8%)	5 (6.5%)	1 (1.3%)
Post-kidney transplantation with CAN	1 (1.3%)	0	1 (1.3%)
Unknown history of CKD	18 (23.4%)	3 (3.9%)	15 (19.5%)

ADPKD: adult dominant polycystic kidney disease; CAN. chronic allograft nephropathy; RRT: renal replacement therapy.

Table 3. Pearson correlation of risk factors.

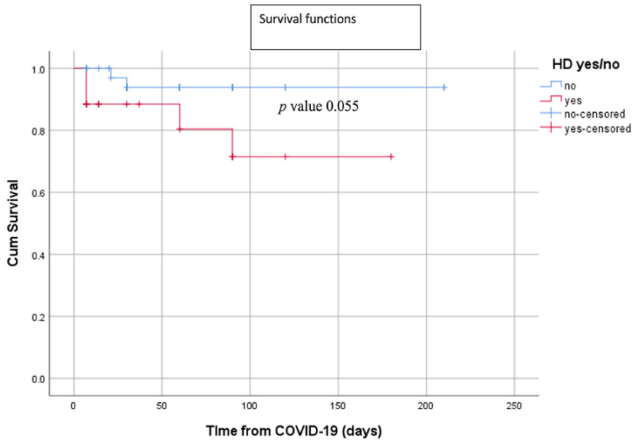
Risk factors		Age (years)	Time from COVID-19 (days)	Lymphocyte (%)	PLT (1000/mm³)	BUN	Creatinine (mg/dL)	Albumin (g/dL)	PCR (mg/dL)	Ferritin (ng/mL)	D-dimer (µg/mL)
Age (years)	Pearson correlation	1	0.168	-0.109	-0.298**	0.273*	0.195	-0.180	-0.064	0.213	0.354**
	Sig. (2-tailed)		0.182	0.345	0.008	0.017	0.096	0.165	0.597	0.317	0.007
	N	77	65	77	77	76	74	61	70	24	56
Time from COVID-19 (days)	Pearson correlation	0.168	1	0.141	0.123	-0.198	0.056	0.375**	0.037	-0.114	0.086
	Sig. (2-tailed)	0.182		0.262	0.329	0.017	0.659	0.007	0.781	0.613	0.565
	N	65	65	65	65	64	64	51	59	22	47
Lymfocyte (%)	Pearson correlation	-0.109	0.141	1	0.082	-0.252*	-0.073	0.124	-0.019	-0.215	-0.238
	Sig. (2-tailed)	0.345	0.262		0.478	0.028	0.537	0.343	0.874	0.313	0.047
	N	77	65	77	77	76	74	61	70	24	56
PLT (1000/mm³)	Pearson correlation	-0.298**	0.123	0.082	1	-0.141	-0.125	-0.117	0.183	-0.082	-0.099
	Sig. (2-tailed)	0.008	0.329	0.478		0.225	0.288	0.371	0.130	0.702	0.466
	N	77	65	77	77	76	74	61	70	24	56
BUN	Pearson correlation	0.273*	-0.198	-0.252*	-0.141	1	0.193	-0.058	-0.155	-0.066	0.140
	Sig. (2-tailed)	0.017	0.117	0.028	0.225		0.102	0.658	0.202	0.759	0.305
	N	76	64	76	76	76	73	60	69	24	56
Creatinine (mg/dL)	Pearson correlation	0.195	0.056	-0.073	-0.125	0.193	1	-0.018	-0.033	-0.080	0.234
	Sig. (2-tailed)	0.096	0.659	0.537	0.288	0.102		0.893	0.788	0.710	0.045
	N	74	64	74	74	73	74	58	68	24	55
Albumin (g/dL)	Pearson correlation	-0.180	0.375**	0.124	-0.117	-0.058	-0.018	1	-0.159	-0.386	-0.256
	Sig. (2-tailed)	0,165	0.007	0.343	0.371	0.658	0.893		0.239	0.076	0.085
	N	61	51	61	61	60	58	61	57	22	46
PCR (mg/dL)	Pearson correlation	-0,064	0.037	-0.019	0.183	-0.155	-0.033	-0.159	1	0.101	0.086
	Sig. (2-tailed)	0.597	0.781	0.874	0.130	0.202	0.788	0.239		0.637	0.544
	N	70	59	70	70	69	68	57	70	24	52
Ferritin (ng/mL)	Pearson correlation	0.213	-0.114	-0.215	-0.082	-0.066	-0.080	-0.386	0.101	1	-0.041
	Sig. (2-tailed)	0.317	0.613	0.313	0.702	0.759	0.710	0.076	0.637		0.863
	N	24	22	24	24	24	24	22	24	24	20
D-dimer (µg/mL)	Pearson correlation	0.354**	0.086	-0.238	-0.099	0.140	0.234	-0.256	0.086	-0.041	1
	Sig. (2-tailed)	0.007	0.565	0.047	0.466	0.305	0.045	0.085	0.544	0.863	
	N	56	47	56	56	56	55	46	52	20	56

BUN: blood urea nitrogen; COVID-19: coronavirus disease 2019; PCR: polymerase chain reaction; PLT: platelets; Sig: significant.

lymphocytes levels were compared, it was noted that patients with low lymphocyte levels had high BUN (p = 0.028) and D-dimer (p = 0.047) levels. Furthermore, it was found that creatinine levels had a positive correlation with D-dimer levels (p = 0.045). Patients who presented with higher creatinine levels also had high D-dimer levels, which is a marker of inflammation and thromboembolism (Table 3).

Out of 77 patients included in the study, 8 died during hospitalization (10.4%). Among these 8 dead patients, 5 were treated with dialysis. The presentation time from the point of recovery from COVID-19 of these patients who underwent RRT was shorter than those who did not. Patients who required RRT tended to have a higher mortality rate (p = 0.055; Figure 2).

Figure 2. Survival rate of patients categorized by requiring hemodialysis (HD) vs. those not requiring HD.



Discussion

The renal damage manifestation in COVID-19 is diverse, ranging from incidence of elevated SCr or BUN, to AKI requiring RRT [11–14]. On the other hand, CKD can increase the risk of COVID-19 associated AKI, which might develop into persistent kidney dysfunction, delayed recovery and the need for long-term dialysis [1,7,12]. Our retrospective study evaluated the long-term association between COVID-19 and a variety of co-morbidities, particularly CKD, which was mostly caused by diabetic nephropathy and hypertension [15,16]. We found that COVID-19 infected patients who had renal insufficiency at the first presentation were at risk for requiring RRT later in the admission, especially in the case of patients with underlying CKD. In our study, the incidence of RRT in COVID-19 patients who had renal insufficiency at the first presentation was 41.6%, whereas 46.4% of patients with diagnosed CKD required dialysis. The incidence rate of RRT in our study was more than that reported by Yang *et al.,* which ranged from 5.4% to 16.3% among COVID-19 patients requiring RRT, and may be due to the different populations under study [17]. We included individuals with baseline renal impairment, who were at high risk of developing AKI and requiring RRT.

We found that patients requiring RRT were associated with a trend toward increased in-hospital mortality, although the increase was not statistically significant due to the smaller sample size. Shi *et al*. reported that patients with CKD showed an 8.37-fold increased risk of mortality and severity post COVID-19 infection [18]. This may be because CKD patients are

prone to developing infections, sepsis, and bacteria, which result in poor outcomes that prolong hospital stays and increase mortality rates [19–22]. Consistent with earlier research, we also discovered that proteinuria was an important predictor of RRT initiation. In addition, the higher peak of SCr and BUN levels were associated with RRT. The robust link between higher BUN levels and decreased lymphocyte counts in our study is an interesting result and is also a significant feature of CKD [23–25]. This distinguishing feature can be explained by the plausible mechanisms including direct viral cytopathic effects, inhibitory effects of cytokines, including TNF-alpha, IL-6, IL-10, and immune cell redistribution into the lungs and lymphoid organs [15]. This immune alteration is aggravated by protein-energy wasting (PEW) [26–28].

To our knowledge, this study is the first retrospective study that investigated long-term renal outcomes of COVID-19 infected patients with baseline renal impairment. We also explored the risk of RRT in these populations. However, our study had some limitations. The sample sizes were small and might not be sufficient to detect the difference in mortality rate. Further studies with a larger number of participants are needed.

Conclusions

The incidence of RRT in COVID-19 patients who had kidney impairment at the first presentation was 41.6%. Individuals who were known to have CKD had a higher probability of requiring RRT during admission. Patients who required RRT were found to have significantly greater peak SCr and BUN levels, lower hemoglobin, lower serum calcium, higher phosphorus, and higher serum LDH, than those who did not. However, patients who underwent RRT were not significantly associated with in-hospital mortality.

Ethical approval

The study was conducted with approval from the Ethical Board of the Hospital.

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Corresponding author

Prof Assoc Edmond Puca.
Service of Infection Disease, UHC Mother Tereza,
Rruga e Dibres, N 372, Tirane, Albania
Tel: +355684062820
Email: edmond_puca@yahoo.com

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