

Comparison of different kidney diseases in patients with COVID-19: Clinical and radiological CT scores assessment

Comparación de diferentes enfermedades renales en pacientes con Covid-19: Evaluación clínica y del score radiológico

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RESUMEN

Antecedentes: Nuestro objetivo fue investigar el curso clínico y las implicaciones radiológicas en diferentes enfermedades renales con COVID-19. **Materiales y métodos:** El presente estudio se realizó en 107 pacientes con COVID-19 que tenían diferentes cursos de enfermedad renal. Se compararon 30 pacientes con enfermedad renal crónica (ERC), 38 pacientes con hemodiálisis de mantenimiento (MHD) y 39 pacientes con trasplante renal (RT). Se obtuvieron datos de características demográficas, marcadores sanguíneos, mortalidad y morbilidad hospitalaria y puntuaciones de la TC de tórax. **Resultados:** Los pacientes con RT eran más jóvenes que los grupos con ERC ($47,0 \pm 11,4$ frente a $71,8 \pm 11,5$ años, respectivamente; $<0,001$) y los pacientes con MHD ($67,7 \pm 10,2$ años, $p <0,001$). Los valores de proteína C

reactiva, procalcitonina, dímero D y ferritina fueron significativamente más bajos en los pacientes con RT ($p <0,05$). La tasa de lesión renal aguda fue menor en los pacientes con RT que con ERC ($p = 0,007$) y la tasa de desarrollo de sepsis fue baja en comparación con los grupos de MHD y ERC ($p = 0,004$). La necesidad de ventilación mecánica ($p = 0,013$) y la tasa de mortalidad fueron significativamente menores en los pacientes con RT que en los pacientes con MHD ($p = 0,008$). Con respecto a la puntuación total de la TC de tórax, no hubo diferencia en los pacientes con MHD en comparación con otros grupos, mientras que se encontró que era menor en los pacientes con RT que con ERC ($p = 0,002$). **Conclusión:** El pronóstico de COVID-19 varía en diferentes enfermedades renales en términos de morbilidad, mortalidad y afectación radiológica.

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PALABRAS CLAVE: Hemodiálisis; Viral; Enfermedad renal crónica; Insuficiencia renal

ABSTRACT

Background: We aimed to investigate the clinical course and radiological involvements in different kidney diseases during the COVID-19 infection. **Materials and Methods:** The present study was conducted on 107 patients with COVID-19 having different kidney disease courses. Thirty patients with chronic kidney disease (CKD), 38 patients with maintenance hemodialysis (MHD), and 39 patients with renal transplantation (RT) were compared. Data on demographic characteristics, blood markers, in-hospital mortality and morbidities, and thorax CT scores were obtained. **Results:** RT patients were younger than the CKD groups (47.0 ± 11.4 vs. 71.8 ± 11.5 years, respectively; $p < 0.001$) and MHD patients (67.7 ± 10.2 years, $p < 0.001$). C-reactive protein, procalcitonin, D-dimer, and ferritin values were significantly lower in RT patients ($p < 0.05$). The acute kidney injury rate was lower in RT patients than in CKD ($p = 0.007$), and the rate of sepsis development was low compared to MHD and CKD groups ($p = 0.004$). The requirement for mechanical ventilation ($p = 0.013$) and the mortality rate were significantly lower in RT patients than in MHD patients ($p = 0.008$). Concerning total thorax CT score, there was no difference in MHD patients compared to other groups, whereas it was found to be lower in RT patients than in CKD ($p = 0.002$). **Conclusion:** The prognosis of COVID-19 infection varies in different kidney diseases regarding morbidity, mortality, and radiologic involvement.

KEYWORDS: Hemodialysis; Viral; Chronic kidney disease; Kidney failure

INTRODUCTION

As the new type of Coronavirus Disease 2019 (COVID-19) outbreak spreads, reviewing the resources of announced pandemic hospitals, hospitalizing non-COVID-19 patients who need to be hospitalized, and guiding public health recommendations and interventions are extremely important for the identification of predictive factors for severe infection. Chronic obstructive pulmonary disease, chronic heart

disease, hypertension, immunocompromising, and uremic patients have been identified as potential risk factors for COVID-19 progression and the requirement for admission to intensive care units (ICU) ⁽¹⁻⁴⁾. The disease has unique implications for patients developing acute kidney injury (AKI), as well as patients with CKD or end-stage renal disease (ESRD) and renal transplant patients (RT). CKD is an independent risk factor for hospitalized and non-hospitalized patients with non-COVID-19 pneumonia ^(1,5). In published meta-analyses and studies, CKD has increased the progression of COVID-19 disease several times more ^(6,7). COVID-19-related mortality rates differ in patients with predialysis CKD, maintenance hemodialysis (MHD), and RT. A multicenter study found mortality rates in these patients to be 28.4%, 16.2%, and 11.1%, respectively. Among these groups, kidney transplant patients had the lowest mortality rate, despite being under chronic immunosuppression and comorbidities ⁽³⁾. However, different studies have shown that mortality rates due to COVID-19 are more heterogeneous in kidney transplant patients ^(2,8). An important factor determining the severity of COVID-19 is computed tomography (CT) radiological findings. A positive correlation was found between the total CT score and disease severity of different lung lobe involvement in non-uremic patients ⁽⁹⁾. Concerning radiologic findings, when comparing patients on MHD with healthy individuals, Wu J et al. showed that the percentage of bilateral abnormalities in the lungs was higher in computed tomographic (CT) scans (82% versus 69%, $p = 0.15$), meanwhile in the unilateral lung the percentage was lower (10% versus 27%, $p = 0.03$) ⁽¹⁰⁾.

The objectives of this retrospective cohort study were to describe the clinical manifestations of SARS-CoV-2 infection in MHD, predialysis, and kidney transplant populations and describe prognostic factors on admission to ICU and mortality.

MATERIALS AND METHODS

This comparative study was conducted on 107 patients with COVID-19, including 30 stage 3-4 CKD, 38 MHD, and 39 RT patients admitted to Sakarya University Faculty of Medicine hospital. The study followed the principles of the Declaration of Helsinki and after approval of the ethics committee of our university faculty of

medicine (No: E-71522473-050.01.04-14848-127). Patients with symptoms of pneumonia and confirmed COVID-19 infection on reverse transcription-polymerase chain reaction (RT-PCR) were consecutively enrolled. All adult (aged ≥ 18 years) patients who were hospitalized from April 15, 2020, to November 29, 2020, were eligible. Patients were included in the study groups when: 1) were over 18 years old, 2) not having a history of malignancy, and 3) had proven radiological involvement on thorax CT, excluding 1) having AKI at admission, 2) NP RT-PCR negative, 3) not having radiological involvement, 4) patients with stable serum creatinine for at least three months for the predialysis CKD group, and 5) patients who underwent intubation on their first admission to the emergency department.

The total number of patients was 140. In addition, patients were not included in the study when they developed AKI based on CKD in the last three months and until the diagnosis of COVID-19 positivity was confirmed. During the study period, the number of patients from all three groups who did not meet the inclusion criteria was 33; 12 patients were in the predialysis group (3 with malignancy before the diagnosis of COVID-19, 8 PCR negative, and AKI in one patient). In the MHD group, 15 patients (9 PCR negative, 4 Catheter infections, and two patients whose data could not be reached), whereas six patients were excluded from the transplant group because of PCR negativity.

The patient's demographic and laboratory findings were recorded. A single radiologist blindly determined the total thorax CT score of the patients at the time of their first admission to the hospital.

Total CT scoring of patients

All patients underwent unenhanced CT with a 64-slices multi-detector CT (MDCT) scanner (Toshiba Aquilion) when they came to clinical attention due to pneumonia symptoms. All images were reviewed by one radiologist independently blinded to the clinical information. Patients were instructed on breath-holding to minimize motion artifacts; CT images were then acquired during a single breath-hold. CT visual, quantitative evaluation was based on summing up the acute lung inflammatory lesions involving each lobe. Using a semiquantitative scoring system to estimate the

pulmonary involvement of all these abnormalities based on the area involved⁽¹¹⁾. Each of the five lung lobes was visually scored from 0 to 5 as 0, no involvement (0%), minimal (1–25%), mild (26–50%), moderate (51–75%), or severe (76–100%); 1, < 5% involvement; 2, 25% involvement; 3, 26%–49% involvement; 4, 50%–75% involvement; 5, > 75% involvement.^(11,12) The total CT score (TCTS) was the sum of the individual lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement).

Statistical analysis

Statistical analysis was performed with SPSS Statistics (IBM Corporation, Somers, NY) software (version 22). The normality of the distribution of continuous variables was determined using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on the normality of their distribution. Frequency tables interpreted categorical variables. Categorical features and relationships between groups were assessed using an appropriate chi-squared test. Variables that were not normally distributed were compared using the Kruskal-Wallis test. When binary comparisons were required, we used the Mann-Whitney U test. Normally distributed variables were compared using a one-way ANOVA test. When an overall significance was observed, pairwise post hoc tests were performed using Tukey's test. The Levene test was used to assess the homogeneity of the variances. The statistically significant two-tailed p-values were considered as <0.05 .

RESULTS

Patients' characteristics

One hundred and seven individuals confirmed with COVID-19 enrolled in the present study. Patients were divided into three groups pre-existing non-dialysis-dependent CKD group (CKD group, no = 30), pre-existing kidney failure maintenance hemodialysis (MHD group, no = 38), and patients with previous kidney transplant patients (RT group, no = 39). CKD patients consisted of patients with stable renal function tests for at least one month before the diagnosis of COVID-19 disease. Convalescent plasma was administered in 6.7% of pre-dialytic patients, 13.9% of HD patients, and

17.9% of transplant patients (p= 0.390). All our patients had no ethnic demographic differences.

All MHD patients were on a regular HD program three days/week for at least six months when they were diagnosed with COVID-19 disease. All RT patients received immunosuppressive treatment with Tacrolimus, mycophenolic acid derivatives, and corticosteroids.

The median time from COVID-19–related symptom onset to admission was 3 (IQR 3-5) days among CKD patients, 3 (IQR 2- 5) days among MHD patients, and 4 (IQR 2-6) days among RT patients (p = 0.458). The frequencies of symptoms

occurring in the disease differed significantly between the three groups (p < 0.05) (**Table 1**). The median (IQR) duration of dialysis in the MHD group was 3.6 years (1–7) and 9 (0-180) months in the RT group before kidney transplantation. The median (IQR) time from kidney transplantation to the onset of COVID-19 disease in the RT group was 47.0 (0-191.3) months, and the type of kidney transplantation was living transplantation in 84.7% of patients.

The demographic data of the patients, comorbidities, and treatment approaches are shown in **Table 1**.

Table 1: Demographic and baseline characteristics of groups with kidney disease diagnosed with COVID-19

Items	CKD Group (n=30)	MHD Group (n=38)	RT Group (n=39)	P value
Age, mean (years)	71.8±11.5	67.7±10.2	47.0*±11.4	<0.001
Sex (F/M), n (%)	9/21 (30/70)	13/25 (34.2/65.8)	12/27 (30.8/69.2)	0.920
Initial symptom, yes (%)				
Cough	18 (60.0)	16 (42.1) *	29 (74.4) *	0.016
Fever	4 (13.3)	8 (21.1)	22 (56.4) *	<0.001
Sore throat	0*	3 (7.9)	11 (28.2) *	0.001
Dyspnea	20 (66.7)	22 (57.9)	19 (48.7)	0.325
Loss of smell	1 (3.3)	0	1 (2.6)	0.555
Myalgia	1 (3.3)	4 (10.5)	20 (51.3) *	<0.001
Diarrhea	1 (3.3)	1 (2.6)	3 (7.7)	0.529
Blood groups, n (%)				
A	15 (50.0)	13 (34.2)	20 (51.3)	0.523
B	6 (20.0)	7 (18.4)	9 (23.1)	
O	8 (26.7)	14 (36.8)	9 (23.1)	
AB	1 (3.3)	4 (10.5)	1 (2.6)	
Comorbid Condition				
Hypertension	20 (66.7)	37 (97.4)	23 (59.0)	<0.001
Diabetes Mellitus	7 (23.3)	20 (52.6)	8 (20.5)	0.005
Heart Disease	8 (26.7)	20 (52.6)	8 (20.5)	0.007
Chronic obstructive pulmonary disease	3 (10.0)	7 (18.4)	0	0.021
Supporting/antiviral treatment, n (%)				
Convalescent plasma	2 (6.7)	5 (13.9)	7 (17.9)	0.390
Dexamethasone	4 (13.3)	8 (21.1)	20 (51.3) *	0.001
Oseltamivir treatment	13 (43.3) *	12 (31.6)	5 (12.8) *	0.017
Favipiravir treatment	14 (46.7)	19 (50.0)	30 (76.9) *	0.016
Antibacterial antibiotics	12 (40.0)	15 (39.5)	6 (15.4) *	0.032
The median time from onset of symptoms to admission, days, IQR	3 (3-5)	3 (2-5)	4 (2-6)	p=0.458

*Continuous variables were expressed as means ± standard deviation, or medians (min-max), depending on the normality of their distribution, and categorical variables as numbers with percentages for the description of baseline characteristics. If p < 0.05, single groups that differ or groups that differ from each other were written in bold and marked with an asterisk. Chronic Kidney Disease (CKD), Maintenance Hemodialysis (MHD), Renal Transplantation (RT)

RT patients were younger than the CKD groups (47.0 ± 11.4 vs. 71.8 ± 11.5 years, respectively; p <

0.001) and MHD patients (67.7 ± 10.2 years, $p < 0.001$). Concerning ABO blood groups, there were no significant differences between patient groups. The most common comorbidity was hypertension (66%, 97.4%, and 59%, respectively), and these were significantly higher in the MHD group than in the other groups ($p < 0.05$). Also, the other comorbidity ratios were significantly higher in the MHD than in the other groups ($p < 0.05$).

While used dexamethasone and favipiravir treatments were at a higher rate in RT patients, hydroxychloroquine and oseltamivir treatments were lower than in the CKD group. Similarly,

antibacterial antibiotics used in the RT group were lower than in other groups ($p < 0.05$) (**Table 1**).

Patient's laboratory data

As expected, serum creatinine levels in MHD patients were significantly higher than in the other groups ($p < 0.001$). C-reactive protein (CRP) and procalcitonin values were markedly lower in RT patients. D-dimer and ferritin levels were significantly lower in kidney transplant patients ($p < 0.001$) (**Table 2**). Other comparative biochemical parameters between groups are shown in **Table 2**.

Table 2: Laboratory findings and comparison before and after COVID-19 infection treatment

Variables	CKD Group (n=30)	MHD Group (n=38)	RT Group (n=39)	P value
Serum creatinine, mg/dL	1.8 (1.5-2.1)	5.7 (5.1-7.4) *	1.3 (1.0-1.9)	<0.001
White blood cell count, $10^3/\text{mm}^3$	7.30 (4.7-9.3)	7.2 (5.18-9.9)	5.77 (4.5-7.4)	0.091
Lymphocyte count, $10^3/\text{mm}^3$	1.01 (0.7-1.3)	0.90 (0.7-1.2)	1.1 (0.7-1.5)	0.489
Neutrophil to lymphocyte ratio	5.7 (2.8-13.2)	5.1 (3.1-14.6)	3.7 (2.7-6.4)	0.065
Platelet count, $10^3/\text{mm}^3$	215* \pm 102	158* \pm 63	190 \pm 68	0.010
C-reactive protein (CRP), mg/L	84.5 (36.5-164.5)	75.8 (15.3-178.3)	19.0* (5.9-43.2)	<0.001
Procalcitonin, ng/mL	0.52(0.11-0.90)	1.55 (0.48-6.92)	0.09*(0.03-0.47)	<0.001
ALT, IU/L	24.0 (14.8-49.0)	16.5*(11.8-27.0)	23.0(17.0-30.0)	0.030
AST, IU/L	36.5*(23.3-69.5)	22.9 (15.0-35.8)	26.0 (19.0-36.0)	0.018
Fibrinogen, mg/dL	383 \pm 182	457 \pm 121	424 \pm 135	0.401
D-dimer, ng/mL	936 (483-1968)	1400 (665-3210)	336*(212-777)	<0.001
Serum albumin, gr/L	3.6 (3.2-4.1)	3.4 (3.1-26.4)	3.6 (3.3-4.3)	0.618
Ferritin, ng/mL	460*(129-1113)	1134*(508-2000)	129*(62-573)	<0.001

*Continuous variables were expressed as means \pm standard deviation or medians (interquartile ranges). Note. If $p < 0.05$, single groups that differ or groups that differ from each other were written in bold and marked with an asterisk. Chronic Kidney Disease (CKD), Maintenance Hemodialysis (MHD), Renal Transplantation (RT)

As shown in **Figure 1**, while AKI in RT patients was less than in CKD, the rate of sepsis development was lower in both groups. In addition, the requirement for mechanical ventilation and the mortality rate were significantly lower in RT patients than in MHD patients. AKI had a higher rate in patients with CKD ($p < 0.05$)

Regarding lung involvement, the total thorax

CT score (TCTS) was calculated blindly by a single radiologist by evaluating the thorax CT taken at the first admission of all patients. While there was no significant difference in TCTS in MHD patients compared to other groups, it was lower in RT patients than in CKD ($p = 0.002$) (**Figure 2**).

A sample chest CT section for each group is shown in **Figure 3**.

Figure 1:

A: Acute kidney injury,
B: Sepsis,
C: Mechanical ventilation,
D: Mortality

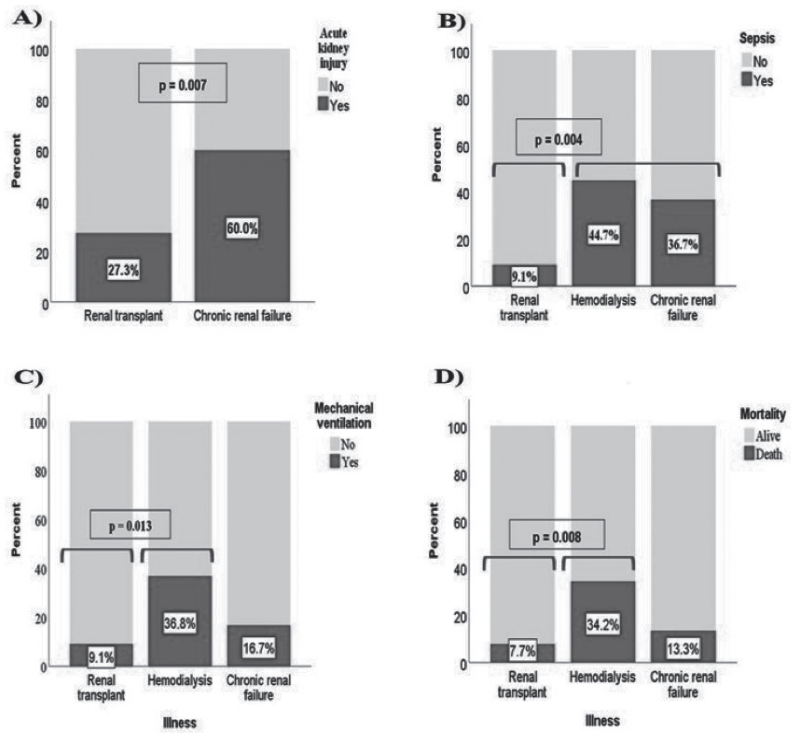


Figure 2: Total thorax computed tomographic score

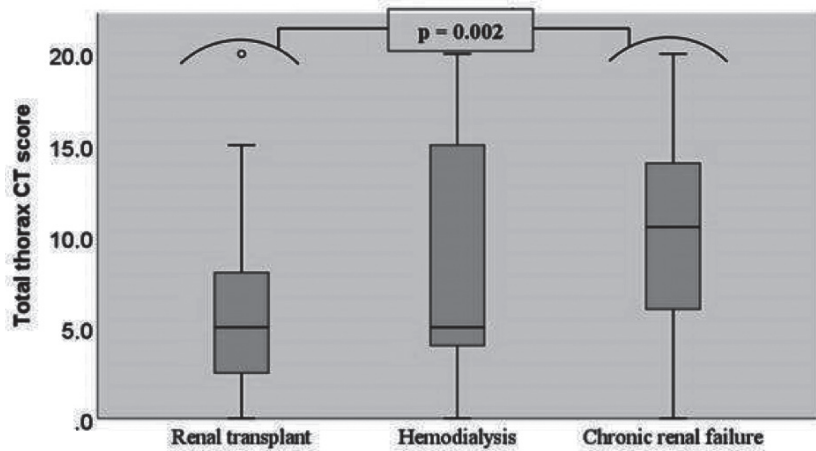
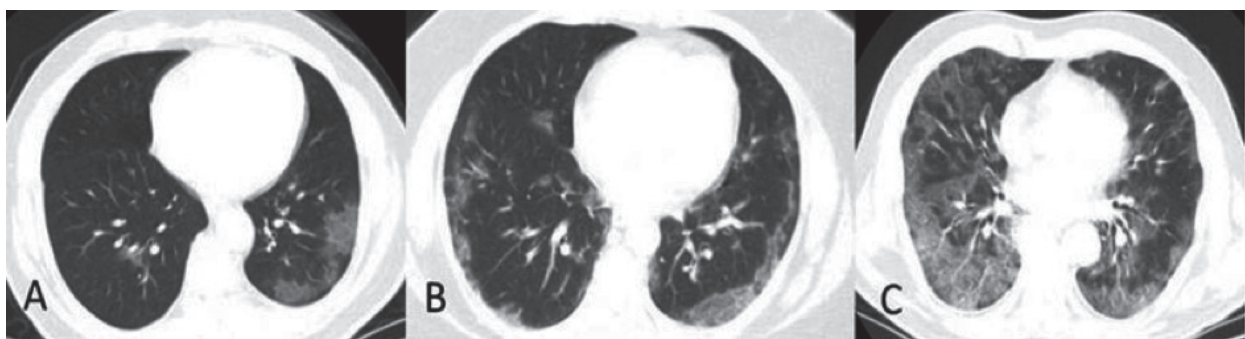


Figure 3: A sample chest CT section for each group



A: Renal transplant, B: Hemodialysis, C: Chronic renal failure

DISCUSSION

This study compared the clinical course and radiological involvements of patients with different kidney diseases diagnosed with COVID-19. We found that patients who underwent chronic hemodialysis programs had a higher mortality rate, more developed sepsis, and more recruitment of mechanical ventilators than pre-existing CKD and kidney recipients. The risk of COVID-19-related death is significantly higher in dialysis and kidney transplant patients than in the previously healthy population^(2,3,13). In a retrospective cohort study including 4,264 critically ill patients with COVID-19 (143 patients receiving maintenance dialysis; 521 patients with pre-dialytic CKD, and 3,600 patients without pre-existing CKD) compared to patients without pre-existing CKD, dialysis patients had a higher risk for 28-day in-hospital death (adjusted HR, 1.41 [95% CI, 1.09 - 1.81]), while patients with pre-dialytic CKD had an intermediate risk (adjusted HR, 1.25 [95% CI, 1.08-1.44])⁽⁷⁾. In another retrospective study, the 28-day mortality rate was 21.3% [95% confidence interval (95% CI) 14.3 - 30.2%] in kidney recipients and 25.0% (95% CI 20.2 - 30.0%) in the dialysis population⁽¹³⁾. Similarly, our single-center study found that mortality rates in the MHD patient group were the highest compared to the other groups.

We found that mortality and recruitment to mechanical ventilator ratios were significantly lower for kidney recipients than for the MHD group. Mortality rates in kidney transplant patients vary depending on factors such as the patients' different demographic characteristics, the transplant source, and the transplant time until the onset of symptoms of COVID-19^(14,15). The low mortality rates in our transplant patients could be that they were younger than the other groups, had a lower incidence of concomitant systemic disease, and 85% of patients received living kidney transplantation compared to other study populations^(8,13).

Chest CT is a complementary diagnostic method for diagnosing COVID-19 pneumonia because the results are available almost immediately and are highly effective for determining disease severity⁽¹⁶⁾. Some radiologic scoring systems such as semiquantitative CT severity score (CTSS), Reporting and Data System (CO-RADS), and TCTS were developed to determine the severity

of the disease and to evaluate the prognosis of the disease^(11,16,17). The present study found that the TCTS values in pre-dialytic CKD patients were significantly higher than in RT patients. The possible reason for low TCTS in immunocompromised patients might be that the patient's white blood cells and neutrophil counts were significantly lower than the other groups, and they may be less likely to form a consolidation area in the lung tissue. To our knowledge, this is the first study comparing the radiologic findings in different kidney diseases.

We found that the development of AKI in the CKD group was more than two-fold higher than in the RT group. Perhaps, the main reason for this result is that the mean age of our patients with CKD was significantly higher than that of RT patients. In the healthy population, AKI due to COVID-19 disease has been reported frequently and is an independent risk factor for mortality⁽¹⁸⁻²⁰⁾. On the other hand, one study including 20,133 patients with COVID-19 defined that 16.2% of patients had CKD (21). Another study detected that the CKD incidence was 12% in critically ill patients, and the AKI was 5% in patients with non-dialysis-dependent CKD⁽⁷⁾. Since the basal serum creatinine values were unknown in most patients diagnosed with COVID-19 at admission, knowing previous values could give clear information about CKD incidence and the incidence of AKI in CKD.

Our paper has several limitations, such as the retrospective study design and the small number of study groups.

CONCLUSION

The prognosis of COVID-19 in kidney diseases is relatively poor. This study compared patients with COVID-19 in three different kidney disease categories and showed disease-related mortality and some morbidity conditions. To our knowledge, we compared, for the first time, using specific radiological involvement scores in patient groups with these three different disease categories. However, extensive, comparative studies with more patients are needed to consolidate our results.

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