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The progress of chronic renal disease patients followed by the diagnosis of COVID-19 in ICU

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ABSTRACT

Aim: The mortality and morbidity of COVID-19 disease are higher in patients with comorbidities. In this study, we staged patients with chronic renal failure hospitalized in the intensive care unit (ICU) and aimed to evaluate the process of the disease according to the stage of failure.

Material and Method: The medical records of 249 patients followed in Ankara City Hospital MH3 ICU were reviewed retrospectively. The patients were divided into three stages according to their estimated glomerular filtration rate (e-GFR) value (stage 1: e-GFR≥90 ml/min/1.73 m^2, stage-2: e-GFR: 15-89 ml/min/1.73 m^2, stage- 3: e-GFR≤15 ml/min/1.73 m^2). Data such as age, gender, comorbidity status, length of stay in the ICU, duration of mechanical ventilation, and mortality rate of the patients were recorded. Patients who were evaluated as stage-2 were also classified into 3 stages (stage-2a: e-GFR: 60-89 ml/min/1.73 m^2, stage-2b: e-GFR:30-59 ml/min/1.73 m^2, stage-2c: e-GFR: 15-29 ml/min/1.73 m^2) and evaluated with the same parameters.

Results: The mean age of all patients was 71 years. It was found that the intubation rate was higher (p=0.012) and the mortality rate was higher (p=0.003) in patients evaluated as stage-3. APACHE II and SOFA scores were higher than the other groups (p=<0.001, p=<0.01). In addition, IL-6, procalcitonin, D-dimer, and ferritin levels were also found to be significantly higher in these patients. Hemoglobin and thrombocyte levels were significantly lower than the other groups. When stage-2 patients were divided into subgroups, it was found that APACHE II and SOFA scores, mechanical ventilation rate, and mortality rate were higher in stage-2c than the other subgroups. While CRP, procalcitonin, and D-dimer values were significantly higher in this group, hemoglobin, thrombocyte, and lymphocyte values were found to be low.

Conclusion: The mortality rate is high in COVID-19 patients with chronic kidney disease(CKD) in ICU. As the stage of the disease increases, the mechanical ventilation rate and mortality rate of the patients increase gradually. For this reason, it may be recommended to be more careful in terms of preventive measures in cases of CKD.

Keywords: COVID-19, chronic kidney disease, mortality, intensive care unit, glomerular filtration rate

INTRODUCTION

Coronavirus disease 2019 (COVID-19) disease started in December 2019 in Wuhan, China. Then, it spread all over the world and was declared a pandemic by the World Health Organization (WHO) as of March 2020 (1-3). One of the targets of COVID-19, which affects many systems, is the kidneys. The effects of COVID-19 disease on kidney functions are thought to be multifactorial. First, it was thought that it might have a direct cytopathic effect on the kidney since SARS-COV-2 RNA could be detected in the urine (4). In addition, it is thought that the virus acts on ACE-2 receptors and that these receptors are found more in the kidneys, which strengthens this thesis (5). Secondly, it was thought that immune complexes might accumulate in the kidney, especially through a T-lymphocyte-mediated mechanism, but this could not be proven by electron microscopy (6). Thirdly, it is thought that viral-derived cytokines may have indirect effects on kidney tissue such as shock, rhabdomyolysis, and hypoxia (7).

In a study by Richardson et al. (8), it was reported that 20% of patients hospitalized with the diagnosis of COVID-19 developed acute kidney injury(AKI) and that 3.2% of these patients required renal replacement therapy(RRT). There are data showing that COVID-19 disease is more severe and the mortality rate is higher in pre-existing chronic

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kidney damage (9). Based on these data, it has been reported that the mortality of patients with signs of renal failure (such as hematuria, proteinuria) is high even after other causes have been excluded (9). For this reason, it has been emphasized that it may be important to monitor kidney function tests and detect abnormalities early, even in patients presenting with mild flu symptoms (9).

Research on COVID-19 continues to increase in all areas and is noticed in the literature. (10-13). Studies on the course of COVID-19 are also ongoing in patients with chronic kidney damage. In this study, we aimed to examine the course and characteristics of the disease in the current population hospitalized in the intensive care unit (ICU).

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No 1 Clinical Researches Ethics Committee (Date: 15.06.2022, Decision No: E1-22-2617). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients Criteria

249 patients diagnosed with COVID-19 in Ankara City Hospital Intensive Care Unit between 01.03.2020-01.01.2022 were included in the study. Patients with pregnancy status and a history of renal transplant were not included in the study.

Study Design

Patients' data, files, and follow-up forms were reviewed retrospectively. The estimated glomerular filtration rate (e-GFR) was calculated and recorded with the modification of diet in renal disease (MDRD) formula. Afterward, the data of these patients such as age, gender, comorbidity, length of stay in the intensive care unit, duration of mechanical ventilation, and mortality rate were recorded. Patients were first classified into three stages (stage 1: e-GFR >90 ml/min/1.73 m^2, stage-2: e-GFR: 15-89 ml/min/1.73 m^2, stage-3: e-GFR ≤ 15 ml/min./1.73 m^2) were separated. Then, the patients who were evaluated as stage-2 were also divided into 3 stages themselves (stage-2a: e-GFR: 60-89 ml/min/1.73 m^2, stage-2b: e-GFR:30-59 ml/min/1.73 m^2, stage-2c: e-GFR: 15-29 ml/min/1.73 m^2) were separated and evaluated with the same parameters. Demographic data and laboratory data of all groups were compared.

Statistical Analysis

Shapiro Wilk test was used for assessing whether the variables follow normal distribution or not. Continuous variables were presented as median (minimum: maximum) and mean±standard deviation values. Categorical variables were reported as n (%). According to the normality test results, the Kruskal Wallis test or ANOVA test was used if the number of groups were more than two. Multiple comparison procedures were performed using the Dunn Bonferroni approach to identify different group or groups after the Kruskal Wallis test. Pearson Chi-square, Fisher's exact test, and Fisher Freeman-Halton test were used for comparing categorical variables. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY-IBM Corp.) was used for statistical analysis, and a p-value; 0.05 was considered statistically significant.

RESULTS

The data of 249 patients were scanned in the study. Of these patients, 63 (25%) were evaluated as Stage-1, 167 (67%) as Stage-2, and 19 (7.6%) as Stage-3. Demographic data, comorbidities, and laboratory data of these groups are shown in **Table 1**.

The patients in stage 2 were also divided into 3 groups and their demographic data, comorbidities, and laboratory data were compared in **Table 2**.

DISCUSSION

It is known that COVID-19 disease has a worse prognosis and is more mortal in patients with comorbidities. In this study, we aimed to show the characteristics of patients admitted to the ICU with chronic kidney disease(CKD) diagnosed with COVID-19 and the effect of CKD on mortality.

Cheng et al. (9) compared patients who have normal serum creatinine (SCr) at admission to patients who have high SCr values at admission in a prospective analysis of 701 patients with COVID-19. In patients presenting with high SCr, higher leukocytes, lower lymphocytes, lower platelets, prolonged partial thromboplastin time, higher D-dimer levels, increased procalcitonin, and increased lactose dehydrogenase (LDH) were found. The incidence of AKI was significantly higher in patients with elevated baseline (9). In addition, admission to the ICU and mechanical ventilation showed a higher prevalence in patients with COVID-19 and high baseline SCr (14). High baseline SCr nearly tripled the risk of in-hospital death (9). It was thought that a more pronounced cytokine storm might develop in patients with chronic renal failure and COVID-19, and more severe systemic inflammation and hypercoagulability could be seen in these patients (9). In our study, patients admitted to the ICU were staged according to their e-GFR levels. It was observed that the median procalcitonin, ferritin, and cytokine storm values such as IL-6, and D-dimer of the patients in the stage-3 group were significantly higher than the other groups. There was no significant difference in LDH, Lymphocyte, and WBC values. A

Tablo 1. Comparison of demographic and laboratory data of stages 1, 2, and 3

	Total (n=249)	Stage 1 (e-GFR≥90 ml/dk/1.73 m²) (n=63)	Stage 2 (e-GFR:15-89 ml/dk/1.73 m²) (n=167)	Stage 3 (e-GFR≤15 ml/dk/1.73 m²) (n=19)	p-value
Age (year)	71(19-97)	57 (19-86)	76 (28-97)	70 (47-93)	<0.001[a]
Length of stay (day)	9 (1-49)	10 (1-49)	9 (1-43)	7 (2-47)	0.583[a]
Duration of intubation (day)	1 (0-29)	0 (0-28)	1 (0-29)	4 (0-23)	0.081[a]
Gender (Male)	166 (66.67%)	47 (74.60%)	105 (62.87%)	14 (73.68%)	0.193
Co-infection (yes)	123 (49.40%)	28 (44.44%)	84 (50.30%)	11 (57.89%)	0.543[b]
Outcome (exitus)	118 (47.39%)	22 (34.92%)	81 (48.50%)	15 (78.95%)	0.003[b]
HFNO (yes)	105 (42.17%)	29 (46.03%)	73 (43.71%)	3 (15.79%)	0.051[b]
NIMV(yes)	81 (32.53%)	19 (30.16%)	57 (34.13%)	5 (26.32%)	0.708[b]
IMV (yes)	132 (53.01%)	26 (41.27%)	91 (54.49%)	15 (78.95%)	0.012[b]
DM (yes)	82 (32.93%)	16 (25.40%)	59 (35.33%)	7 (36.84%)	0.335[b]
HT (yes)	154 (61.85%)	25 (39.68%)	118 (70.66%)	11 (57.89%)	<0.001[b]
CAD (yes)	122 (49%)	22 (34.92%)	85 (50.90%)	15 (78.95%)	0.002[b]
COPD (yes)	42 (16.87%)	10 (15.87%)	30 (17.96%)	2 (10.53%)	0.693[b]
Cancer (yes)	26 (10.48%)	8 (12.70%)	17 (10.24%)	1 (5.26%)	0.640[b]
Neurological disease (yes)	47 (18.95%)	10 (15.87%)	30 (17.96%)	8 (42.11%)	0.027[b]
IVIG (yes)	3 (1.21%)	2 (3.17%)	1 (0.60%)	0	0.357[c]
Anakinra (yes)	28 (11.24%)	12 (19.05%)	16 (9.58%)	0	0.035[b]
Inotropic agents (yes)	117 (46.99%)	24 (38.10%)	77 (46.11%)	16 (84.21%)	0.002[b]
Corticosteroid					
No	78 (31.33%)	16 (25.40%)	52 (31.14%)	10 (52.63%)	
<250 mg Methylprednisolone	95 (38.15%)	17 (26.98%)	70 (41.92%)	8 (42.11%)	0.002[b]
≥250 mg Methylprednisolone	76 (30.52%)	30 (47.62%)	45 (26.95%)	1 (5.26%)	
APACHE II	14 (2-57)	10 (2-36)	14 (3-57)	32 (3-54)	<0.001[a]
SOFA	5 (3-41)	4 (3-13)	5 (3-41)	11 (6-18)	<0.001[a]
Ferritin (μg/L)	500 (1.55-62904)	524 (7-5195)	455 (1.55-62904)	883 (209-40284)	0.003[a]
CRP (mg/L)	0.11 (0-0.80)	0.11 (0-0.80)	0.10 (0-0.43)	0.16 (0.01-0.33)	0.258[a]
Procalcitonin (μg/L)	0.20 (0-397)	0.08 (0-397)	0.20 (0.02-57.32)	6.90 (0.21-195.53)	<0.001[a]
IL-6 (pg/mL)	47 (2.72-14585)	45 (3.45-14585)	43.60 (2.72-5066)	159 (6.09-2582)	0.004[a]
Fibrinogen (g/L)	5.16 (1-678)	5.13 (2.45-678)	5.44 (1.06-10.10)	4.53 (1-7.68)	0.353[a]
D-dimer (mg/L)	1.60 (0.19-135)	1.26 (0.19-135)	1.60 (0.20-56.36)	3.82 (0.87-104)	0.007[a]
LDH (U/L)	500 (37-4897)	500 (166-4897)	492 (37-3800)	520 (189-1255)	0.744[a]
ALT (U/L)	34 (1-1684)	41 (6-126)	33 (1-1684)	30 (3-435)	0.252[a]
AST (U/L)	46 (4-4088)	44 (12-332)	48 (4-4088)	47 (14-1413)	0.486[a]
WBC (×10⁹/L)	9.8 (2.40-88.0)	10.2 (24.0-37.6)	9.7 (1.08-8.8)	9.1 (1.7-27.0)	0.857[a]
Neutrophil (×10⁹/L)	8.6 (1-14)	8.7 (3.7-14)	8.7 (1-28.2)	7.9 (14.8-25.3)	0.957[a]
Lymphocyte (×10⁹/L)	0.6 (0.1-10.1)	0.72 (0.1-3.6)	0.62 (0.14-10.1)	0.66 (0.19-3)	0.896[a]
NLR	13.20 (0.05-238)	13.32 (0.05-238)	13.20 (1.25-89.36)	12.30 (3.16-44.34)	0.944[a]
Hemoglobin (g/dL)	12.60 (6.20-92)	13.20 (7.30-92)	12.60 (6.20-17.50)	10.70 (7.60-16.40)	0.013[a]
Platelet (×10⁹/L)	231 (9-672)	283 (9-582)	225 (318-672)	162 (32-381)	0.001[a]

HFNO: High flow nasal oxygen; NIMV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; IVIG: intravenous immunoglobulin; CRP: C-reactive protein; IL: interleukin; LDH: lactate dehydrogenase; ALT: alanine amino transferase; AST: aspartate amino transferase; WBC: white blood cell; NLR: neutrophil lymphocyte ratio.

significant decrease in Hb value was observed. However, this may be due to the fact that this group of patients in end-stage renal disease patients. The platelet count was significantly higher than the other groups. In addition, mechanical ventilation and mortality rates were found to be higher. In our study, the stage-2 patient group was also evaluated by dividing it into 3 groups. While the median CRP, procalcitonin, d-dimer values, and N/L ratio were found to be high in the stage 2c group, the lymphocyte count and Hb values were found to be low. Mechanical ventilation and mortality rates were also higher. Although the mechanical ventilation rate of stage 2c patients was higher than stage 2b, no significant difference was found in terms of mortality rate.

In a study, it was suggested that the development of kidney damage during hospitalization and patients with pre-existing CKD are independent risk factors for poor prognosis (14). Scoring systems such as APACHE II and SOFA are used to evaluate mortality in ICU patients (15). In our study, it was determined that APACHE II and

SOFA scores increased as the stage grade increased, as e-GFR decreased, the mechanical ventilation rates and inotropic needs of these patients were higher, and the mortality rates were higher.

In a study conducted on 3,319 patients in New York, it was found that patients with CKD increased mortality up to 7 times in SARS-COV-2 infection. Specifically, when we look at this group, it has been reported that the mortality rate is higher in patients with atrial fibrillation, coronary artery disease(CAD), and ischemic heart failure associated with CKD (16). In our study, the incidence of CAD was found to be significantly higher in the stage-3 group than in the stage-1 group, but its relation to mortality was not evaluated. In addition, it was observed that the group with the neurological disease was more common in this stage. However, when compared with the stage-2 group, no significant difference was found in terms of CAD association.

Tablo 2. Demographic data, comorbidities, and laboratory data of the patients in stage 2

	Stage 2a (e-GFR: 60-89 ml/dk/1.73 m²) (n=83)	Stage 2b (e-GFR: 30-59 ml/dk/1.73 m²) (n=60)	Stage 2c (e-GFR: 15-29 ml/dk/1.73 m²) (n=24)	*p*-value
Age (year)	73 (28-93)	78.50 (45-97)	80.50 (30-93)	0.114[a]
Length of stay (day)	10 (1:40)	8 (1:43)	6 (1:32)	0.108[a]
Duration of intubation (day)	0 (0:29)	1 (0:25)	2 (0:16)	0.167[a]
Gender (Male)	52 (62.65%)	37 (61.67%)	16 (66.67%)	
Outcome (exitus)	34 (40.96%)	30 (50%)	17 (70.83%)	0.034[b]
HFN (yes)	37 (44.58%)	26 (43.33%)	10 (41.67%)	0.966[b]
NIMV (yes)	27 (32.53%)	23 (38.33%)	7 (29.17%)	0.661[b]
IMV (yes)	40 (48.19%)	31 (51.67%)	20 (83.33%)	0.008[b]
DM (yes)	32 (38.55%)	19 (31.67%)	8 (33.33%)	0.680[b]
HT (yes)	53 (63.86%)	50 (83.33%)	15 (62.50%)	0.026[b]
CAD (yes)	38 (45.78%)	32 (53.33%)	15 (62.50%)	0.316[b]
COPD (yes)	14 (16.87%)	12 (20%)	4 (16.67%)	0.876[b]
Canser (yes)	9 (10.84%)	8 (11.86%)	1 (4.17%)	0.558[b]
Neurological Disease (yes)	15 (18.07%)	13 (20.34%)	2 (8.33%)	0.417[b]
IVIG (yes)	1 (1.20%)	0	0	>0.99[c]
Anakinra (yes)	9 (10.84%)	5 (8.33%)	2 (8.33%)	0.859[b]
Inotropic agents (yes)	30 (36.14%)	27 (45%)	20 (83.33%)	<0.001[b]
Corticosteroid				
No	26 (31.33%)	14 (23.33%)	12 (50%)	
<250 Mg Methylprednizolone	31 (37.35%)	30 (50%)	9 (37.50%)	0.098[b]
≥250 Mg Methylprednizolone	26 (31.33%)	16 (26.67%)	3 (12.50%)	
APACHE II	11 (3-36)	14.50 (3-38)	26 (5-57)	<0.001[a]
SOFA	4 (3-12)	5 (4-41)	8 (4-14)	<0.001[a]
Ferritin (μg/L)	488 (7-62904)	384 (1.55-19215)	472.50 (15-3440)	0.479[a]
CRP (mg/L)	0.09 (0.01-0.37)	0.11 (0-0.43)	0.17 (0.01-0.38)	0.043[a]
Procalcitonin (μg/L)	0.16 (0.02-12.34)	0.21 (0.03-28.13)	1.29 (0.06-57.32)	<0.001[a]
IL-6 (pg/mL)	33 (2.72-2718)	55.35 (5.40-2972)	62.90 (7-5066)	0.051[a]
Fibrinogen (g/L)	5.38±1.54	5.65±1.85	5.01±1.99	0.293[d]
D-dimer (mg/L)	1.55 (0.30-35.20)	1.27 (0.20-53)	4.02 (0.27-56.36)	0.013[a]
LDH (U/L)	505 (37-3800)	470.50 (129-2972)	459 (217-1507)	0.612[a]
ALT (U/L)	39 (2-1270)	29 (1-1684)	37 (8-440)	0.055[a]
AST (U/L)	52 (4-2871)	42.50 (8-4088)	66.50 (17-603)	0.062[a]
WBC ($\times 10^9$/L)	8.8 (10.8-23.2)	9.9 (16.1-88.0)	9.7 (3.5-30.9)	0.358[a]
Neutrophil ($\times 10^9$/L)	8.2 (1.0:21.8)	8.8 (27.8-27.3)	8.4 (10.8-28.2)	0.295[a]
Lymphocyte ($\times 10^9$/L)	0.67 (0.14-1.01)	0.64 (0.18-2.9)	0.48 (0.15-0.97)	0.026[a]
NLR	11.74 (1.25-89.36)	12.50 (1.38-79)	15.62 (4.39-75.85)	0.033[a]
Hb (g/dL)	12.50±2.35	12.95±1.95	10.47±2.64	<0.001[d]
Platelet ($\times 10^9$/L)	259 (62-672)	205 (72-491)	182 (31-448)	0.002[a]

Data are expressed as n(%), median(minimum: maximum), and mean±standard deviation.
a:Kruskal-Wallis Test, b: Pearson Chi-Square Test, c: Fisher Freeman-Halton Test, d: ANOVA Test.
HFNO: High flow nasal oxygen; NIMV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; IVIG: intravenous immunoglobulin; CRP: C-reactive protein; IL: interleukin; LDH: lactate dehydrogenase; ALT: alanine amino transferase; AST: aspartate amino transferase; WBC: white blood cell; NLR: neutrophil lymphocyte ratio.

In a retrospective study conducted on 1210 patients in Turkey, the mortality rates of stage 3-5 CKD patients and routine hemodialysis (HD) patients were found to be similar, but higher than the normal population (17). It has been stated that it is difficult to obtain meaningful data due to the small number of renal transplantation patients (17). Renal transplantation patients were not included in our study. According to our discrimination scale, all stage-3 patients were in HD, and mortality rates were higher than the other groups. Although the mortality rates of stage 2c patients were higher than stage 2a, no significant difference was found with stage 2b.

In meta-analyses performed on ICU patients followed up with COVID-19, the incidence of AKI was reported as approximately 23%, and it was shown that the patients in need of RRT were 5% (18). In another study, it was reported that 42 (42.9%) of 99 COVID-19 patients developed AKI, and 13 (13.4%) needed RRT (19). In our study, according to Kidney Disease Improving Global Outcomes (KDIGO) criteria, 19 (30%) of stage-1 patients and 108 (64%) of stage-2 patients developed AKI. We found that 4 (21%) of stage-1 patients with AKI and 28 (25%) of stage-2 patients with AKI needed HD. The emergence of such different results regarding the incidence of AKI may be due to the different designs of the studies and the lack of a clear AKI protocol.

There are some limitations of this study. First of all, our study is a retrospective study and is single-centered. The second is to calculate the kidney functions of the patients with the MDRD formula. For this reason, there may be uncertainty about whether the errors will show the kidney functions effectively or not because the parameters other than age and weight are not taken into account. Finally, these data were not recorded because it was thought that the evaluation of hematuria and proteinuria in the ICU would not be accurate.

CONCLUSION

It has been determined that COVID-19 disease is more severe and mortal in CKD patients. In addition, it can be predicted that more severe inflammation values are observed in this group and hypercoagulopathy may be more common due to D-dimer elevation. For this reason, it should be questioned whether there is a known history of CKD in every patient hospitalized with COVID-19 disease and care should be taken about protective measures.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No 1 Clinical Researches Ethics Committee (Date: 15.06.2022, Decision No: E1-22-2617).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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