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Characteristics and outcomes of hospitalised older patients with chronic kidney disease and COVID-19: A multicenter nationwide controlled study

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Abstract

Objective: Older adults with co-morbidities have been reported to be at higher risk for adverse outcomes of coronavirus disease 2019 (COVID-19). The characteristics of COVID-19 in older patients and its clinical outcomes in different kidney disease groups are not well known.

Methods: Data were retrieved from a national multicentric database supported by Turkish Society of Nephrology, which consists of retrospectively collected data between 17 April 2020 and 31 December 2020. Hospitalised patients aged 18 years or older with confirmed COVID-19 diagnosis suffering from stage 3-5 chronic kidney disease (CKD) or on maintenance haemodialysis (HD) treatment were included in the database. Non-uraemic hospitalised patients with COVID-19 were also included as the control group.

Results: We included 879 patients [388 (44.1%) female, median age: 63 (IQR: 50-73) years]. The percentage of older patients in the CKD group was 68.8% (n = 188/273), in the HD group was 49.0% (n = 150/306) and in the control group was 30.4% (n = 70/300). Co-morbidities were higher in the CKD and HD groups. The rate of presentation with severe-critical disease was higher in the older CKD and HD groups (43.6%, 55.3% and 16.1%, respectively). Among older patients, the intensive care unit (ICU) admission rate was significantly higher in the CKD and HD groups than in the control group (38.8%, 37.3% and 15.7%, respectively). In-hospital mortality or death and/or ICU admission rates in the older group were significantly higher in the CKD (29.3% and 39.4%) and HD groups (26.7% and 30.1%) compared with the control group (8.6% and 17.1%). In the multivariate analysis, in-hospital mortality rates in CKD and HD groups were higher than control group [hazard ratio (HR): 4.33 (95% confidence interval [CI]: 1.53-12.26) and HR: 3.09 (95% CI: 1.04-9.17), respectively].

Conclusion: Among older COVID-19 patients, in-hospital mortality is significantly higher in those with stage 3-5 CKD and on maintenance HD than older patients without CKD regardless of demographic characteristics, co-morbidities, clinical and laboratory data on admission.

1 | INTRODUCTION

Older adults and patients with co-morbidities have been reported to be at higher risk for adverse outcomes of coronavirus disease 2019 (COVID-19).[1-3] COVID-19-related hospitalisation, need for intensive care support, and mortality rate were also higher in this group.[4] For example, in early Chinese data, althoughj the case fatality rate was 2.3% across the entire cohort, it was 8% between 70 and 79 years of age and 15% in those aged 80 and over.[1] In our early nationwide cohort, including a total of 16 942 hospitalised older adults with COVID-19, mortality was 18.5%, intensive care unit (ICU) admission was 28.8%, and co-morbidities, including chronic kidney disease (CKD), were independently associated with mortality.[5]

CKD is one of the most common diseases among older adults. Some studies showed that COVID-19 patients with CKD might have differences in clinical presentation and outcome, especially in patients with advanced-stage CKD and haemodialysis (HD).[6] Moreover, adjusted mortality in CKD and HD patients seems to be 2 to 3 times higher.[7,8] Although some characteristics (demographic characteristics, medicines, etc) in patients with stage 3-5 CKD are partially similar to the HD group, the clinical approach and outcomes may differ due to some reasons such as volume burden, selected treatment

What's known

- Older adults with co-morbidities have been reported to be at higher risk for adverse outcomes of coronavirus disease 2019 (COVID-19).
- The characteristics of COVID-19 in elderly patients and its clinical consequences in different kidney disease groups are not well known.

What's new

- In-hospital mortality or death and/or ICU admission rates in the older group were significantly higher in stage 3-5 CKD and HD group compared with the control group.
- In-hospital mortality rates were higher in stage 3-5 CKD and HD groups compared with the control group.
- Among older COVID-19 patients, in-hospital mortality is significantly higher in those with stage 3-5 CKD and on maintenance HD than older patients without CKD regardless of demographic characteristics, co-morbidities, clinical and laboratory data on admission.

modalities, drug doses, or dietary restrictions during the pandemic. As far as we know, there is no study examining the characteristics of COVID-19 and their effect on clinical outcomes in different kidney disease groups in older patients.

In our country, all hospitals were accepted as pandemic hospitals during the pandemic period. Therefore, non-uraemic COVID-19 patients could also be accepted in nephrology clinics. As a result, we had the opportunity to compare uraemic and non-uraemic patients within the same clinic.

Herein, we aimed to investigate the presentation characteristics and clinical outcomes of COVID-19 in hospitalised older patients suffering from several stages of chronic kidney disease (stages 3-5 or HD) and to compare them with the older but non-uraemic hospitalised COVID-19 control group. We also compared each older group with their younger counterparts.

2 | MATERIALS AND METHODS

This study was a retrospective cohort following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[9] Health Sciences University, Haseki Training and Research Hospital Ethics Committee approved the study (number: 2020-41).

2.1 | Population and setting

This national multicentric observational study included hospitalised stage 3-5 CKD or maintenance HD patients over 18 years of age with a confirmed diagnosis of COVID-19. A non-uraemic control group of hospitalised patients with COVID-19 in the same centres was also included.

The data of this study were retrieved from the database supported by Turkish Society of Nephrology, which has been collecting national data in a web-based system from volunteer nephrology centres since 17 April 2020. This database included adult HD, peritoneal dialysis, renal transplant recipient, stage 3-5 CKD patients hospitalised with the diagnosis of COVID-19. In addition, to form a control group, for each of these patients, the first admitted patient without kidney disease from each centre was recorded as the control group. Some earlier results from this database have already been published.[8,10] Data in this study included newly added patients into this database till 31 December 2020.

All included patients had a confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by a positive reverse transcriptase-polymerase chain reaction (RT-PCR) testing of a nasopharyngeal swab. Peritoneal dialysis patients, patients presenting with acute kidney injury, current inpatients, pregnant patients, re-hospitalisations, patients for whom outcome data could not be obtained (missing data or referred to another centre), patients with suspicion in diagnosis, patients with temporary haemodialysis were excluded.

In the current study, we have only included confirmed cases of COVID-19 (with a positive result for SARS-CoV-2 on polymerase chain reaction (PCR) testing of a nasopharyngeal swab), but the previous study has involved both confirmed cases and possible cases (patients with negative SARS-Cov-2 PCR but had clinical symptoms and a chest computed tomography).[8] The present study did not include the patients with a kidney transplant and the patients that were referred to other hospitals (34 patients were excluded for this reason). The previous study did not include the presenting symptoms, but this study included. Although the number of patients included to the current study is significantly lower than the previous study, a total of 605 patients were included in this paper and also in the previous publication. The previous study had a propensity-score matching (PSM) in order to create similar study groups (ie CKD vs. HD, or control vs. renal transplant groups), and these were calculated by the logistic regression analysis. In the current study, we did not use PSM.

2.2 | Measurements and definitions

We recorded demographic data, co-morbidities and medications, primary kidney diseases, presenting symptoms, possible sources for COVID-19 transmission, computerised chest tomography (CT) results, and COVID-19 treatment from the hospital database.

The control group patients had no known kidney disease, and their estimated glomerular filtration rate (eGFR) was >60 mL/min/1.73 m^2 calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation.[11] Patients with a known CKD diagnosis and eGFR <60 mL/min/1.73 m^2 represented

stages 3-5 CKD. Patients undergoing HD for at least 3 months represented the HD group. We presented comparative data for all older groups (control, CKD and HD groups) in the main tables and presented similar comparative data for subgroups (older-younger) of all these groups in the supporting information. We accepted 65 and over as the older age group and those under 65 as the younger group.

The disease's clinical severity was classified as mild-moderate or severe-critical illness, which was compatible with the Ministry of Health guideline.[12] Mild-moderate disease defines patients with mild clinical symptoms such as fever and respiratory system symptoms, with or without a sign of viral pneumonia on chest CT findings. Patients who met any of the following criteria at admission were classified as a severe-critical disease: respiratory rate 30 breaths/min, oxygen saturation 93% at rest; arterial PO2/oxygen concentration ≤300 mm Hg, pulmonary lesion progression >50% within 24-48 hr on radiological imaging, and/or more severe disease that may require treatment in the ICU.

There were three main groups (HD, CKD and control groups) in the study, and each group has older and younger subgroups. In Tables 1-4, we only presented the data of older patients and made comparisons between these groups. On the other hand, we have also presented all data, including older and younger patients, in the supporting information. In the supporting information, we compared data of older and younger subgroups within the disease groups.

2.3 | Follow-up and outcome

The total length of stay of the patients in the hospital was accepted as the follow-up time. Leukopenia (<4000/mm^3), lymphopenia (<1500/mm^3), anaemia (haemoglobin <10 g/dL), thrombocytopenia (<150 × 103/mm^3), 2× increase in lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) during hospitalisation were recorded. Data for admission to ICU, mechanical ventilation and death in the ICU were also obtained. The database contained only the hospitalisation period data and did not contain any information about the post-discharge period. We determined death as the primary outcome in the study.

2.4 | Statistical analyses

We used the IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) for statistical analyses. We analysed the normality of variables using visual methods (histograms and probability plots) and Kolmogorov–Smirnov tests.

We presented numbers and percentages for categorical variables, median and interquartile ranges (25-75%) for numeric variables in descriptive statistics. We used the χ^2 test for two or multiple group comparisons of categorical variables. In the comparison of numerical variables, we used independent *t*-test or Mann–Whitney *U* test as appropriate. In the multiple group comparisons of numerical variables, we used the analysis of variance (ANOVA) test for numerical variables with normal distribution and Kruskal–Wallis test for numerical variables that are not normally distributed. Bonferroni corrected Mann–Whitney *U* test was used for subgroup analysis of variables that did not show normal distribution in post hoc analysis, and Bonferroni corrected χ^2 test was used for subgroup analysis of categorical variables. Multivariate Cox regression analysis was performed using the clinical parameters related to survival in the univariate analyses. We have also included diabetes and gender into the model, which were critical factors on mortality in the previous publications, even they were not significant in univariate analyses. Final multivariate models were derived using a stepwise backward LR method from the initial model created with the candidate variables in Cox regression analysis; $P < .05$ was accepted as the level of significance.

3 | RESULTS

3.1 | Demographic and baseline characteristics

The main database had 1854 hospitalised COVID-19 patients from 47 centres in Turkey and 879 of them were included in this study. The flow chart of the study was presented in Figure 1 [306 HD, 273 CKD, and 300 control patients, the median age of 63 (IQR: 50-73) years, 388 (44.1%) female]. The proportion of older patients was highest in the CKD group [number and percentage of older patients: CKD group: 188 (68.8%), HD group: 150 (49.0%) and control group: 70 (30.4%)]. The median HD duration of the HD group was 4.0 (IQR: 2-7) years.

Table 1 represents the baseline demographics, co-morbidities, medications, symptoms and baseline laboratory tests of the older patients. Gender was not different between the groups. In the CKD and HD groups, diabetes mellitus, hypertension and cardiac diseases were significantly more common than in the control group. Chronic obstructive pulmonary disease (COPD) and smoking habits did not differ significantly between the groups. In consistent with the co-morbidities, medications varied between the groups.

Gender distribution was similar among older groups and within each older group (Tables 1 and S1). Although the DM rate in the control and CKD groups was not different between the older and younger subgroups, it was significantly higher in the older subgroup than the younger patients in the HD group. On the other hand, HT rate was higher in the older HD group compared with younger, but it was not significantly different in subgroups of control and CKD groups. Ischaemic heart disease and heart failure were more prevalent in older patients than younger in all three groups. The older patients of the control and CKD groups had significantly higher COPD than younger ones. There was no difference in terms of malignancy. Medications in all three groups and primary kidney diseases in CKD and HD groups also showed a distribution consistent with co-morbidities.

TABLE 1 Baseline demographics, co-morbidities, medications, symptoms and lab tests at the admission of the older adult patients according to the study groups

	Control group (N = 70)		CKD group (N = 188)		Dialysis group (N = 150)		Total (N = 408)	
	N	(%)	N	(%)	N	(%)	N	(%)
Age (year)*	73[a]	(69-78)	76[b]	(71-82)	72[a]	(69-78)	74	(70-80)
Gender (woman)	30[a]	(42.9)	78[a]	(41.5)	71[a]	(47.3)	179	(43.9)
Diabetes mellitus	11[a]	(16.7)	85[b]	(47.2)	84[b]	(57.5)	180	(45.9)
Hypertension	46[a]	(67.6)	174[b]	(92.6)	115[a]	(79.3)	335	(83.5)
Ischaemic heart disease	19[a]	(30.2)	94[b]	(54.3)	79[b]	(59.4)	192	(52.0)
Heart failure	10[a]	(15.4)	53[b]	(33.5)	39[a.b]	(30.0)	102	(28.9)
Ischaemic heart disease or Heart failure	22[a]	(39.3)	52[a.b]	(51.5)	49[b]	(66.2)	123	(53.2)
COPD	13[a]	(20.3)	39[a]	(23.1)	20[a]	(15.0)	72	(19.7)
Malignancy	3[a]	(4.6)	13[a]	(7.4)	3[a]	(2.1)	19	(5.0)
Chronic liver disease	0	(0)	2[a]	(1.1)	5[a]	(3.5)	7	(1.8)
Smoking								
Never smoked	30[a]	(62.5)	81[a]	(57.4)	65[a]	(58.0)	176	(58.5)
Ex-smoker	16[a]	(33.3)	53[a]	(37.6)	42[a]	(37.5)	111	(36.9)
Active smoker	2[a]	(4.2)	7[a]	(5.0)	5[a]	(4.5)	14	(4.7)
ACEi	19[a.b]	(30.6)	45[b]	(32.6)	23[a]	(17.7)	87	(26.4)
ARB	10[a]	(16.4)	54[b]	(38.3)	11[a]	(8.5)	75	(22.7)
Calcium channel blocker	27[a]	(42.2)	108[b]	(65.9)	54[a]	(39.1)	189	(51.6)
Beta-blocker	19[a]	(31.1)	93[b]	(60.0)	68[b]	(51.5)	180	(51.7)
Other antihypertensives	5[a]	(8.6)	40[b]	(30.3)	9[a]	(7.4)	54	(17.3)
Insulin	4[a]	(6.6)	46[c]	(33.1)	65[b]	(47.4)	115	(34.1)
Oral antidiabetic	8[a]	(13.3)	41[a]	(28.3)	5[b]	(3.8)	54	(16.0)
Statin	15[a]	(25.0)	37[a]	(27.4)	30[a]	(22.4)	82	(24.9)
Antiaggregant or anticoagulant	25[a]	(39.7)	108[b]	(65.5)	95[b]	(69.9)	228	(62.6)
The possible source of COVID-19								
Family-home environment	18[a.b]	(47.4)	71[b]	(61.7)	32[a]	(40.5)	121	(52.2)
Workplace/nursing home/ detention centre etc	1[a]	(2.6)	1[a]	(0.9)	1[a]	(1.3)	3	(1.3)
Social life (meeting-dinner-house invitation etc)	14[a]	(36.8)	34[a]	(29.6)	9[b]	(11.4)	57	(24.6)
Getting abroad/abroad	3[a]	(7.9)	3[a]	(2.6)	01	(0)	6	(2.6)
Healthcare facility	2[a]	(5.3)	6[a]	(5.2)	37[b]	(46.8)	45	(19.4)
Start of symptom-admission time (days)*	3[a]	(3-5)	3[a]	(3-5)	3[a]	(2-4)	3	(2-5)
Clinically severity of disease								
Mild-moderate disease	49[a]	(71.0)	106[a.b]	(56.4)	67[b]	(44.7)	222	(54.5)
Severe-critical disease	20[a]	(29.0)	82[a.b]	(43.6)	83[b]	(55.3)	185	(45.5)
Fever	40[a]	(57.1)	120[a]	(63.8)	81[a]	(54.0)	241	(59.1)
Fatigue	25[a]	(35.7)	107[b]	(56.9)	78[a.b]	(52.0)	210	(51.5)
Dyspnoea	28[a]	(40.0)	109[b]	(58.0)	96[b]	(64.0)	233	(57.1)
Dry cough	37[a]	(52.9)	113[a]	(60.1)	78[a]	(52.0)	228	(55.9)
Productive cough	8[a]	(11.4)	15[a]	(8.0)	12[a]	(8.0)	35	(8.6)

(Continues)

TABLE 1 (Continued)

	Control group (N = 70)		CKD group (N = 188)		Dialysis group (N = 150)		Total (N = 408)	
	N	(%)	N	(%)	N	(%)	N	(%)
Anorexia	3[a]	(4.3)	13[a]	(6.9)	14[a]	(9.3)	30	(7.4)
Myalgia	14[a]	(20.0)	51[a]	(27.1)	34[a]	(22.7)	99	(24.3)
Headache	10[a]	(14.3)	13[a]	(6.9)	12[a]	(8.0)	35	(8.6)
Throat ache	13[a]	(18.6)	24[a]	(12.8)	17[a]	(11.3)	54	(13.2)
Diarrhoea	2[a]	(2.9)	6[a]	(3.2)	5[a]	(3.3)	13	(3.2)
Chest CT imaging	66[a]	(95.7)	182[a]	(96.8)	142[a]	(95.3)	390	(96.1)
CT Findings								
Completely normal	11[a]	(17.7)	22[a.b]	(12.5)	8[b]	(5.7)	41	(10.8)
Single lesion	4[a]	(6.5)	9[a]	(5.1)	9[a]	(6.4)	22	(5.8)
Unilateral multiple lesions	6[a]	(9.7)	9[a]	(5.1)	13[a]	(9.2)	28	(7.4)
Bilateral multiple lesions	41[a]	(66.1)	136[a]	(77.3)	111[a]	(78.7)	288	(76.0)
Ground glass opacity	51[a]	(91.1)	153[a]	(91.1)	124[a]	(91.2)	328	(91.1)
Pleural effusion	2[a]	(3.6)	26[a.b]	(15.5)	35[b]	(25.7)	63	(17.5)
Lymphadenopathy	4[a]	(7.1)	11[a]	(6.5)	7[a]	(5.1)	22	(6.1)
Pleural thickening	0[1]	(0)	0[1]	(0)	0[1]	(0)	0	(0)
Vascular thickening	3[a]	(5.4)	16[a]	(9.5)	9[a]	(6.6)	28	(7.8)
Reticular opacity	7[a]	(12.5)	27[a]	(16.1)	25[a]	(18.4)	59	(16.4)
Lab tests								
CRP (>×10-fold increased)	23[a]	(32.9)	85[a]	(45.2)	94[b]	(62.7)	202	(49.5)
Creatinine (mg/dL)*	0.88[a]	(1-1)	1.72[b]	(1-2)	6.97[c]	(5-8)	2.16	(1-6)
eGFR (mg/dL/1.73 m^2)*	76[a]	(60-92)	23[b]	(12-33)	–	–	13.8	(3-37)
Albumin (g/dL)*	3.7[a]	(3-4)	3.4[b]	(3-4)	3.4[b]	(3-4)	3.45	(3-4)
Ferritin (ng/dL)*	231[a]	(129-641)	273[a]	(132-576)	1027[b]	(614-1838)	499	(181-1077)
Haemoglobin (g/dL)*	12.7[a]	(12-14)	11.5[b]	(10-13)	10.8[c]	(10-12)	11.5	(10-13)
Lymphocyte count (/mm^3)*	1090[a]	(618-1790)	890[a]	(500-1300)	900[a]	(500-1280)	900	(515-1360)
Platelet count (/mm^3)*	219[a]	(161-269)	212[a]	(158-275)	176[a]	(145-227)	198	(153-262)

Note: Values in the same row not sharing the same superscript are significantly different at $P < .05$. Cells with no superscript are not included in the test.

Abbreviations: ACEİ, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease-2019; CRP, C-reactive protein; CT, computerised chest tomography; eGFR, estimated glomerular filtration rate.

*Median (interquartile range).

3.2 | Possible sources of COVID-19 and its symptoms during hospital admission

Older patients were hospitalised within a median of 3 (IQR: 2-5) days after the onset of symptoms. The patients in the control and CKD groups were mostly reported 'social life' as the possible source of COVID-19, but approximately half (46.8%) of the patients in the HD group reported 'healthcare facility' (Table 1). These rates were not significantly different between older and younger subgroups in all three groups (Table S2).

Significant differences were observed among the three older groups in terms of the presenting symptoms (Tables 1 and S2). The most striking finding was that dyspnoea was similar in the CKD and HD groups but significantly higher than the control group (58.0%, 64.0% and 40.0%, respectively). There was no significant difference in fever and other symptoms. On the other hand, the most common admission symptoms in the control group were dry cough (58.3%), fever (56.3%) and fatigue (40.7%), whereas these were not different in younger patients than older patients. In the CKD group, the most common presenting symptoms were fever (68.9%), dry cough (62.6%) and dyspnoea (56.8%). Although fever was higher in the younger group, dyspnoea and cough did not differ significantly in each subgroup. Similar to the CKD group, in the HD group, the most common

TABLE 2 The drugs given for the COVID-19 treatment and outcomes of the patients according to older age groups during in-hospital follow-up

	Control group (N = 70)		CKD group (N = 188)		Dialysis group (N = 150)		Total (N = 408)	
	N	(%)	N	(%)	N	(%)	N	(%)
Follow-up time (days)*	9.5[a]	(7-15)	10[a]	(6-15)	12[a]	(7-16)	10	(7-16)
Medications								
Oseltamivir	46[a]	(69.7)	97[a,b]	(63.8)	70[b]	(51.1)	213	(60.0)
Macrolide	59[a]	(86.8)	143[a]	(85.6)	114[a]	(80.3)	316	(83.8)
Hydroxychloroquine	691	(100.0)	183[a]	(98.4)	148[a]	(98.7)	400	(98.8)
Lopinavir-ritonavir	2[a,b]	(3.4)	12[b]	(9.9)	3[a]	(2.3)	17	(5.5)
Favipiravir	22[a]	(35.5)	89[b]	(59.7)	66[a,b]	(47.1)	177	(50.4)
Glucocorticoid	2[a,b]	(3.5)	14[b]	(12.2)	4[a]	(3.1)	20	(6.6)
Tocilizumab	1[a]	(1.7)	2[a]	(1.8)	3[a]	(2.3)	6	(2.0)
Convalescent plasma	0	(0)	3[a]	(2.8)	1[a]	(0.8)	4	(1.3)
Anakinra	0	(0)	0	(0)	1[a]	(0.8)	1	(0.3)
Only supportive treatment	1[a]	(1.9)	6[a]	(5.8)	7[a]	(6.4)	14	(5.2)
Side effects	2[a]	(3.1)	6[a]	(3.3)	5[a]	(3.8)	13	(3.4)
During hospitalisation								
Leukopenia	8[a]	(11.6)	27[a]	(14.4)	27[a]	(18.4)	62	(15.4)
Lymphopenia	32[a]	(46.4)	134[b]	(72.8)	98[b]	(66.7)	264	(66.0)
Anaemia (<10g/dL)	10[a]	(14.3)	81[b]	(44.5)	74[b]	(51.0)	165	(41.6)
Thrombocytopenia	12[a]	(17.4)	45[a]	(24.5)	38[a]	(25.7)	95	(23.7)
LDH increase (×2-fold)	19[a]	(27.5)	74[a]	(40.9)	45[a]	(33.1)	138	(35.8)
AST increase (×2-fold)	13[a]	(18.8)	55[a]	(29.9)	31[a]	(21.4)	99	(24.9)
Outcomes								
ICU admission								
Yes	11[a]	(15.7)	73[b]	(38.8)	56[b]	(37.3)	140	(34.3)
No	59[a]	(84.3)	115[b]	(61.2)	94[b]	(62.7)	268	(65.7)
Mechanical ventilation								
Yes	6[a]	(60.0)	57[a]	(79.2)	36[a]	(64.3)	99	(71.7)
No	4[a]	(40.0)	15[a]	(20.8)	20[a]	(35.7)	39	(28.3)
Final situation								
Discharged	62[a]	(88.6)	126[b]	(67.0)	107[b]	(71.3)	295	(72.3)
Still at ICU	2[a]	(2.9)	7[a]	(3.7)	3[a]	(2.0)	12	(2.9)
Dead	6[a]	(8.6)	55[b]	(29.3)	40[b]	(26.7)	101	(24.8)
Survival								
Survivor	64[a]	(91.4)	133[b]	(70.7)	110[b]	(73.3)	307	(75.2)
Non-survivor	6[a]	(8.6)	55[b]	(29.3)	40[b]	(26.7)	101	(24.8)
Composite Outcome								
Exitus and/or ICU admission	12[a]	(17.1)	74[b]	(39.4)	57[b]	(38.0)	143	(35.0)
Discharged	58[a]	(82.9)	114[b]	(60.6)	93[b]	(62.0)	265	(65.0)

Note: Values in the same row not sharing the same superscript are significantly different at $P < .05$. Cells with no superscript are not included in the test.
Abbreviations: AST, aspartate aminotransferase; CKD, chronic kidney disease; ICU, intensive care unit; LDH, lactate dehydrogenase.
*Median (interquartile range).

TABLE 3 Comparison of the older patients according to mortality

	Survivors (N = 307)		Non-survivors (N = 101)	
	N	(%)	N	(%)
Group				
Control group	64[a]	(20.8)	6[b]	(5.9)
HD group	110[a]	(35.8)	40[a]	(39.6)
CKD group	133[a]	(43.3)	55[a]	(54.5)
Age (year)*	73[a]	(69-79)	75[b]	(71-81)
Gender (women)	141[a]	(45.9)	38[a]	(37.6)
Diabetes mellitus	130[a]	(44.4)	50[a]	(50.5)
Hypertension	258[a]	(84.9)	77[a]	(79.4)
Ischaemic heart disease or heart failure	81[a]	(47.6)	42[b]	(68.9)
COPD	55[a]	(20.0)	17[a]	(18.7)
Malignancy	18[a]	(6.3)	1[b]	(1.0)
Chronic liver disease	6[a]	(2.1)	1[a]	(1.0)
Symptoms at admission				
Start of symptom-hospitalisation duration (days)*	3[a]	(2-4)	3[a]	(2-5)
Fever	182[a]	(59.3)	59[a]	(58.4)
Fatigue	153[a]	(49.8)	57[a]	(56.4)
Dyspnoea	152[a]	(49.5)	81[b]	(80.2)
Dry cough	167[a]	(54.4)	61[a]	(60.4)
Productive cough	25[a]	(8.1)	10[a]	(9.9)
Anorexia	22[a]	(7.2)	8[a]	(7.9)
Myalgia	74[a]	(24.1)	25[a]	(24.8)
Headache	29[a]	(9.4)	6[a]	(5.9)
Throat ache	43[a]	(14.0)	11[a]	(10.9)
Diarrhoea	10[a]	(3.3)	3[a]	(3.0)
Clinically severity of disease				
Mild-moderate disease	208[a]	(67.8)	14[b]	(14.0)
Severe-critical disease	99[a]	(32.2)	86[b]	(86.0)
CT findings				
Completely normal	37[a]	(13.0)	4[b]	(4.2)
Single lesion	19[a]	(6.7)	3[a]	(3.2)
Bilateral multiple lesions	204[a]	(71.8)	84[b]	(88.4)
Unilateral multiple lesions	24[a]	(8.5)	4[a]	(4.2)
Ground-glass opacity	239[a]	(89.5)	89[a]	(95.7)
Follow-up time*	11[a]	(7-16)	10[a]	(5-15)
CRP (>×10-fold increased)	129[a]	(42.0)	73[b]	(72.3)
Creatinine (mg/dL)*	2.06[a]	(1.23-5.62)	2.5[a]	(1.42-6.19)
eGFR (mg/dL/1.73 m^2)*	15.5[a]	(3.09-40.88)	8.6[b]	(2.89-28.54)
Albumin (g/dL)*	3.5[a]	(3.20-3.80)	3.2[b]	(2.70-3.60)
Ferritin (ng/dL)*	432[a]	(158-966)	644[a]	(284-1345)
Haemoglobin (g/dL)*	11.4[a]	(10.10-12.90)	11.7[a]	(9.85-13.10)
Lymphocyte count (/mm^3)*	970[a]	(600-1440)	710[b]	(290-1200)
Platelet count (/mm^3)*	204[a]	(156-264)	172[a]	(143-234)

Note: Values in the same row not sharing the same superscript are significantly different at $P < .05$.

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computerised chest tomography; eGFR, estimated glomerular filtration rate; HD, haemodialysis.

*Median (interquartile range).

TABLE 4 Multivariate Cox regression analysis of mortality in older patients

		95.0% CI for HR		
	HR	Lower	Upper	*P*
Age (year)	1.069	1.024	1.117	.003
Clinical severity (Severe-critical disease vs. mild-moderate disease)	7.173	3.234	15.908	<.001
Patients group (Control group reference)				.004
Haemodialysis group	3.099	1.046	9.175	.041
CKD group	4.332	1.531	12.263	.006

Note: The model included age, patients group, presence of cardiac disease (ischaemic heart disease and/or heart failure), dyspnoea, clinical severity, presence of multiple bilateral lesions in chest computerised tomography, baseline CRP level, and baseline lymphocyte count, which were found significantly related with mortality in univariate analyses. Albumin and ferritin were not included due to high missing value. We also included gender and diabetes mellitus into the model, which were found as critical factors on mortality in the literature.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

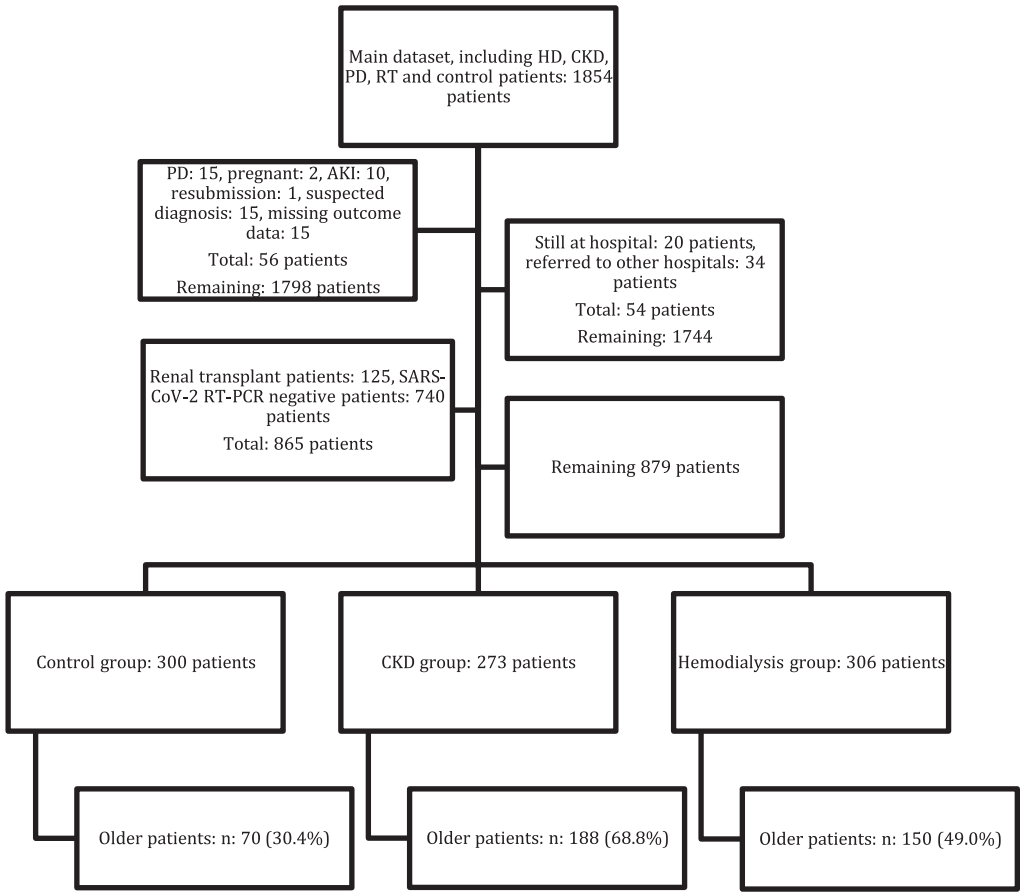

FIGURE 1 Flowchart of the study demonstrating population selection. AKI, acute kidney injury; CKD, chronic kidney disease; HD, haemodialysis; PD, peritoneal dialysis; RT, renal transplantation; RT-PCR, reverse transcriptase-polymerase chain reaction

presenting symptoms were fever (56.2%), dyspnoea (56.8%) and dry cough (47.7%). Dyspnoea was more in the older group.

When the clinical severity of the disease was evaluated, it was found that approximately half of the patients (43.6% and 55.3%) in the older CKD and HD groups had severe-critical disease at admission, and this rate was significantly higher than the control group (16.1%) (Table 1). On the other hand, the rate of severe-critical patients in the subgroups in the control and HD groups in older patients was significantly higher than in the younger group, whereas this rate did not differ significantly in the CKD group (51.8% vs. 43.6%, respectively) (Table S2).

3.3 | Chest CT and baseline laboratory values

Almost all (97.0%) of the patients included in the study had chest CT (Table S2). All three older groups had multiple bilateral lesions (76.0% of all patients), and there was no difference between the groups (Table 1). The lowest rate was in the control group (57.6%). The majority of the lesions were ground-glass infiltrations (91.1% in older patients). The pleural effusion rate was significantly higher in the HD group than in the control group (25.7% vs. 3.6%). In the subgroup analyses within all three groups, there was no significant difference between older and younger patients regarding lesion location and shape.

The median serum albumin level in the older groups was below 3.5 g/dL in the CKD and HD groups (Table 1). The older patients of the control and HD groups had significantly lower serum albumin levels than younger patients (Table S3). Haemoglobin level was the lowest in HD group and the highest in control group among older groups. Ferritin level was significantly higher in HD group than in other groups. There was no difference in lymphocyte and platelet counts between older groups. In all three groups, lymphocyte, haemoglobin and ferritin were not significantly different between younger and older subgroups. Among older patients, approximately half of the patients in the CKD and HD groups had a baseline CRP level ≥10 times the upper limit of the laboratory value (45.2% and 62.7%, respectively). This ratio was significantly higher in the older HD group than the CKD and control groups. In addition, it was significantly higher in the older subgroup in the control and HD groups than younger.

3.4 | In-hospital follow-ups, treatments and outcomes

In the study, the median length of stay in hospital was 10 (IQR: 7-16) days, and it was not significantly different in all three older groups (Table 2). Almost all patients used hydroxychloroquine (98.8%). Macrolides and oseltamivir were other commonly used treatments. There was no significant difference in these treatments among older patients. The rate of use of any treatment was not significantly different between older and younger subgroups of three patients' groups (Table S3).

Among older patients, the ICU admission rate was significantly higher in the CKD and HD group than in the control group (38.8%, 37.3% and 15.7%, respectively), but the mechanical ventilation rates were not different (79.2%, 64.3% and 60.0%, respectively). Although ICU admission rates were significantly higher in the control and HD groups in older patients, it did not differ significantly between older and younger patients in the CKD group. There was no difference between old and younger patients in terms of mechanical ventilation rates in all three groups.

In-hospital mortality or death and/or ICU admission rates in the older group were significantly higher in the CKD (29.3% and 39.4%) and HD group (26.7% and 30.1%) compared with the control group (8.6% and 17.1%). Although these rates were higher in the older patients in the control and HD groups, there was no significant difference between the older and younger patients in the CKD group.

Table 3 shows in-hospital survival status of the older patients. Patients age, patients group, presence of cardiac disease (ischaemic heart disease and/or heart failure), dyspnoea, clinical severity, presence of multiple bilateral lesions in chest CT, CRP, albumin and ferritin levels, and lymphocyte count were found to be different between the groups in terms of survival. In the multivariate Cox regression model consisting of these parameters, the independent parameters associated with in-hospital mortality in older patients were age, clinical severity at admission, and patient group (Table 4). In-hospital mortality rates in CKD and HD groups were higher than control group in-hospital mortality compared with the control group [Hazard ratio (HR): 4.33 (95% confidence interval [CI]: 1.53-12.26) and HR: 3.09 (95% CI: 1.04-9.17), respectively]. Figure 2 illustrates the survival plot of the model, separated lines for the patients' group.

4 | DISCUSSION

In this multicentre, retrospective study including hospitalised patients with confirmed COVID-19 suffering from stage 3-5 CKD, on maintenance HD treatment and a control group, we have found that both in unadjusted and in adjusted in-hospital mortality, CKD and HD groups had significantly higher mortality rate than the control group among older patients [HR: 4.33 (95% CI: 1.53-12.26) and HR: 3.09 (95% CI: 1.04-9.17), respectively]. These results clearly show that older patients with severe chronic kidney disease, whether on dialysis or not, are among the most affected patient groups in the COVID-19 pandemic.

It has been stated in many studies that CKD and HD may be associated with increased COVID-19 mortality.[13-17] However, as far as we know, there is no study involving older groups that included both CKD and HD groups and compared them with a control group. However, some studies have indirect findings that support our data. In a study involving 5256 nursing home residents with COVID-19 [median age, 79 years (IQR, 69-88)], the presence of CKD was associated with death from any cause within 30 days [OR, 1.33 (95%, 1.11-1.61)].[18] In a study including 255 randomly selected hospitalised patients with COVID-19 (mean age 66 ± 17 years) who were followed up with the Clinical Frailty Scale, 27% died at 60 days of follow-up, and in multivariate analyses, age, presence of CKD and previous stroke have been associated with death.[19] Data obtained from ERA-EDTA registry records, which included 3285 HD patients, showed that the 28-day mortality risk associated with COVID-19 was 21.1 times higher than the propensity scoring matched historical controls. In this study, the researchers also found significant differences between age groups; the 28-day mortality was 31.4% among the >75 years of age dialysis patients. Geographical differences and the presence of multimorbidities also affected results.[13] The control group in this study was historical, and it is difficult to evaluate it with a non-current control group

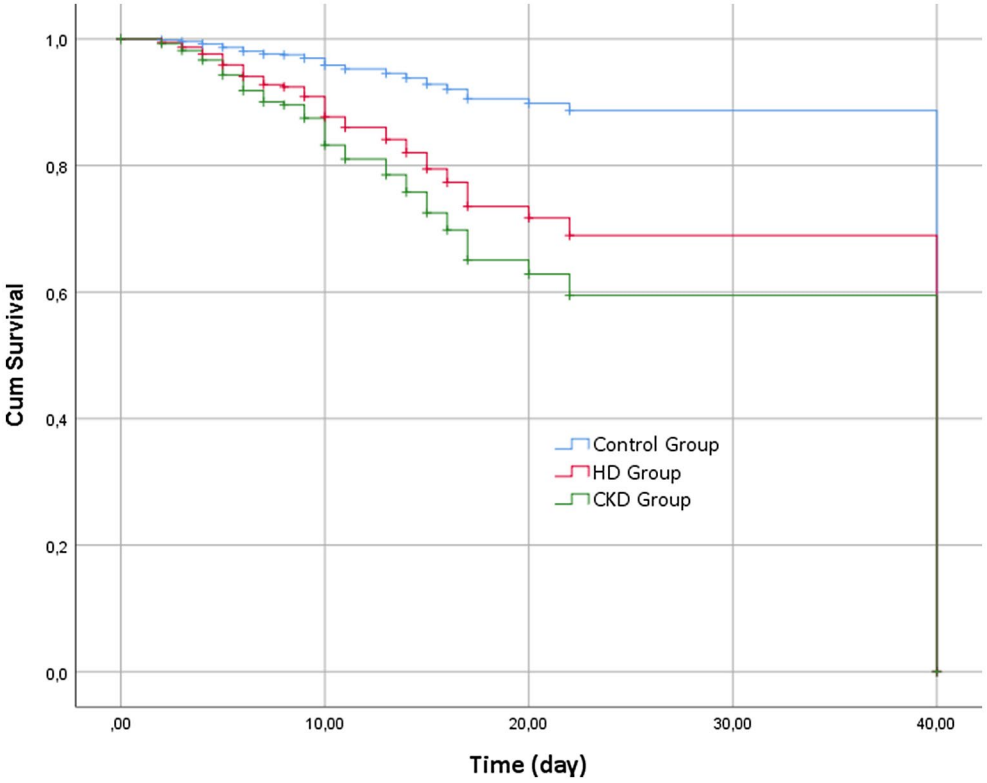

FIGURE 2 Survival plot of multivariate Cox regression model, which was presented in Table 4. Lines separate patients' groups. CKD, chronic kidney disease; HD, haemodialysis

due to the possibility of any healthcare being affected during the COVID-19 pandemic. CKD and HD patients have many negative risk factors (uraemic immunosuppression, volume load, toxic effects of drugs and metabolites, etc), and these patients live with diseases (HT, DM, etc) that cause cardiovascular disease burden for many years.[20-23] Cardiovascular mortality of dialysis patients is 10 to 30 times higher than the general population.[24] Infection is the second leading cause of death among dialysis patients, after cardiovascular disease.[25] According to the United States Renal Data System (USRDS) registry, the annual mortality rate due to pneumonia and sepsis in dialysis patients is 10 and 100 times higher in the 65-74 age category compared with the general population.[25] Hence, the frailty and vulnerability could impact survival during COVID-19. Our findings might have reflected the possible effects of these unconfounded factors that could not be revealed by the analysis.

We found that dyspnoea was more common in the CKD and HD groups compared with the control group (58.0%, 64.0% and 40.0%, respectively), and this was in line with the rates of referral to severe-critical disease in these groups. We found that dyspnoea was higher in uraemic and older subgroups, whereas fever was more pronounced in non-uraemic and younger groups. This may show that older age and uraemia may hide the fever response in COVID-19 patients. In older COVID-19 patients, cough and fever were significantly less prevalent, but no dyspnoea, in older adults compared with younger patients.[26]

Another important finding in our study was that in this cohort, lesions in the form of ground glass were detected in 91.1% of older patients whose almost all (97.0%) had chest CT. The possibility of multiple bilateral lesions was higher in the older and uraemic groups, which was consistent with clinical findings. The mildest findings were found in the younger control group (Table S2). On the other hand, the presence of patients without pulmonary involvement in chest CT might show that some patients' symptoms and signs are not associated with pulmonary involvement. Besides, pleural effusion in the HD group was higher than in other studies,[27] suggesting the presence of excess volume in this patient group. Serum albumin and haemoglobin levels were lower, and CRP was higher in the older and uraemic groups. There was not any significant relationship between these parameters with survival in multivariate analyses. Therefore, their effects were not seen in the multivariate analyses. In the HD group, health centres have been identified as a possible major source of COVID-19 transmission (46.8% of patients). There were data indicated that the frequency of COVID-19 in HD centres is higher than in the population.[28] During the pandemic, HD centres patients are exposed to the risk of recurrent transmission due to the patient and staff mobility.[29,30] For this reason, taking into account that the mortality risk of the HD group is higher, the older group should be treated more carefully. This finding points the importance of vigilant care for older HD patients as their mortality risk is very high.

The mortality rates in our study are generally below the rates reported in the literature.[13,15,16] Many factors might play a role in this

(such as our patients' mean ages were lower), as well as the fact that the older or severe kidney patients are at a disadvantage in this situation due to the overload on health systems in pandemic conditions. For example, in some studies, a significant portion of the deaths was reported in the clinic without transfer to ICU.[16,31] Lack of ICU care, when needed, is expected to be related to higher mortality rates. In our study, the deaths mostly occurred in ICU, and there was not a considerable number of deaths in the clinic. Therefore, we suggest that a lesser mortality rate in this study, when compared with the other studies, might be at least partly due to the availability of ICU care in severe COVID-19 cases. Moreover, in our study, all these patient groups could benefit from our health system at a similar rate even in the pandemic chaos regardless of the age of the patients (such as the time between the onset of symptoms and hospitalisation, drug use rates, mechanical ventilation ratio in the ICU, the ratio of the number of patients who died/the number of ICU admission patients were similar between the older and younger subgroups). Hence, there is no additional factor in this respect in our survival results.

This study has some limitations, such as being retrospective and the groups not being randomised. Various data such as urine analysis, vital parameters, changes in kidney functions and treatment details in ICU care were not presented. Because the drug use rates given for COVID-19 in the study are similar for both older groups and subgroups, analysis and interpretation cannot be made in this respect. The main reason for this is that during the pandemic, all hospital stays, payments, drug supply and treatment algorithms related to COVID-19 have been organised and standardised by our Ministry of Health. Nevertheless, these data show that these treatments can be given to the older, even if the kidney disease is severe, like patients without kidney disease.

In conclusion, we found that the clinical and laboratory severity of COVID-19, and the possibility of multiple bilateral lesions at presentation were significantly higher in the older and uraemic groups compared with the younger control group among hospitalised COVID-19 patients. Moreover, in-hospital mortality among older COVID-19 patients, is significantly higher in those with stage 3-5 CKD and on maintenance HD when compared with older patients without CKD regardless of demographic characteristics, comorbidities, clinical and laboratory data on admission. Therefore, a more careful approach is required for the uraemic older group.

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DISCLOSURE

The authors declare no conflict of interests.

ETHICAL APPROVAL

Health Sciences University, Haseki Training and Research Hospital Ethics Committee approved the study (number: 2020-41).

INFORMED CONSENT

Informed consent was waived due to acute need for data collection in the pandemic time.

AUTHOR CONTRIBUTIONS

SO, KT and MA contributed to data collection, study design, manuscript writing, literature review and revision. SO contributed to data analysis. MG, MI, MRA, ZA, BD, NE, ES, SK, TEO, HD, IP, DGT, GS, SB, MED, ZS, EH, EK, TB, MBO, NG, IS, MDA, ZST, GS, BT, HZT, AY, SS, ARO, KA contributed to data collection. All authors approved the final version of the article for submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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