North Clin Istanb 2022;9(6):541–549
doi: 10.14744/nci.2022.87360

ORIGINAL ARTICLE NEPHROLOGY

Evaluation of the relationship between acute kidney injury and renin angiotensin system inhibition in COVID-19 patients

Ezgi Ersoy Yesil,[1] Hasan Kayabasi,[1] Dede Sit,[1] Mustafa Behcet Demirbas,[1] Ozlem Pehlivan,[2] Aylin Arslan,[3] Tutku Aydin,[3] Zeynep Gokcin[3]

[1]Department of Nephrology, Umraniye Training and Research Hospital, Istanbul, Turkiye
[2]Department of Rheumatology, Umraniye Training and Research Hospital, Istanbul, Turkiye
[3]Department of Internal Medicine, Umraniye Training and Research Hospital, Istanbul, Turkiye

ABSTRACT

OBJECTIVE: In patients with coronavirus disease 2019 (COVID-19), acute kidney injury (AKI) may alter the clinical course and outcome of the disease. In this study, the association of AKI with renin angiotensin system (RAS) inhibitor treatment and its clinical consequences were examined in COVID-19 patients admitted to our hospital during the initial stages of the pandemic.

METHODS: A total of 407 patients between 18 and 85 years of age (202 male and 205 female) admitted to the Umraniye Research And Training Hospital between May 2020 and August 2020 with a diagnosis of COVID-19 were included in the study. Patients were categorized as follows: Group 1, subjects with no chronic conditions (n=150); and Group 2, subjects with comorbid conditions (n=257). Group 2 was subdivided into Group 2A (receiving angiotensin receptor blocker [ARB])/ (angiotensin converting enzyme inhibitor [ACEI], n=81), and Group 2B (not receiving ARB/ACEI, n=176).

RESULTS: Hypertension was the most frequent comorbid condition (36.4%). There was no difference in survival rates between the patients who used RAS inhibitor and the ones who did not based on log rank test (p=0.342). Fifty-four patients (13.4%) had developed AKI during the time frame of the disease. In patients with chronic diseases such as hypertension, the use of RAS inhibitory medication was not associated with developing AKI (OR 95% CI: 0.317–1.358; p=0.256). The survival rate of the patients with AKI was significantly lower than patients without AKI (p<0.0001).

CONCLUSION: COVID-19 may cause renal injury represents a risk factor for mortality. Therefore, detection of renal injury has a particular prognostic importance.

Keywords: Acute kidney injury; COVID-19; renin angiotensin inhibitors.

Cite this article as: *Ersoy Yesil E, Kayabasi H, Sit D, Demirbas MB, Pehlivan O, Arslan A, et al. Evaluation of the relationship between acute kidney injury and renin angiotensin system inhibition in COVID-19 patients. North Clin Istanb 2022;9(6):541–549.*

The pandemic caused by Severe Acute Respiratory Syndrome CoV-2 (SARS-CoV-2) resulted in the death of more than 13 million people worldwide in the past 2 years [1]. Although lungs are the primary site of involvement, other vital organs may also be involved with subsequent effects on morbidity and mortality [2–6]. Comorbid conditions such as diabetes, hypertension, asthma, cardiac failure, and chronic kidney disease (CKD) not only increase the risk of contracting the coronavirus disease 2019 (COVID-19) caused by SARS-Cov-2, but also have prognostic significance [7]. For example, kidney injury has been reported to have an important role in the clinical course of the disease with an incidence of 1–46% [8]. Again, serum creatinine and urinary protein at presentation have been proposed to have prognostic implications [3].

Received: August 02, 2022 *Revised:* August 12, 2022 *Accepted:* September 28, 2022 *Online:* December 22, 2022

Correspondence: Hasan KAYABASI, MD. Umraniye Egitim ve Arastirma Hastanesi, Nefroloji Klinigi, Istanbul, Turkiye.
Tel: +90 216 632 18 18 e-mail: drkayabasi@yahoo.com

At the initial stages of the pandemic, two commonly prescribed class of antihypertensives, that is, angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), have been suggested to worsen the disease course through increased number of ACE2 receptors, which represent the entry route for SARS-CoV2, and several studies reported beneficial effects after switching to other antihypertensives [9], although more recent studies indicated no increased risk [10].

In the light of these data, we assessed acute kidney injury (AKI), comorbid conditions, and ARB/ACEI use in COVID-19 patients presenting to our unit during the initial stages of the pandemic between May 2020 and August 2020, to examine the effect of these parameters on clinical outcomes.

Highlight key points

- RAS (renin angiotensin system) inhibitory medication does not make any difference in survival of patients with COVID-19 infection.
- In patients with chronic diseases such as hypertension the use of RAS inhibitory medication is not associated with developing acute kidney injury (AKI) in patients with COVID-19.
- COVID-19 may cause renal injury represents as a risk factor for mortality.
- Detection of renal injury has a particular prognostic importance.

MATERIALS AND METHODS

Study Design and Data Collection

This was a single center Umraniye Research and Training Hospital retrospective cohort study. Ethics committee approval number B.10.1TKH.4.34.H.G.P. 0.01/156 was received from the ethics committee of our hospital on May 12, 2020. A total of 407 patients (202 male and 205 female) aged between 18 and 85 years and admitted to clinical wards between May 2020 and August 2020 with a diagnosis of symptomatic COVID-19 were included in the study. Patients were broadly divided into two categories as those with no chronic disease (Group 1, n=150), and those with chronic diseases such as hypertension, CKD, diabetes, malignancy, stroke, and COPD/asthma (Group 2, n=257). Then patients in Group 2 were subcategorized into those receiving RAAS inhibitor treatment (Group 2A, n=81) and not receiving RASS inhibitors (Group 2B, n=176). AKI was defined as follows according to Kidney Disease: Improving Global Outcomes (KDIGO): (1) a ≥0.3 mg/dl increase in serum creatinine levels within the past 48 h; or (2) a confirmed or estimated ≥1.5-fold increase in serum creatinine compared to baseline within the past 7 days; or (3) urinary output of <0.5 ml/kg/h within the past 6 h [11]. Patients developed AKI had no dehydration or a history of nephrotoxic drug or iodinated contrast administration which contribute to AKI. All patients used hydroxychloroquine and 120 patients who were unresponsive to first line treatment used Favipiravir for 5 days according to the guidelines published by the Turkish Ministry of Health's Scientific Committee. Medical data, epidemiologic and demographic information, clinical manifestations, and laboratory/radiological findings were recorded and examined by two experienced clinicians. The study was carried out in accordance with the Helsinki Declaration.

Procedures

COVID-19 was diagnosed with realtime reverse transcription polymerase chain reaction (PCR) testing on nasal and pharyngeal swab samples. Treatment protocols were based on the algorithms issued by the COVID-19 Scientific Committee of the Turkish Ministry of Health [12]. Symptoms at presentation, comorbidities, and treatments were recorded. Complete blood count, serum biochemistry, myocardial enzymes, coagulation profile, ferritin, D-dimer, C-reactive protein (CRP), procalcitonin, urinalysis, and urinary protein/creatinine ratio were tested in all patients. The estimated glomerular filtration rate was calculated using the CKD Epidemiology Collaboration formula [13]. A thorax CT examination was performed in patients with cough, sputum production, and suspected lung involvement in physical examination. The presence of peripheral, bilateral (multi-lobar) ground-glass opacities (GGOs) (sometimes in conjunction with consolidation or cobblestone appearance), multifocal round GGOs (sometimes with consolidation and cobblestone appearance), reverse halo, or organized pneumonia was considered typical radiological involvement.

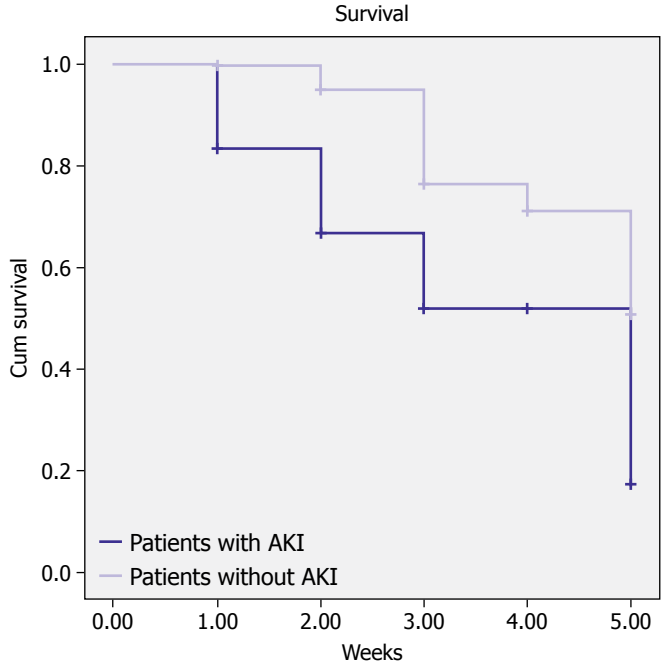
Statistical Analysis

Statistical Package for the Social Science (IBM SPSS Statistics New York, USA) version 20.0 was used to perform statistical analyses. Descriptive statistics are reported as means±SDs for continuous variables and as number and frequencies for binary and categorical variables. The data showed a normal distribution; hence, independent samples t-test was used to compare continuous variables, whereas categorical variables were compared with

TABLE 1. Dermographic data of all patients

	All patients (n=407)
Age (years)	55.66±17.28
Gender (F/M)	205/202
Smoking (%)	8.8
Complications	
AKI (%)	13.4
CVA (n-%)	0.2
Cardiac complications (%)	7.2
ARDS (%)	8.1
Need for mechanical ventilation (%)	10.6
Exitus (%)	10.1
Use of favipiravir (%)	29.4
Use of tocilizumab (%)	5.4
COVID-19 related symptoms	
Asymptomatic (%)	4.9
Cough (%)	61.9
Myalgia/arthralgia (%)	23.6
Fever (%)	34.9
Sore throat (%)	7.4
Dyspnea (%)	39.8
Diarrhea (%)	7.6
Vomiting (%)	9.6
SBP (mm/Hg)	122.06±18.413
DBP (mm/Hg)	74.03±36.32
Body temperature (°C)	36.78±0.55
$Sa0_2$ %	94.77±7.032
Duration of hospital stay (days)	8.78±6.28

AKI: Acute kidney injury; CVA: Cerebrovascular accident; CVD: Cardiovascular disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; $Sa0_2$: Oxygen satura-tion; COVID-19: Coronavirus disease 2019; F: Female; M: Male.



	Patients without AKI (n=350)	Patients with AKI (n=54)	p
1 week	99.7	83.3	
2 week	94.9	66.7	
3 week	76.5	51.9	**<0.0001**
4 week	–	–	
>1 month	50.7	17.3	

AKI: Acute kidney injury.

FIGURE 1. Survival rates of patients with and without acute kidney injury.

Chi-square test. Kaplan–Meier test was used for survival estimation and the groups compared with the logrank test. Multinomial and binary logistic regressions were used to investigate the associations. The statistical level of significance was set at $p<0.05$.

RESULTS

A total of 407 patients with COVID-19 were included in the study. The mean age of our study was 55.66±17.28 years and 49.6% of the patients were male and 50.4% were female. Average time of hospitalization was 8.78 days. Hypertension was the most frequent comorbid condition (36.4%) leaded by diabetes mellitus with the incidence of 23.8%. Table 1 presents the demographic data of all patients, dermographic data of patients in Groups 1 and 2 are showed in Table 2. Blood parameters of patients in Groups 1 and 2 are showed in Table 3. About 31.5% of the patients who have comorbid conditions were under renin angiotensin system (RAS) inhibitor medication and there was no difference in survival rates between the patients who used RAS inhibitor and the ones who did not based on long rank test ($p=0.342$). Fiftyfour patients (13.4%) had AKI during the time frame of the disease. There was significant difference according to age between patients with AKI and patient who did not develop AKI ($p<0.0001$). Three patients had a missing data on development of AKI; therefore, they were excluded from the study. Dermographic data and blood parameters of patients according to developing AKI are showed in Table 4. In patients with chronic diseases such as hypertension, the use of RAS inhibito-

Table 2. Comparison of dermographic data of group 1 and group 2

	Patients with no chronic disease (n=173)	Patients with chronic disease (n=234)	p
Age (years)	46.36±16.3	62.53±14.6	<0.0001*
Gender (F/M)			
Smoking (%)			
Complications (%)			
AKI	5.8	19.0	<0.0001*
CVA	0	0.4	1.000
Cardiac complications	5.2	8.6	0.243
ARDS	3.5	11.6	0.003*
Need for mechanical ventilation	5.2	14.7	0.002*
Exitus	4.6	14.3	0.001*
Use of favipiravir	22.5	34.5	0.011*
Use of tocilizumab	4.0	6.5	0.387
COVID-19 related symptoms			
Asymptomatic (%)	2.3	6.8	0.039*
Cough (%)	69.4	56.4	0.01*
Myalgia/arthralgia (%)	27.7	20.5	0.099
Fever (%)	40.5	30.8	0.046*
Sore throat (%)	12.1	3.8	0.002*
Dyspnea (%)	31.8	45.7	0.006*
Diarrhea (%)	8.7	6.8	0.571
Vomiting (%)	9.8	9.4	1.000
SBP (mm/Hg)	117.07±14.47	125.74±20.1	<0.0001*
DBP (mm/Hg)	75.39±54.26	73.03±11.15	0.519
Body temperature (°C)	36.88±0.62	36.71±0.48	0.002*
$Sa0_2$ %	96.27±3.2	93.67±8.69	<0.0001*
Duration of hospital stay (days)	8.17±6.2	9.25±6.31	0.086

*: P<0.05; F: Female; M: Male; AKI: Acute kidney injury; ARDS: Acute respiratory dis-tress syndrome; CVA: Cerebrovascular accident; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; $Sa0_2$: Oxygen satura-tion; COVID-19: Coronavirus disease 2019.

ry medication was not associated with developing AKI (OR:95% CI: 0.317–1.358; p=0.256). The frequencies of other developed problems were 7.2%, 14.8% and 0.2% for cardiacomplications, liver dysfunction, and cerebrovascular disease. In addition, 33 patients (8.1%) had developed acute respiratory distress syndrome (ARDS) whereas, 43 patients (10.6%) needed mechanical ventilation. There was significant difference between Subgroups 1 and 2 based on AKI according to D-dimer, ferritin, LDH, CRP, and albumin and neutrophil levels (p<0.0001, P=0.019, p=0.035, p<0.0001, p=0.0001, and p<0.0001). Unlike most of studies, there was no significant difference between these groups based on AKI according to lymphocyte (p=0.612). Nevertheless there was no significant difference between groups of patients using RAS inhibitory medications and the ones not using according to hospital stay, CT changes and laboratory findings accept D-dimer (p=0.032), and uric acid (p=0.000). Table 5 presents clinical data based on using RAS inhibitory medication.

In overall, 41(10%) patients passed away at the ward. Figure 1 shows the comparison of patients with and without AKI based on survival rates. The survival rate of the patients with AKI was significantly lower than patients without AKI (p<0.0001). It was also associated with longer hospital stay (OR: 0,914; 95% CI: 0.876–0.954; p<0.0001). Sat O_2 levels were significantly lower in patients with AKI (95.64±4.41, 89.09±14.52, p<0.0001). AKI developed more in patients with diabetes mellitus,

TABLE 3. Blood parameters of patients in group 1 and 2

	Patients with no chronic disease (n=173)	Patients with chronic disease (n=234)	p
BUN (mg/dl)	28.11±13.71	47.16±46.21	<0.0001*
Creatinine (mg/dl)	0.85±0.22	1.38±1.78	<0.0001*
GFR (ml/min/1.73 m^2)	98.56±17.88	75.84±49.37	<0.0001*
Sodium (mEq/L)	138.44±3.22	137.46±4.09	0.001*
Potassium (mEq/L)	4.12±0.38	192.78±2877.41	0.056
Uric Acid (mg/dl)	14.5±2.27	15.15±3.39	0.04*
HCO_3 (mmol/L)	24.11±5.72	25.36±26.61	0.786
PCO_2 (mmHg)	37.93±11.32	38.98±13.35	0.687
Creatinine Kinase (U/L)	160.84±245.28	109.52±200.34	0.077
Lactate dehydrogenase (U/L)	297.16±118.57	332.35±178.798	0.027*
D-dimer (ng/ml)	904.54±1462.21	1487.0±1785.45	0.001*
Ferritin (ng/ml)	275.42±354.57	606.12±1591.18	0.037*
Fibrinogen (mg/dl)	582.32±1800.0	443.62±155.66	0.299
C-reactive protein(mg/dl)	4.29±9.69	5.84±6.81	0.068
Pro-calcitonin (ng/ml)	0.69±5.1	3.17±18.18	0.171
AST (U/L)	29.83±21.13	34.10±43.98	0.240
GGT (U/L)	42.26±54.87	56.93±116.43	0.193
Albumin (g/L)	4.09±0.41	3.83±0.56	<0.0001*
WBC (UL)	6664.75±3191.14	10315.42±21556.16	0.028*
Neutrophil (UL)	4506.79±2883.08	6265.71±5349.62	<0.0001*
Lymphocyte (UL)	1761.24±1642.26	2839.12±19287.35	0.464
Hemoglobin (g/dl)	13.18±1.63	12.41±1.99	<0.0001*

*: P<0.05; AKI: Acute kidney injury; BUN: Blood urea nitrogen; GFR: Glomerular filtration rate; HCO_3: Bicarbonate; PCO_2: Partial pressure of carbon dioxide; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; WBC: White blood cell.

prior CVA, CKD, and malignancy (p=0.04, p=0.007, p=0.0001, and p=0.026). There was a significant difference on developing ARDS and need for mechanical ventilation between groups (p<0.0001 for both). The odds ratio for developing ARDS in patients with AKI was 6.613 (95%CI: 4.335–10.088) whereas the odds ratio of need for mechanical ventilation was 7.217 (95% CI: 4.688–11.111) in patients with AKI. In addition, multinomial logistic regression revealed that AKI was associated with changes, as well (p=0.008). Table 6 presents the association between AKI and CT changes.

DISCUSSION

Although COVID-19 mainly affects lungs, multiorgan involvement is also common, particularly in those with underlying comorbid conditions. Kidneys are among the organs that are most malignancy in infections with SARS-CoV-2 virus [3–5]. As suggested by Li et al. [5], kidneys were the third most frequently involved organs after lungs and heart. COVID-19 may impair renal functions through several mechanisms. Entry of SARS-CoV-2 into organs is mediated by ACE2 receptors [9]. While the virus may cause renal dysfunction with direct invasion [14], it may also result in injury through disruption of the RAS system or because of systemic inflammatory response [15]. Studies of kidney biopsy samples or identification of PCR particles in urinary sediments are supportive of the notion that SARS-CoV-2 may cause cytopathic effects in kidney cells [16]. COVID-19 infection may cause severe complications due to DIC and hypercoagulability, and acute tubular necroses were detected in most of the postmortem kidney biopsy studies [17–22]. Furthermore, inflammatory responses are a characteristic of COVID-19 disease and are thought to be responsible for dysfunction of many vital organs, including kidneys [23].

Table 4. Dermographic, clinical data, and blood parameters of patients according to developing AKI (n=404)

	Patients without AKI (n=350)	Patients with AKI (n=54)	p
Age (years)	67.5±14.21	53.91±17.05	<0.0001*
Gender (F/M)	180/170	25/29	0.483
Smoking (%)	9.14	7.4	0.677
Comorbidities (%)			
Diabetes mellitus	21.71	37.04	0.014*
Hypertension	35.42	44.44	0.201
Prior CVA	2.28	10.2	0.007*
CVD	12.57	18.51	0.232
CKD	5.14	20.37	<0.0001*
Malignancy	5.14	12.96	0.026*
COPD/asthma	14.57	18.51	0.451
COVID-19 related symptoms (%)			
Asymptomatic	5.1	3.7	0.65
Cough	62.9	55.6	0.304
Myalgia/arthralgia	24.3	20.4	0.529
Fever	34.9	33.3	0.827
Sore throat	8.6	0	0.025*
Dyspnea	38.0	50.0	0.093
Diarrhea	8.0	3.7	0.26
Vomiting	9.4	11.1	0.697
SBP (mm/Hg)	122.83±18.37	117.0±18.33	0.031*
DBP (mm/Hg)	72.83±10.4	81.98±96.27	0.085
Body temperature (°C)	36.79±0.56	36.75±0.45	0.617
$Sa0_2$ %	95.64±4.41	89.09±14.52	<0.0001*
Duration of hospital stay (days)	8.26±5.49		<0.0001*
ARDS (%)	3.7	37.0	<0.0001*
Mechanic ventilation (%)	5.2	46.3	<0.0001*
BUN (mg/dl)	32.49±18.19	81.43±79.16	<0.0001*
Creatinine (mg/dl)	0.97±0.78	2.34±2.96	<0.0001*
GFR (ml/min/1.73 m^2)	90.63±39.18	48.09±30.56	<0.0001*
Sodium (mEq/L)	138.0±3.22	137.2±6.29	0.364
Potassium (mEq/L)	4.35±0.51	4.59±0.88	0.056
Uric Acid (mg/dl)	0.03±0.24	0.27±0.91	0.083
HCO_3 (mmol/L)	25.94±27.62	23.33±9.35	0.549
PCO_2 (mmHg)	38.45±10.29	39.1±16.88	0.816
Creatinine kinase (U/L)	117.84±176.89	179.2±351.58	0.265
Lactate dehydrogenase(U/L)	311.23±152.4	361.26±180.55	0.035*
D-dimer (ng/ml)	1106.44±1597.65	2130.45±1937.22	<0.0001*
Ferritin (ng/ml)	315.61±666.18	1384±2717.22	0.019*
Fibrinogen (mg/dl)	494.25±1215.34	523.33±176.36	0.88
C-reactive protein (mg/dl)	4.35±7.74	10.55±8.92	<0.0001*
Pro-calcitonin (ng/ml)	0.59±3.23	9.19±32.4	0.082
AST (U/L)	31.02±33.89	40.92±47.84	0.152
GGT (U/L)	51.94±103.88	47.15±48.64	0.75
Albumin (g/L)	4.01±0.45	3.48±0.66	<0.0001*
WBC (UL)	8567.52±17500.88	10055.98±8213.98	0.543
Neutrophil (UL)	5115.35±3706.6	8161.23±7748.03	<0.0001*
Lymphocyte (UL)	3158.56±16537.38	1867.93±2059.69	0.612
Hemoglobin (g/dl)	12.89±1.79	11.71±2.16	<0.0001*

*: P<0.05; AKI: Acute kidney injury; CVA: Cerebrovascular accident; CVD: Cardiovascular disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; $Sa0_2$: Oxygen saturation; BUN: Blood urea nitrogen; GFR: Glomerular filtration rate; HCO_3: Bicarbonate; PCO_2: Partial pressure of carbon dioxide; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; WBC: White blood cell.

Table 5. Clinical data based on Ras inhibitory use (n=407)

	All patients (n=407)	RAS inhibition (+) (n=81)	Ras inhibition (-) (n=321)	p
Age (years)	55.66	67.56	52.65	0.000
Saturation O_2 (%)	94.77	94.74	94.78	0.967
BUN (mg/dl)	39.004	50.81	59.28	0.001
Serum creatinine (mg/dl)	1.1504	1.300	1.1126	0.270
eGFR (ml/min/1.73 m²)	85.69	70.23	89.37	0.259
Uric acid (mg/dl)	5.24	6.21	4.93	0.000
Sodium (mEq/l)	137.87	137.658	137.935	0.555
Potassium (mEq/l)	4.208	4.156	4.221	0.341
LDH (U/l)	317.24	331.39	313.61	0.363
D-dimer (ng/ml)	1234.599	1600.34	1136.72	0.032
Ferritin (ng/ml)	474.09	346.98	508.47	0.397
Fibrinogen (mg/dl)	498.092	450.68	510.53	0.710
C-reactive protein (mg/dl)	5.19	5.60	5.09	0.629
Procalcitonin (ng/ml)	2.11	5.49	1.30	0.064
AST (U/l)	32.27	31.29	32.51	0.780
ALT (U/l)	29.22	29.12	29.25	0.975
Albumin (g/l)	3.94	3.90	3.95	0.486
Troponin I(µg/l)	0.068	0.121	0.054	0.291
White blood cell (UL)	8755.99	8359.31	8856.70	0.808
Neutrophile (UL)	5514.37	6007.80	5389.10	0.272
Lymphocyte (UL)	2377.55	1520.74	2592.41	0.556
Trombocyte (UL)	226418.91	229941.96	225521.74	0.648
Hospital stay (day)	8.78	8.80	8.78	0.979
AKI (%)	13.4	15.9	12.7	0.469
Bt scan absent (%)	6.6	7.4	92.6	0.052
Mild	67.8	23.6	76.4	
Moderate	18.2	16.2	83.8	
Severe	6.1	8	92.0	

BUN: Blood urea nitrogen; GFR: Glomerular filtration rate; AST: Aspartate aminotransferase; ALT: Alanin transaminase; LDH: Lactate dehydrogenase.

Table 6. Association between AKI and CT changes

CT changes	OR (95% CI)	p
Mild	1.058 (0.301–3.713)	0.93
Moderate	1.125 (0.281–4.509)	0.868
Severe	5.333 (1.26–22.567)	0.023*

AKI: Acute kidney injury; CT: Computer Tomography; OR: Odd ratios; CI: Confidence interval.

It has been suggested that drugs that cause ACE2 inhibition may lead to an elevated risk of COVID-19 in diabetic or hypertensive patients receiving these types of medications, due to the increased expression of ACE2 receptors, which represent a route of entry for SARS-CoV-2 virus into the cells [24]. In the initial stages of the pandemic, controversial opinions have been expressed regarding ACEI and ARB use in these patients [25]. Monteil et al. [9] proposed that ACE2 enzyme may protect lungs against SARS-CoV-2, and therefore ACEI and ARB class of drugs may even be beneficial. In Fosbol et al.'s [26] study involving 1000 patients, no significant associations between ACEI or ARB use and mortality could be observed. Similarly, Bean et al. [10] did not observe an increase in the severity of the disease during short-term use of ACEI, and event found that these agents could have beneficial effects in terms of reduced intensive care unit admission

and lowered mortality rate in the first 7 days of admission. According to our results, there was no difference in survival rates between the patients who used RAS inhibitor and the ones who did not based on log rank test (p=0.342). Furthermore, in patients with chronic diseases such as hypertension, the use of Ras inhibitory medication was not associated with developing AKI (OR 95% CI: 0.317–1.358; p=0.256). Based on these results and like the recommendations of the World Health Organization, we do not recommend a switch from ACEI/ARB therapy in COVID-19 patients.

Several reports suggested that impaired renal functions in COVID-19 patients may worsen the clinical course and increase mortality. Cheng et al. [2] observed a significant association between elevated serum creatinine and worsening of clinical signs. Again, patients with elevated serum creatinine at presentation were significantly more likely to have more severe course (52.5% vs. 40.7%, p=0.026), with higher serum urea, higher serum creatinine, proteinuria, and hematuria in those with in hospital mortality (p<0.001) [2]. Again, in another study, 29% of the patients with COVID-19 pneumonia were also found to have AKI [27]. While Yang et al. [6] found increased risk of AKI among COVID-19 patients with kidney related comorbidities (such as CKD) as compared to other patient groups (54.5% vs. 2.0%, p<0.0001). Yang et al. [6] observed significantly higher rate of AKI among diabetic COVID-19 patients than in nondiabetic COVID-19 patients.

In a study from the US by Hansrivijit et al. [28] involving 283 patients, 40% of these subjects (115/283) were found to develop AKI. Furthermore, several factors were found to be associated with increased likelihood of AKI, such as advanced age, male gender, hypertension, diabetes mellitus, arrhythmia, and CKD. Again, Thomson et al. [29] in a UK study found that 33.4% of their 470 COVID-19 patients admitted for inpatient care had AKI, with a significant association between AKI and mortality (OR 3.20; 95% CI 2.15 –+ 0.81). In our study, a similar association between AKI and survival was detected among the 407 patients included (p<0.0001), with significantly lower survival in the presence of AKI. In addition, according to our study, we found that patients with AKI were significantly younger than patients without AKI. This may be result of that older patients with COVID 19 infection who develop AKI during disease had serious disease course and generally hospitalized in intensive care units in our hospital; however, older patients that not had AKI had mild disease course so that they were included in our study. Again similar with the previous reports, patients with diabetes mellitus, CKD, previous cerebrovascular disease, or malignancy were found to have significantly increased risk of developing AKI (p<0.014, p<0.0001, p=0.007, and p=0.026) and patients with AKI had increased need for mechanical ventilation (OR: 7.217, 95% CI: 4.6888–11.111), risk of ARDS (OR 6.613, 95% CI: 4.335–10.088), and duration of hospital stay (p<0.0001, p<0.0001, p<0.0001). Furthermore, AKI patients had significant elevations of ferritin, D-dimer, and CRP, which are all intricately linked with more severe disease (p=0.019, p<0.0001, and p<0.0001).

In the light of these data, serum creatinine and urea levels at presentation may provide significant prognostic information for COVID-19 patients, particularly in those at an increased risk of AKI and severe disease, including patients with chronic conditions such as diabetes mellitus and chronic renal disease. In patients requiring hospital admission or in those with severe pneumonia and ARDS, frequent monitoring of kidney functions as well as avoidance from nephrotoxic treatments/interventions is especially important.

Limitations of our study include its single center design and absence of certain admission criteria, leading to variable clinical manifestations. Furthermore, although the diagnosis of AKI was based on KDIGO criteria, renal biopsies were not performed and therefore no pathological data are available. Since the patients were hospitalized in the emergency room and the service circulation was fast, each patient was not requested to have a full urine analysis, and BMI was not calculated. Again, the AKI staging of the patients could not be performed for the same reason.

Despite these limitations, we believe that here we provide some valuable data regarding the identification of COVID-19 patients at risk and in predicting mortality and morbidity. Furthermore, the demonstrated association between the severity of lung findings in CT imaging and renal functions may be considered significant.

Conclusion

In addition to lungs, SARS-CoV-2 may also lead to kidney injury through several pathogenic mechanisms that may represent a risk factor for more severe disease course and mortality. Therefore, early identification and proper monitoring of renal injury may prove to have additional prognostic implications.

Ethics Committee Approval: The Umraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 12.05.2020, number: B.10.1.TKH.4.34.H.GP.0.01/156).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – HK; Supervision – HK, DS; Fundings – HK, EEY; Materials – HK, EEY; Data collection and/or processing – OP, MBD, TA, ZG, AA; Analysis and/or interpretation – HK, EEY, DS; Literature review – HK, EEY; Writing – EEY, HK; Critical review – HK, DS.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33. [CrossRef]
2. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97:829–38. [CrossRef]
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506. [CrossRef]
4. Perico L, Benigni A, Remuzzi G. Should COVID-19 concern nephrologists? Why and to what extent? The emerging impasse of angiotensin blockade. Nephron 2020;144:213–21. [CrossRef]
5. Li X, Wang L, Yan S, Yang F, Xiang L, Zhu J, et al. Clinical characteristics of 25 death cases with COVID-19: A retrospective review of medical records in a single medical center, Wuhan, China. Int J Infect Dis 2020;94:128–32. [CrossRef]
6. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81. [CrossRef]
7. Farouk SS, Fiaccadori E, Cravedi P, Campbell KN. COVID-19 and the kidney: what we think we know so far and what we don't. J Nephrol 2020;33:1213–8. [CrossRef]
8. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 2020;367:1444–8. [CrossRef]
9. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell 2020;181:905–13.
10. Bean D, Kraljevic Z, Searle T, Bendayan R, Pickles A, Folarin A, et al. Treatment with ACE-inhibitors is associated with less severe disease with SARS-COVID-19 infection in a multi-site UK acute Hospital Trust. MedRxiv 2020 May, 12, doi: 10.1101/2020.04.07.20056788.
11. Turkish Ministry of Health. The guidelines published by the Turkish Ministry of Health's Scientific Committee. Available at: https://covid19-bilgi.saglik.gov.tr/tr/covid-19-rehberi.html. Accessed Nov 1, 2022.
12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12. [CrossRef]
13. DiaoB, WangC, WangR, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. medRxiv Apr 10, 2020, doi: 10.1101/2020.03.04.20031120. [CrossRef]
14. Martinez-Rojas MA, Vega-Vega O, Bobadilla NA. Is the kidney a target of SARS-CoV-2? Am J Physiol Renal Physiol 2020;318:F1454–62. [CrossRef]
15. Naicker S, Yang CW, Hwang SJ, Liu BC, Chen JH, Jha V. The Novel Coronavirus 2019 epidemic and kidneys. Kidney Int 2020;97:824–8.
16. Rudiansyah M, Lubis L, Bandiara R, Supriyadi R, Afiatin, Gondodiputro RS, et al. Java barb fish gallbladder-induced acute kidney injury and ischemic acute hepatic failure. Kidney Int Rep 2020;5:751–3. [CrossRef]
17. Kudose S, Batal I, Santoriello D, Xu K, Barasch J, Peleg Y, et al. Kidney biopsy findings in patients with COVID-19. J Am Soc Nephrol 2020;31:1959–68. [CrossRef]
18. Golmai P, Larsen CP, DeVita MV, Wahl SJ, Weins A, Rennke HG, et al. Histopathologic and ultrastructural findings in postmortem kidney biopsy material in 12 patients with AKI and COVID-19. J Am Soc Nephrol 2020;31:1944–7. [CrossRef]
19. Santoriello D, Khairallah P, Bomback AS, Xu K, Kudose S, Batal I, et al. Postmortem Kidney Pathology Findings in Patients with COVID-19. J Am Soc Nephrol 2020;31:2158–67. [CrossRef]
20. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020;98:219–27. [CrossRef]
21. Li Z, Wu M, Yao J, Guo J, Liao X, Song S, et al. Caution on kidney dysfunctions of COVID-19 paitents. Medrxiv Mar 27, 2020, doi: 10.1101/2020.02.08.20021212. [CrossRef]
22. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844–7. [CrossRef]
23. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8:e21. [CrossRef]
24. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259–60. [CrossRef]
25. Sommerstein R, Gräni C. Preventing a COVID-19 pandemic: ACE inhibitors as a potential risk factor for fatal COVID-19. BMJ 2020;368:m810. [CrossRef]
26. Fosbøl EL, Butt JH, Østergaard L, Andersson C, Selmer C, Kragholm K, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. JAMA 2020;324:168–77. [CrossRef]
27. Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol 2020;127:104364. [CrossRef]
28. Hansrivijit P, Gadhiya KP, Gangireddy M, Goldman JD. Risk factors, clinical characteristics, and prognosis of acute kidney injury in hospitalized COVID-19 patients: a retrospective cohort study. Medicines (Basel) 2021;8:4. [CrossRef]
29. Thompson JV, Meghani NJ, Powell BM, Newell I, Craven R, Skilton G, et al. Patient characteristics and predictors of mortality in 470 adults admitted to a district general hospital in England with Covid-19. Epidemiol Infect 2020;148:e285. [CrossRef]