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Original Article

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The Impact of COVID-19 on Patients with Chronic Kidney Disease and Predictive Factors for Disease Mortality

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ABSTRACT

Objective: We aimed to describe clinical characteristics and course of chronic kidney disease patients with COVID-19 and to identify determinants of in-hospital mortality.
Methods: Seventy-one chronic kidney disease patients with COVID-19 were enrolled. The primary endpoint was death from all causes discussed in this article. The relationship between mortality and demographic, clinical, and laboratory data were examined.
Results: Of 71 patients, 29 (40.8%) died. Dead were older, were more likely to have low critical oxygen saturation (SpO_2) and deterioration of renal function, and exhibited less favorable laboratory features, including higher neutrophils, neutrophil to lymphocyte ratio, and systemic immune-inflammation index, as well as a lower lymphocyte. Acute kidney injury rate was high (71.8%) and 23.5% needed dialysis. Disease outcome did not differ across baseline chronic kidney disease stages. Systemic immune-inflammation index had a higher prediction accuracy for in-hospital mortality (AUC = 0.732). Patients in the high systemic immune-inflammation index group were older, had higher peak Cr, higher rate of acute kidney injury (85.3% vs. 59.5%), severe disease (79.4% vs. 35.1%), and mortality (64.7% vs. 18.9%) compared to those in low systemic immune-inflammation index group. Older age (>72 years), $SpO_2 \leq 90\%$, high systemic immune-inflammation index, and severe acute kidney injury requiring dialysis were predictors of in-hospital mortality.
Conclusion: Chronic kidney disease patients with COVID-19 had a high mortality rate associated with older age, acute kidney injury requiring dialysis, higher systemic immune-inflammation index, and lower SpO_2. Systemic immune-inflammation index at admission may be used for early identification of those at risk. Interventions for optimal oxygenation, early attenuation of the inflammatory response, and prevention of acute kidney injury may improve the prognosis of chronic kidney disease patients with COVID-19.
Keywords: COVID-19, chronic kidney disease, mortality, systemic immun inflammation index, hypoxia

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new type of β-coronavirus, and has affected millions in all age groups, of all ethnicities, both males and females. Given their chronic state of inflammation, dysregulated immune function, and additional comorbidities, patients with chronic kidney disease (CKD) are at high risk for infection and rapid severe progression of COVID-19 with increasing rates of hospitalization, intensive care unit (ICU) admission, and mortality.[1-4] The study by Williamson et al[5] demonstrated the importance of CKD as a risk factor for COVID-19 mortality and showed that patients with CKD stages 4-5 have a very high risk of COVID-19 mortality, which was even higher than patients with hypertension, obesity, chronic heart disease, or lung disease.

Due to the poor outcome of COVID-19 in CKD, early detection of patients who will deteriorate more is a priority. Based on this proposal, several immuno-inflammatory parameters have been evaluated in patients with COVID-19. Systemic immune-inflammation index (SII), which is a new inflammation-related index, is a comprehensive combination integrating peripheral lymphocyte, neutrophil, and platelet count. The elevated SII has been proven to be a prognostic marker in predicting in-hospital mortality of COVID-19.[6] In this study, we described the details of clinical characteristics and outcomes of CKD patients with COVID-19, investigated the capacity of SII to predict mortality, and determined other factors associated with in-hospital death.

METHODS

Study Population

This retrospective study was conducted at Bakırköy Dr. Sadi Konuk Training and Research Hospital and included all adult CKD cases with COVID-19 hospitalized between March 11, 2020 and May 31, 2020. CKD was defined as sustained estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 for more than 3 months. Information about eGFR values prior to COVID-19 hospitalization was extracted from the electronic database of our hospital. Viral infection was confirmed with a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis of nasal and pharyngeal swab samples or chest tomography (CT) scan criteria (bilateral distribution of patchy shadows or ground-glass opacities). Renal transplant recipients (n = 11), patients undergoing maintenance dialysis (n = 25), and those without previous registered eGFR (n = 19) value were excluded. This study was approved by Clinical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2020-13-05 and approval date: June 22, 2020) and carried out in accordance with the Declaration of Helsinki.

MAIN POINTS

- Chronic kidney disease (CKD) patients with COVID-19 had a high rate of severe disease (56%), acute kidney injury (AKI) (71.8%), intensive care unit admission (39.4%), and mortality (40.8%).
- Deceased patients exhibited unfavorable laboratory features upon admission including higher values of neutrophils, C-reactive protein, procalcitonin, neutrophil to lymphocyte ratio, and systemic immune-inflammation index (SII), as well as lower lymphocyte.
- Age (>72 years), low oxygen saturation, high SII (≥1052), and AKI requiring dialysis are independently associated with a higher risk of mortality.
- Since it is easy to calculate SII on basis of complete blood count at admission, it might be applied in clinic for risk stratification and appropiate risk-based individualised management of CKD patients with COVID-19.
- Interventions for optimal oxygenation, early attenuation of inflammatory response, and prevention of AKI may improve the prognosis of CKD patients with COVID 19.

Study Data

The demographic characteristics, symptoms, laboratory data, in-hospital treatment, and clinical outcomes of the patients were obtained from electronic database of our hospital. The following laboratory parameters at hospital admission and at the time of discharge or death were noted: complete blood count, renal function tests (urea, creatinine, and eGFR), hemostasis parameters, C-reactive protein (CRP), procalcitonin (PCT), creatinine kinase (CK), lactate dehydrogenase (LDH), electrolyte (sodium, potassium), calcium, phosphate, D-dimer, and ferritin. Peak creatinine level during hospital stay was also recorded. Neutrophil to lymphocyte ratio (NLR = neutrophil count/lymphocyte count) and SII (neutrophil count × platelet count/lymphocyte count) were calculated. Estimated glomerular filtration rate was determined using the Chronic Kidney Disease Epidemiology Collaboration formula. Chest tomography severity score proposed by Pan et al[7] was recorded.

Severe disease was defined as (1) respiratory rate >30 breaths/min, (2) oxygen saturation (SpO_2) <92%, or (3) PaO_2/FiO_2 ratio <300 mm Hg. Oxygen therapy provided during hospitalization, non-invasive mechanical ventilation (NIMV), and ICU needs were noted.

Outcome and Study Definition

The primary endpoint of the study was in-hospital death. Acute kidney injury (AKI) was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines using peak serum creatinine.[8] The lowest reported oxygen saturation during the hospital course before any ventilatory support was accepted as critical SpO_2.

Demographic, clinical, and laboratory data were compared between dead and discharged patients. The analysis was performed concerning the eGFR at baseline, to evaluate the impact of kidney failure severity on the outcome of COVID-19

Statistical Analysis

Continuous variables were expressed as the mean ± standard deviation (SD), and categorical variables were presented as percentages. Variables were compared across outcome groups and CKD stages. Characters between the groups were compared using Student's *t*-test, Pearson's chi-squared test, Fisher's exact test, Mann–Whitney *U* test, and Fisher Freeman Halton test where appropriate. Receiver operating characteristics (ROC) curve analysis was used to evaluate the predictive value of SII and oxygen saturation for in-hospital mortality in patients with COVID-19. Logistic regression analysis was used to identify the risk factors associated with death in terms of odds ratio and 95% CIs. Statistical analyses were performed by Number Cruncher Statistical System, 2007 (Kaysville, Utah, USA) with statistical significance set at two-tailed $P < .05$.

RESULTS

This study analyzed the demographic and clinical features of 71 adult CKD patients with COVID-19. As presented in Table 1, the

Table 1. Comparison of the Patient' Characteristics Based on Mortality

	All (n = 71)	Dead (n = 29)	Discharged (n = 42)	*P*
Age (years)	70.04 ± 13.31	74.24 ± 8.13	67.14 ± 15.38	.014[a]
Male	69.9 ± 13.77	77.8 ± 6.75	65.52 ± 14.79	.004[a]
Female	70.24 ± 12.86	70.43 ± 7.94	70.07 ± 16.49	.941[a]
Sex				
Male	42 (59.2)	15 (51.7)	27 (64.3)	.290[b]
Female	29 (40.8)	14 (48.3)	15 (35.7)	
Baseline CKD stage				
3	49 (69)	18 (62)	31 (73.9)	.721[e]
4	17 (23.9)	8 (27.6)	9 (21.4)	
5	5 (7)	3 (10.3)	2 (4.8)	
Comorbid diseases				
Diabetes mellitus	34 (47.9)	16 (55.2)	18 (42.9)	.307[b]
Hypertension	42 (59.2)	15 (51.7)	27 (64.3)	.290[b]
COPD	8 (11.4)	4 (14.3)	4 (9.5)	.705[c]
Coronary heart disease	25 (35.2)	7 (24.1)	18 (42.9)	.105[b]
Malignancy	1 (1.4)	0 (0)	1 (2.4)	1.000[c]
Cerebrovascular disorders	5 (7)	1 (3.4)	4 (9.5)	.642[c]
Symptoms on admission				
Fever	20 (28.2)	8 (27.6)	12 (28.6)	.928[b]
Dyspnea	42 (59.2)	20 (69)	22 (52.4)	.162[b]
Cough	33 (46.5)	12 (41.4)	21 (50)	.474[b]
Fatigue	20 (28.2)	2 (6.9)	18 (42.9)	.001[b]
Myalgia	2 (2.8)	0 (0)	2 (4.8)	.510[c]
Headache	3 (4.2)	1 (3.4)	2 (4.8)	1.000[c]
Sore throat	5 (7)	2 (6.9)	3 (7.1)	1.000[c]
Anorexia	10 (14.3)	4 (13.8)	6 (14.6)	1.000[c]
Diarrhea	8 (11.3)	4 (13.8)	4 (9.5)	.708[c]
Taste/smell disorder	5 (7.1)	1 (3.4)	4 (9.8)	.395[c]
COVID-19 diagnosis				
RT-PCR positive	34 (47.9)	14 (48.3)	20 (47.6)	.957[b]
CT scan				
Normal	3 (4.2)	0 (0.0)	3 (7.1)	.181[e]
Mild	24 (33.8)	7 (24.1)	17 (40.5)	
Moderate	31 (43.7)	15 (51.7)	16 (38.1)	
Severe	13 (18.3)	7 (24.1)	6 (14.3)	
Oxygen saturation				
Low saturation (<92)	49 (69)	23 (79.3)	26 (61.9)	.119[b]
SpO_2 admission	92.38 ± 5.2	91.17 ± 6.3	93.21 ± 4.16	.207[d]
SpO_2 critical	89.24 ± 6.01	85.17 ± 7.39	91.53 ± 3.48	.001[d]

(*Continued*)

Table 1. Comparison of the Patient' Characteristics Based on Mortality (*Continued*)

	All (n = 71)	Dead (n = 29)	Discharged (n = 42)	*P*
Outcomes				
Severe disease	40 (56.3)	28 (96.6)	12 (28.6)	.001[b]
Intensive care need	28 (39.4)	25 (86.2)	3 (7.1)	.001[b]
AKI	51 (71.8)	24 (82.8)	27 (64.3)	0.089[b]
RRT	12 (16.9)	9 (31)	3 (7.1)	.011[c]
Secondary infection	32 (45.1)	26 (89.7)	6 (14.3)	.001[b]
Length of stay (days)	16.27 ± 11.94	19.97 ± 14.15	13.71 ± 9.5	.135[d]
Length of stay at ICU (days)	6.97 ± 3.38	6.93 ± 3.58	7 ± 3.27	.873[d]
Treatments				
Hydroxychloroquine	64 (90.1)	27 (93.1)	37 (88.1)	.692[c]
Azithromycin	47 (66.2)	19 (65.5)	28 (66.7)	.920[b]
Oseltamivir	42 (59.2)	16 (55.2)	26 (61.9)	.571[b]
Favipiravir	32 (45.1)	18 (62.1)	14 (33.3)	.017[b]

Data were expressed as mean ± SD for quantitative variables and n (%) for nominal parameters. AKI, acute kidney injury; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; RT-PCR, reverse transcription polymerase chain reaction; RRT, renal replacement therapy; SpO_2, oxygen saturation.
[a]Student's *t*-test; [b]Pearson's chi-squared test; [c]Fisher's exact test; [d]Mann–Whitney *U* test; [e]Fisher Freeman Halton test.

mean age was 70.04 ± 13.31 years and male participants were 59.2%. Among them, 49 patients suffered moderate kidney failure with eGFR 30-60 mL/min/1.73 m^2 and 22 had severe kidney failure with eGFR <30 mL/min/1.73 m^2. All patients displayed symptoms. Thirty-four patients (47.9%) had a positive RT-PCR result and the remaining 37 (52.1%) were diagnosed radiologically. Hypertension (59.2%) was the most common comorbid disease, followed by diabetes mellitus (47.9%). Severe disease was developed in 40 (56%) patients, of which 28 were transferred to ICU on mechanical ventilation. In total, 29 patients died (40.8%).

As shown in Table 1, the age of the patients was older in the dead group (74.2 ± 8.1 years) compared to the discharged group (67.1 ± 15.3 years) (*P* = .01) and there was no difference in gender and prevalence of comorbidities between the 2 groups. Dyspnea and cough were common presenting symptoms. Except for fatigue, which was more frequently present in the discharged group than in the dead group (42.9% vs. 6.9%, *P* = .001), other symptoms were similar in the 2 groups.

As presented in Table 2 and Figure 1, dead patients had higher values of neutrophils, CRP, PCT, NLR, and SII, as well as a lower level of lymphocytes compared to those of discharged group. Renal function test (urea, creatinine, and eGFR) was more impaired and immuno-inflammatory indices (leucocyte, neutrophil, CRP, PCT, and ferritin) were higher in the dead group during the hospital course. Treatment patterns were similar for both groups except for favipiravir, which was used less frequently among discharged patients (*P* = .017).

Compared to the patients in the discharged group, critical SpO_2 was significantly reduced in the dead group (91.5 ± 3.4% vs. 85.1 ± 7.3%, *P* = .001). Out of 71, 49 patients (69%) required oxygen supplement as follows: 9 patients (14%) required nasal canula or facemask, 12 required a bilevel positive airway pressure or a high flow nasal cannula, and 28 required invasive mechanical ventilation, out of which 24 patients eventually died. The receiver operating characteristic curve (ROC) analysis showed that SpO_2 of 90% was the optimal arterial oxygen tension cut-off point for predicting survival, demonstrating 77.7% sensitivity, 65.6% specificity, and 70% accuracy. The overall area under the curve (AUC) was 78% (Figure 2).

Overall, 71.8% of the patients developed AKI. Remarkably, a high percentage of patients had superimposed AKI on CKD on hospital admission (64.5%). Comparably, the peak creatinine and urea levels at the last follow-up of the dead cases were significantly higher than those of discharged cases (*P* = .022 and *P* = .001, respectively). Although dead patients had a higher rate of AKI, it did not reach statistical significance (82.8% vs. 62.3%, *P* = .089). Fourteen patients with AKI (27.4%) had returned to the baseline level of kidney function by the time of discharge. However, 12 out of 51 patients with AKI required dialysis and almost all had an eGFR <30 mL/min/1.73 m^2 prior to admission. Of the patients who had renal support, almost 75% died. Two of 3 survived patients still required dialysis at the discharge from hospital.

Baseline characteristics, laboratory results, and outcomes of the groups according to the glomerular filtration rate are shown

Table 2. Comparison of Patients' Laboratory Findings Based on Mortality

	All (n = 71)	Dead (n = 29)	Discharged (n = 42)	*P*
Creatinine (mg/dL)				
Baseline	1.96 ± 1.05	2.04 ± 1.11	1.91 ± 1.02	.578[d]
Admission	2.58 ± 2.13	2.45 ± 1.62	2.68 ± 2.44	.874[d]
Peak	3.58 ± 2.68	4.38 ± 2.94	3.03 ± 2.37	.022[d*]
Event	2.68 ± 1.84	3.32 ± 1.96	2.24 ± 1.63	.002[d*]
eGFR (mL/min/1.73 m^2)				
Baseline	36.9 ± 15.82	35.27 ± 16.12	38.02 ± 15.71	.450[d]
Admission	31.17 ± 15.13	31.14 ± 15.44	31.19 ± 15.1	.989[a]
Event	29.51 ± 15.4	22.17 ± 13.69	34.57 ± 14.58	.001[a*]
Urea (mg/dL)				
Admission	103.68 ± 71.78	100.21 ± 58.73	106.07 ± 80.16	.797[d]
Event	104.21 ± 67.37	145.48 ± 76.43	75.71 ± 41.52	.001[d*]
LDH (U/L)				
Admission	326.54 ± 117.87	353.17 ± 127.86	308.14 ± 108.21	.142[d]
Event	386.31 ± 414.74	571.55 ± 598.79	258.4 ± 88.17	.001[d*]
CK (U/L)				
Admission	203.04 ± 245.69	225.59 ± 294.12	187.48 ± 208.26	.494[d]
Event	111.45 ± 129.79	160.9 ± 166.86	77.31 ± 82.6	.015[d*]
D-dimer (μg/mL)				
Admission	1.2 ± 1.42	1.34 ± 1.43	1.11 ± 1.42	.294[d]
Event	1.9 ± 2.29	2.63 ± 2.56	1.41 ± 1.98	.009[d**]
Fibrinogen (mg/dL)				
Admission	504.12 ± 122.26	522.26 ± 125.61	491.88 ± 119.98	.322[a]
Event	483.74 ± 128.14	506.22 ± 156.61	468.93 ± 104.86	.283[a]
CRP (mg/L)				
Admission	96.37 ± 85.09	126.45 ± 90.27	75.61 ± 75.6	.014[d*]
Event	93.06 ± 97.93	167.51 ± 101.84	41.64 ± 51.6	.001[d*]
Procalcitonin (ng/mL)				
Admission	2.32 ± 11.92	5.33 ± 18.86	0.38 ± 0.56	.0010[d*]
Event	3.13 ± 9.2	7.37 ± 13.72	0.4 ± 1.18	.001[d*]
Ferritin (ng/mL)				
Admission	521.08 ± 1465.03	812.93 ± 2243.02	319.57 ± 355.94	.254[d]
Event	542.7 ± 743.54	909.5 ± 1017.9	289.3 ± 274.2	.001[d*]
Hemoglobin (g/dL)				
Admission	10.7 ± 2.41	10.2 ± 2.58	11.05 ± 2.26	.143[a]
Event	10.13 ± 2.15	9.37 ± 2.23	10.66 ± 1.94	.012[a*]
Leucocyte (10^3/μL)				
Admission	8.78 ± 5.23	10.18 ± 4.28	7.82 ± 5.64	.002[d*]
Event	8.98 ± 4.48	11.25 ± 5.47	7.42 ± 2.77	.001[d*]

(*Continued*)

Table 2. Comparison of Patients' Laboratory Findings Based on Mortality (*Continued*)

	All (n = 71)	Dead (n = 29)	Discharged (n = 42)	*P*
Neutrophils (10^3/μL)				
Admission	6.64 ± 4.83	7.85 ± 3.92	5.8 ± 5.25	.002[d*]
Event	7.07 ± 4.33	10.05 ± 4.67	5.02 ± 2.57	.001[d*]
Lymphocytes (10^3/μL)				
Admission	1.43 ± 1.47	1.44 ± 2.12	1.43 ± 0.78	.042[d*]
Event	1.27 ± 0.73	0.87 ± 0.56	1.55 ± 0.7	.001[a*]
Platelets (10^3/μL)				
Admission	215.8 ± 93.57	229 ± 94.9	206.69 ± 92.68	.136[d]
Event	235.77 ± 100.41	205.24 ± 103.3	256.86 ± 93.88	.032[a*]

Event was defined as death or discharge from hospital. Data were expressed as mean ± SD. CK, creatine kinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; NLR, neutrophils to lymphocytes ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index.
[a]Student's *t*-test; [d]Mann–Whitney *U* test. *$P < .05$; **$P < .01$.

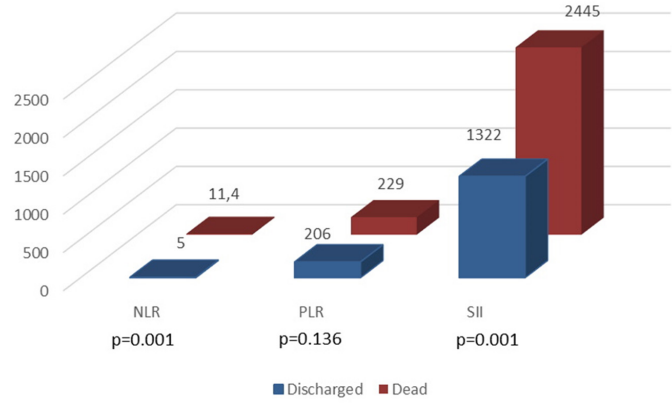

Figure 1. Comparison of NLR, PLR and SII between dead and discharged CKD patients with COVID-19. NLR, neutrophils to lymphocytes ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index.

in Table 3. When we compared both groups, we observed that 86.4% of the patients with severe kidney failure presented a worsening of their renal function versus 65.3% in the patients with moderate kidney failure (*P* = .068) and a significantly higher proportion of the patients with severe kidney failure required dialysis (50% vs. 2%, *P* = .001). Rate of severe disease, ICU admission, and death rate did not differ between the groups. By contrast, the severe kidney failure group had a statistically significant longer length of hospital stay when compared to that of the moderate kidney failure group (22.95 ± 12.73 days vs. 13.27 ± 10.35 days, *P* = .001).

The optimized cut-off point of SII value identified by ROC analysis for predicting in-hospital death was 1052 (AUC = 0.732; *P* < .001; 95% CI = 0.609-0.856) (Figure 1). Table 4 presents characteristics of the patients stratified according to the cut-off value of SII. We observed that the patients with high SII (≥1052) were significantly older (73.4 years vs. 66.9 years, *P* = .040), had higher rate of AKI (85.3% vs. 59.5%, *P* = .016), and demonstrated poor prognosis, defined by a greater percentage of the severe disease (79.4% vs. 35.1%, *P* = .001) and the higher rate of death (64.7% vs. 18.9%, *P* = .001).

The multivariate analysis showed that age (>72 years) (6.641 [95% CI 1009-34 572]; *P* = .049), low SpO_2 (<90%) (14.209 [95% CI 1.77-113.79]; *P* = .012], high SII (≥1052) (9.962 [95% CI 1.55-63.84]; *P* = .015), and AKI requiring dialysis (53.089 [95% CI 2.398-1175.37]; *P* = .012) were significantly associated with in=hospital death. However, gender, NLR, CKD severity, or AKI superimposed on CKD were not predictors of mortality in this sample (Table 5).

DISCUSSION

In this single-center, retrospective, and observational study, we described clinical characteristics and outcomes of CKD patients with COVID-19 and confirmed that patients with CKD have a high rate of severe disease (56%) and mortality (40.8%). Through the comparison of dead and discharged patients, we provided diagnostics that can predict the severity course of the disease. This study described the value of SII to predict the in-hospital mortality risk of CKD patients with COVID-19.

COVID-19-related mortality rates in patients with CKD stages 3-5 have been reported at an average of 35%.[9-11] In the present study, the in-hospital mortality rate was 40.8% and increased to 75% in patients requiring dialysis. The high mortality rate may be explained by differences in baseline demographics, respiratory disease severity, and degree of AKI. Also, secondary bacterial infections may be associated with a high mortality rate in our patients. In previous studies, age, comorbidities, and sex have been implicated in COVID-19 outcomes.[5] However, in our study, only older age was determined as an independent strong predictor for in-hospital mortality.

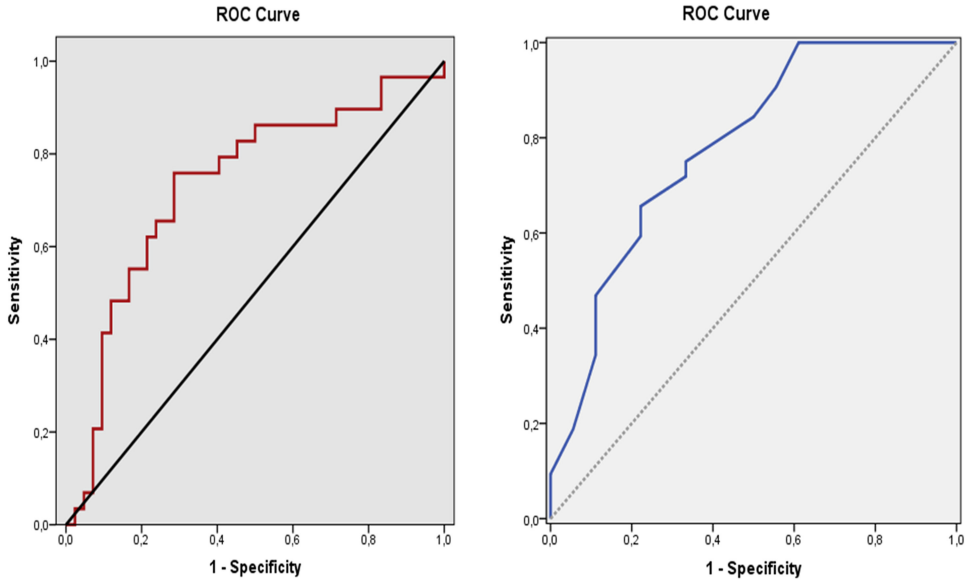

Figure 2. Analysis showing the predictive cut-off value of SII and SpO_2: (A) ROC curves of SII (AUC = 0.732; 95% CI = 0.609-0.856; P < .001) for in-hospital mortality. (B) ROC curves of SpO_2 (AUC = 0.781; 95% CI = 0.943-0.919; P < .001) for in-hospital mortality. AUC, area under the curve; ROC, receiever operator characteristics; SII, systemic immune-inflammation index; SpO_2, oxygen saturation.

Dead patients had a significantly higher level of neutrophil, leucocyte, NLR, and SII, as well as a lower level of lymphocyte, suggesting the role of immuno-inflammatory response in the development and progression of COVID-19. Although NLR, which has been widely used as a prognostic marker in COVID-19, was not associated with disease mortality, a higher value of SII was closely associated with in-hospital mortality. Since it is easy to calculate SII on the basis of the blood routine at admission, it might be applied in the clinic for risk stratification and appropriate risk-based individualized management of CKD patients with COVID-19. Also, greater attention should be paid to changes in immuno-inflammatory indicators in CKD patients to reduce mortality.

We also found a remarkably elevated level of urea and creatinine as well as decreased eGFR values at discharge in the dead group, demonstrating that SARS-CoV- 2 virus has a significant effect on the kidneys. Similar to the multicenter, observational, nationwide study from Turkey,[12] the current study did not display any differences in disease severity and mortality as the level of baseline eGFR decreased, despite survival rates of patients who required dialysis being dramatically low.

The rate of AKI superimposed on CKD in COVID-19 patients ranged from 35.6% to 62.3% and AKI seemed to be one of the main determinants behind CKD-associated mortality in COVID-19.[9,10,13] We observed that 71.8% of all cases developed AKI. The increased incidence rate of AKI may be explained by participants' older age and a higher degree of kidney dysfunction on admission. We demonstrated that patients with lower eGFR had a higher incidence of severe AKI and severe AKI requiring dialysis increased the risk of death 53 times. Since severe AKI appears to be a predictor of strikingly poor prognosis, regular monitorization of kidney function to detect AKI early in the course is important, and measures should be taken to prevent progression of kidney injury. Nonetheless, AKI, when occurring in patients with CKD, is known to be more difficult to recover. In the current study, approximately 48% of the patients who were discharged did not show improvement in their kidney function. To better judge the long-term recovery of the kidney, COVID-19 patients with AKI superimposed on CKD should be regularly followed for kidney function every 3-6 months after the infection.

The major reason for death in COVID-19 is hypoxemic respiratory failure. Hypoxemia (SpO_2 <90%) has been described in 9-38% of general COVID-19 patients and results from interstitial pneumonia, reduced alveolar oxygen diffusion, microthrombi, and intrapulmonary shunts (V/Q mismatch).[14-17] Data on hypoxemia in CKD patients with COVID-19 are scarce. Three reports on hospitalized maintenance hemodialysis patients show decreased SpO_2 levels at admission in 16-62% of patients.[18-20] Acute hypoxemia augments cytotoxic functions of neutrophils and leads to increased vascular permeability, inflammatory cells accumulation, and elevated serum cytokine levels. Thus, hypoxia contributes to progressive lung damage after the initial injury. In the current study, mortality risk increased by approximately 6.6 times for each 1-U decrease in SpO_2 (<90%) and patients receiving invasive mechanical ventilation had a very poor outcome with an 85.7% mortality rate. Furthermore, hypoxia and respiratory failure can cause insufficient oxygen supply to the myocardium, which itself leads to an unbalanced oxygen supply

Table 3. Demographic and Clinical Characteristics of the Patients, Stratified by Baseline eGFR

	>30 (n = 49)	≤30 (n = 22)	*P*
Age	72.22 ± 10.59	65.18 ± 17.28	.088[a]
Sex			1.000[b]
Female	29 (59.2)	13 (59.1)	
Male	20 (40.8)	9 (40.9)	
Laboratory results on admission			
Hemoglobin (g/dL)	11.32 ± 2.31	9.32 ± 2.07	.001[a*]
Leucocyte (10^3/μL)	8.76 ± 5.48	8.84 ± 4.73	.862[d]
Neutrophils (10^3/μL)	6.71 ± 5.11	6.48 ± 4.22	.975[d]
Lymphocyte	1.36 ± 0.82	1.61 ± 2.37	.323[d]
SII	1788.98 ± 2402.61	1763.91 ± 1906.12	.911[d]
PLR	214.82 ± 93.18	218 ± 96.59	.546[d]
NLR	7.85 ± 10.11	7.29 ± 6.2	.794[d]
CRP (mg/L)	63.03 ± 75.61	111.35 ± 85.56	.021[d*]
Procalcitonin (ng/mL)	0.64 ± 0.72	3.1 ± 14.41	.279[d]
D-dimer (μg/mL)	1.12 ± 1.4	1.37 ± 1.48	.369[d]
Fibrinogen (mg/dL)	497.22 ± 120.75	519.24 ± 127.17	.498[a]
Oxygen saturation <92%	34 (69.3)	15 (68.1)	1.000[b]
Outcomes			
Severe disease	26 (53.1)	14 (63.6)	.193[b]
ICU need	19 (38.8)	9 (40.9)	.865[b]
AKI	32 (65.3)	19 (86.4)	.068[b]
AKI requiring RRT	1 (2.0)	11 (50.0)	.001[b*]
Length of stay (days)	13.27±10.35	22.95±12.73	.001[d*]
Mortality	18 (36.7)	11 (50.0)	.293[b]

Data were expressed as mean ± SD for quantitative variables and n (%) for nominal parameters. AKI, acute kidney injury; CRP, C-reactive protein; eGFR, estimated glomeruler filtration rate; ICU, intensive care unit; NLR, neutrophils to lymphocytes ratio; PLR, platelet to lymphocyte ratio; SII, systemic immuneinflammation index; RRT, renal replacement therapy.
[a]Student's *t*-test; [b]Pearson's chi-squared test; [d]Mann–Whitney *U* test. *$P < .05$; **$P < .01$.

in the body and contributes to kidney function impairment as variable severity of acute tubular necrosis (ATN) was observed in the histopathologic examination of COVID-19 non-survivors, implying ischemic ATN.[21] Therefore, ameliorating hypoxia may be of value for both kidney and patient survival.

Table 4. Comparison of the Patient Characteristics According to the Cut-off Level of SII

	<1052 (n = 37)	≥1052 (n = 34)	*P*
Age	66.95 ± 15.82	73.41 ± 8.99	.040[a*]
Sex			
Male	24 (64.9)	18 (52.9)	.307[b]
Female	13 (35.1)	16 (47.1)	
Basal CKD stage			
3	26 (70.2)	23 (67.6)	.517[e]
4	10 (27.0)	7 (20.6)	
5	1 (2.7)	4 (11.8)	
Creatinine, admission (mg/dL)	2.77 ± 2.60	2.39 ± 1.48	.872[d]
Creatinine, peak (mg/dL)	3.14 ± 2.64	4.07 ± 2.68	.032[d*]
AKI	22 (59.5)	29 (85.3)	.016[b*]
Severe disease	13 (35.1)	27 (79.4)	.001[b*]
Mortality	7 (18.9)	22 (64.7)	.001[b*]
Length of hospitalization (days)	15.35 ± 9.73	17.26 ± 14.04	.963[d]
Length of stay at ICU (days)	6.84 ± 3.40	7.12 ± 3.40	.898[d]

Data were expressed as mean ± SD for quantitative variables and n (%) for nominal parameters.
AKI, acute kidney injury; CKD, chronic kidney disease; ICU, intensive care unit; SII, systemic immune-inflammation index.
[a]Student's *t*-test; [b]Pearson's chi-square test, [d]Mann–Whitney *U* test, [e]Fisher Freeman Halton test. *$P < .05$

Table 5. Logistic Regression for Risk Factors Associated with In-Hospital Mortality

	P	Odds Ratio	CI	
			Lower	Upper
Age (>72 years)	.049*	6.641	1.009	34.572
Sex (female)	.303	3.056	0.364	25.654
eGFR (<30 mL/min/1.73 m^2)	.470	2.761	0.176	43.372
SpO_2 critical (≤90%)	.012*	14.209	1.774	113.79
NLR	.704	1.025	0.901	1.167
SII (≥1052)	.015*	9.962	1.555	63.839
AKI	.961	1.053	0.132	8.389
AKI necessitated RRT	.012*	53.089	2.398	1175.37

AKI, acute kidney injury; eGFR, estimated glomeruler filtration rate; NLR, neutrophils to lymphocytes ratio; RRT, renal replacement therapy; SII, systemic immune-inflammation index; SpO_2, oxygen saturation. *$P < .05$.

The limitations of our study are as follows: the follow-up time is short and further studies are necessary to describe the impact of COVID-19 on long-term renal function and survival. It was unfortunate that the data on drug history, height, and weight were lacking due to the retrospective design of the study. AKI was diagnosed based on creatinine level since we did not include urine output to determine AKI given the high degree of missing data. But this study has an important strength. To the best of our knowledge, our study is the first study specifically focused on SII to assess and predict clinical severity in CKD patients with COVID-19. This should be confirmed in further studies.

As a result, the present study reports the high mortality rate of COVID-19 in CKD patients, associated with older age, severe AKI requiring dialysis, higher SII, and lower SpO_2. Taken together, we suggest that SII at admission might be used for risk stratification of the patients and every effort should be made for optimal oxygenation, early attenuation of the inflammatory response, and prevention of progression of kidney injury in order to improve the prognosis of CKD patients with COVID-19.

Ethics Committee Approval: Ethics committee approval for this study was received from the Clinical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (Approval Date: June 22, 2020; Approval Number: 2020-13-05).

Informed Consent: Informed consent was not obtained due to the retrospective design of this study.

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