Original Article

Is Chronic Kidney Disease, a Predictor of In-Hospital Mortality in Coronavirus Disease 2019 (COVID-19) Patients?

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Abstract

Background: Chronic kidney disease (CKD) is an important comorbidity in Coronavirus Disease 2019 (COVID-19) patients considering its high prevalence. We aimed to figure out the relationship between CKD and COVID-19 mortality in this study.

Materials and Methods: In total, 116 CKD patients (estimated glomerular filtration rate [eGFR] lower than 60 mL/min/1.73 m^2) and 147 control subjects confirmed with COVID-19 were studied. Data regarding demographics, sign and symptoms, laboratory findings, and chest computed tomography were collected. Association between CKD and in-hospital mortality were analyzed using logistic regression models adjusted for confounders.

Results: Mortality rate was significantly higher in CKD than non-CKD (30.17 vs 4.76, $P < 0.001$) COVID-19 patients. Multivariate logistic regression showed that CKD was significantly correlated with in-hospital mortality in the total sample (Odds ratio (OR) = 8.64, confidence interval (CI): 3.67–20.35) and gender subgroups (females: OR = 4.77, CI: 1.38–16.40, males: OR = 13.43, CI: 3.85–46.87) ($P < 0.05$) of COVID-19 patients in the crude model. Whereas, the correlation did not remain significant in the fully adjusted model in the total sample (OR = 1.70, CI: 0.35–8.19) and gender subgroups (females: OR = 1.07 CI: 0.06–19.82, males: OR = 0.87, CI: 0.07–10.33) ($P > 0.05$) of COVID-19 patients.

Conclusion: This study suggested an independent association between CKD and in-hospital mortality in COVID-19 patients. Therefore, more intensive surveillance of COVID-19 patients with CKD is to be warranted.

Keywords: Chronic kidney disease, COVID-19, in-hospital mortality, risk factors

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Introduction

In late 2019, a novel coronavirus, known as the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), was recognized as the cause of coronavirus disease 2019 (COVID-19). This infectious disease first emerged in Wuhan, China, and rapidly spread to several countries across the world.[1,2] The infection has a broad range of clinical manifestations ranging from symptoms mimicking common cold to acute respiratory distress syndrome and septic shock.[3-5] Previous studies have shown that elderly patients and those with comorbidities such as obesity, cardiovascular disorders, diabetes mellitus, chronic obstructive pulmonary disease, cancer, and renal failure have a greater risk of mortality, and severe disease from COVID-19 compared with the general population.[6,7] As a result, special attention should be devoted

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to COVID-19 patients with comorbidities by healthcare professionals and researchers.

Several conditions such as older age, the presence of comorbidities, increased inflammatory state, and immunodeficiency in chronic kidney disease (CKD) patients make them more vulnerable to the infection. However, studies investigating COVID-19 in CKD patients are scarce. Few studies have been revealed that COVID-19 patients with CKD are subjected to increased risk of severe disease and mortality.[8-12] To our knowledge, no previous study has investigated whether CKD is an independent predictor of mortality in COVID-19 patients. In this study, we aimed to explore (a) the association between CKD and the risk of in-hospital mortality in COVID-19 patients and (b) possible factors that mediate the association such as age, clinical, and laboratory findings. The results of this study can help physicians in defining treatment targets to improve survival rate in COVID-19 patients with CKD.

Materials and Methods

Study design and patients

This observational, case-control study was performed on real time reverse transcription polymerase chain reaction confirmed COVID-19 patients or based on typical chest computerized tomography (CT) scan, hospitalized from March 21 to July 21, 2020, at four referral hospitals of COVID-19 disease, Isfahan, Iran. The protocol of the study was approved by the ethics committee of Isfahan University of Medical Sciences (no. IR.MUI.MED.REC.1399.155), and the need for an informed consent form was waved. The cases comprised hospitalized adult COVID-19 patients diagnosed as CKD stages 3 to 5 ND (eGFR lower than 60 mL/min/1.73 m^2) 3 months ago. However, non-CKD patients hospitalized for COVID-19 were considered as controls. Patients who received dialysis and those who were diagnosed with acute renal injury were excluded from the study.

Data collection

All information was extracted from medical records onto a standard research-made checklist by a trained medical staff. The following information was collected for all patients: demographics (age (year) and sex), current smoking, underlying diseases (based on Charlson comorbidity score), signs/symptoms (fever, cough, shortness of breath, sputum, fatigue, headache, nausea, vomiting, diarrhea, abdominal pain, and loss of appetite), complications (gastrointestinal bleeding and sepsis), biochemical data on admission (white blood cell count (10^3/μL), lymphocytes (10^3/μL), platelet (10^3/μL), hemoglobin (g/dl), serum creatinine (mg/dl), sodium (mEq/L), potassium (mEq/L), calcium (mg/dL), lactate dehydrogenase (U/L), creatinine phosphokinase (U/L), erythrocyte sedimentation rate (mm/hr), and high sensitivity-c-reactive protein (mg/dL)), radiological data (ground-glass opacity, bilateral sub-pleuritic consolidation, and bilateral ground-glass opacity), duration of intensive care unit (ICU) stay (days), oxygen saturation (SpO2) (%) and respiratory rate (per minute) on admission, administered drugs (antivirals, antibiotics, corticosteroids, and interferons) according to national protocol of that date, and disease severity (sever). Patients who met one of the following criteria were considered as severe cases: respiratory rate ≥30 bpm, oxygen saturation (SpO2) ≤93% at rest, and the ratio of the partial pressure of arterial oxygen to fraction of inspired oxygen (FIO2) ≤300 mmHg.[13]

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables with a normal distribution, median (interquartile range) for continuous variables with a non-normal distribution, and as frequency (%) for categorical variables. Student's t-test and the Mann–Whitney U-test were used for comparing continuous variables with normal and non-normal distributions, respectively. Categorical variables were compared using the Chi-squared or Fisher exact tests.

Univariate and multivariable binomial logistic regression were used to explore the association of CKD with the risk of in-hospital mortality. In univariate logistic regression, the association CKD with the risk of mortality was evaluated and in multivariable logistic regression, the association of CKD with the risk of mortality in the presence of effective confounders was evaluated. In the first multivariable logistic regression, the effects of age were adjusted. In the second model, further adjustment was made for sepsis, the ICU admission duration, and intubation. In the third multivariable logistic regression, the association of CKD with in-hospital mortality was evaluated in the presence of second model's confounder along with disease severity and Charlson comorbidity score. Fourth multivariable logistic regression model was adjusted additionally for high sensitivity-c-reactive protein at admission and finally in fifth model, further adjustment was conducted for hemoglobin and white blood cell. The results of logistic regression were reported as Odds ratios (ORs) and 95% confidence intervals (CIs). All statistical analyses were conducted for total sample and separately in women and men using Statistical Package for Social Sciences version 16 (SPSS Inc., Chicago, IL, USA).

Results

Comparing cases to controls across the total sample and gender subgroups

Basic characteristics

Basic characteristics of studies population are summarized in Table 1. The study population comprised a total of 116 cases (63.79% males and 36.21% females) and 147 controls (55.78% males and 44.22% females). The mean age in the case group was significantly higher than the control group across the total sample (70.66 ± 15.70 vs 54.43 ± 16.14) and gender subgroups (females: 68.12 ± 16.07 vs 56.42 ± 17.16, males: 72.09 ± 15.39 vs 52.85 ± 15.21) ($P < 0.05$). The mean of Charlson comorbidity score was also significantly different between cases and controls in the total sample (6.32 ± 2.19 vs 2.09 ± 2.03) and gender subgroups (females: 5.88 ± 2.11 vs 2.51 ± 2.21, males: 6.57 ± 2.21 vs 1.76 ± 1.82) ($P < 0.05$). The prevalence of diabetes mellitus, cardiovascular disorders,

Table 1: The comparison of basic, clinical, radiological, and biochemical characteristics between cases and controls across the total sample and gender subgroups

Variables	Total (n=263)		P	Female (n=107)		P	Male (n=156)		P
	Cases (n=116)	Controls (n=147)		Cases (n=42)	Controls (n=65)		Cases (n=74)	Controls (n=82)	
Age (years)	70.65±15.70	54.43±16.14	<0.001	68.12±16.07	56.42±17.16	0.001	72.09±15.39	52.85±15.21	<0.001
Smoking	12.93	12.24	1.00	4.76	3.08	0.65	17.57	19.51	0.84
Comorbidities									
Diabetes mellitus	45.69	22.45	<0.001	50.00	33.85	0.11	43.24	13.41	<0.001
Hypertension	21.55	21.09	1.00	26.19	23.08	0.82	18.92	19.51	1.00
Chronic obstructive pulmonary disease	6.90	8.16	0.82	7.14	9.23	1.00	6.76	7.32	1.00
Cardiovascular diseases	20.69	10.20	0.02	11.90	9.23	0.75	25.68	10.97	0.02
Cancer	9.48	2.74	0.03	7.14	4.61	0.68	10.81	1.23	0.01
Charlson comorbidity index	6.32±2.19	2.09±2.03	<0.001	5.88±2.11	2.51±2.21	<0.001	6.57±2.21	1.76±1.82	<0.001
Signs/Symptoms									
Fever	37.20±0.72	37.26±0.66	0.45	37.11±0.59	37.21±0.64	0.43	37.25±0.79	37.31±0.68	0.62
Cough	50.00	72.11	<0.001	47.62	69.23	0.04	51.35	74.39	0.004
Shortness of Breath	68.10	73.47	0.41	69.05	61.54	0.54	67.57	82.93	0.04
Sputum	11.21	13.61	0.58	14.28	16.92	0.79	9.46	10.97	0.80
Fatigue	44.83	61.22	0.009	40.48	64.61	0.02	47.30	58.54	0.20
Headache	4.31	21.09	<0.001	9.52	21.54	0.12	1.35	20.73	<0.001
Nausea	14.65	20.41	0.26	21.43	26.15	0.65	10.81	15.85	0.48
Vomiting	14.65	12.93	0.72	23.81	15.38	0.31	9.46	10.97	0.80
Diarrhea	6.90	16.33	0.02	9.52	15.38	0.56	5.41	17.07	0.02
Abdominal pain	5.17	8.84	0.34	4.76	12.31	0.31	5.41	6.10	1.00
Loss of appetite	9.48	13.61	0.34	9.52	16.92	0.39	9.46	10.97	0.80
GI bleeding	1.72	1.36	1.00	2.38	0.00	0.39	1.35	2.44	1.00
Sepsis	12.07	1.36	<0.001	11.90	3.08	0.11	12.16	0.00	0.001
Clinical variables									
Oxygen Saturation at admission (%)	86.87±8.94	90.68±5.61	<0.001	87.27±9.41	90.49±6.05	0.03	86.65±8.73	90.83±5.26	<0.001
Respiratory rate (per minute)	20.81±4.49	20.20±3.53	0.22	22.05±4.37	20.42±3.59	0.04	20.13±4.44	20.04±3.50	0.89
Mean duration of ICU stay (days)	5.16±8.15	1.16±3.33	<0.001	5.78±10.05	1.77±4.39	0.01	4.81±6.90	0.57±1.80	<0.001
Intubation	33.62	6.80	<0.001	35.71	10.77	0.003	32.43	3.66	<0.001
Severe COVID-19 infection	44.64	4.76	<0.001	46.34	4.61	<0.001	43.66	4.88	<0.001
Mortality	30.17	4.76	<0.001	23.81	6.15	0.02	33.78	3.66	<0.001
Administered drugs									
Antibiotics	93.10	89.11	0.29	95.24	89.23	0.48	91.89	89.02	0.60
Antivirals	39.65	47.62	0.21	30.95	46.15	0.16	44.59	48.78	0.63
Corticosteroids	12.93	27.89	0.004	16.66	30.77	0.12	10.81	25.61	0.02
Interferons	6.89	23.97	<0.001	9.52	26.15	0.05	5.41	22.22	0.003

Contd...

Table 1: Contd...

Variables	Total (n=263)		P	Female (n=107)		P	Male (n=156)		P
	Cases (n=116)	Controls (n=147)		Cases (n=42)	Controls (n=65)		Cases (n=74)	Controls (n=82)	
Radiological variables									
Ground Glass Opacity	81.41	87.05	0.19	82.93	83.87	0.46	80.55	89.61	0.23
Bilateral subpleuretic consolidations	16.81	12.95		14.63	16.13		18.05	10.39	
BilateralGround Glass Opacity	1.77	0.00		2.44	0.00		1.39	0.00	
Biochemical variables									
White blood cells (10^3/μL)	9375.95±5368.84	6548.22±3477.09	<0.001	8116.19±5171.73	7280.15±4150.48	0.36	10090.95±5380.98	5960.86±3292.76	<0.001
Lymphocytes (10^3/μL)	1332.10±1073.30	1421.14±809.87	0.45	1170.47±689.14	1439.44±1404.90	0.04	1423.84±1234.69	1406.39±945.29	0.92
Hemoglobin (g/dl)	12.46±2.79	13.53±2.13	0.001	11.82±2.56	12.62±1.81	0.06	12.83±2.87	14.26±2.10	<0.001
Platelet (103/μL)	183253.45±86872.77	184006.85±70895.50	0.94	192619.05±86586.19	205123.08±66546.16	0.40	177937.84±87172.64	167061.73±70101.42	0.39
Serum Creatinine (mg/dL)	2.42±1.67	1.02±0.22	<0.001	2.32±1.64	0.97±0.25	<0.001	2.47±1.69	1.06±0.18	<0.001
Sodium (mEq/L)	137.91±7.32	138.38±3.93	0.51	137.88±6.71	138.48±3.82	0.56	137.93±7.70	138.30±4.04	0.71
Potassium (mEq/L)	4.57±0.81	4.23±0.58	<0.001	4.51±0.88	4.2±5.59	0.08	4.60±0.77	4.23±0.57	0.001
Calcium (mg/dL)	8.64±1.04	8.61±0.83	0.84	8.78±0.84	8.37±0.94	0.07	8.56±1.14	8.79±0.69	0.23
Lactate dehydrogenase (U/L)	802.58±551.59	543.37±320.06	<0.001	733.13±544.79	569.46±303.61	0.10	847.81±557.64	520.65±334.90	0.001
Creatin phosphokinase (U/L)	395.47±486.63	160.48±172.85	<0.001	288.21±267.66	173.51±221.24	0.07	463.21±577.67	147.79±108.43	0.001
Maximum Erythrocyte sedimentation rate (mm/h)	45.43±29.49	36.83±29.11	0.03	47.89±27.24	41.37±28.43	0.27	44.03±30.81	33.14±29.34	0.04
HS-C-reactive protein (mg/dL)	50.08±31.49	37.20±30.26	0.001	55.20±33.66	38.22±24.38	0.004	47.15±30.04	36.41±34.22	0.04

Values in table are meanstandard deviation for continuous variables and percentage for categorical variables, P values were obtained from Student's t-test and the Mann-Whitney U-test for continuous variables with normal and non-normal distributions. *Variable was considered statistically significant different at a P<0.05

and cancer was significantly higher in the case group compared with the control group in the total sample and male subgroup ($P < 0.05$). However, there was not any significant difference in the prevalence of comorbidities between the case and control group in the female subgroup ($P > 0.05$) [Table 1].

Signs/symptoms

The comparison of signs/symptoms between two groups showed that the prevalence of cough (50.00% vs 72.11%), headache (4.31% vs 21.09%), fatigue (44.83% vs 61.22%), and diarrhea (6.90% vs 16.33%) was significantly lower in cases than controls in the total sample ($P < 0.05$). A significantly lower prevalence of cough (51.35% vs 74.39%), shortness of breath (67.5% vs 82.93%), headache (1.35% vs 20.73%), and diarrhea (5.41% vs 17.07%) was also observed in cases compared with controls in the male subgroup ($P < 0.05$). Moreover, the prevalence of cough (47.62% vs 69.23%) and fatigue (40.48% vs 64.61%) was significantly lower in cases compared with controls in the female subgroup ($P < 0.05$) [Table 1].

Clinical variables

There was a significantly higher prevalence of sepsis in cases than controls in the total sample (12.07% vs 1.36%) and male subgroup (12.16% vs 0.00%) ($P < 0.05$). Our results indicated that the prevalence of intubation, severe COVID-19, and in-hospital mortality was significantly higher in cases than controls in the total sample and gender subgroups ($P < 0.05$). The mean duration of ICU stay was also significantly higher in cases than controls in the total sample and gender subgroups ($P < 0.05$). The mean value of SpO2 on admission was significantly lower in cases than controls in the total sample and gender subgroups ($P < 0.05$). The comparison of cases and controls regarding the type of administered medications showed that the prevalence of patients who received corticosteroids and interferons were significantly lower in cases compared with controls in the total sample and gender subgroups ($P < 0.05$) [Table 1].

Biochemical and radiological variables

The comparison of biochemical variables between cases and controls showed that the mean values of white blood cells, potassium, lactate dehydrogenase, creatinine phosphokinase, and maximum erythrocyte sedimentation rate were significantly higher in cases than controls in the total sample and male subgroups ($P < 0.05$). However, the mean value of hemoglobin was significantly lower in cases than controls in the total sample (12.46 ± 2.79 vs 13.53 ± 2.13) and male subgroup (12.83 ± 2.87 vs 14.26 ± 2.10) ($P < 0.05$). The mean values of serum creatinine and high sensitivity C-reactive protein were significantly higher in cases than controls in the total sample and gender subgroups ($P < 0.05$). There was not any significant difference between the two groups in terms of radiological features ($P > 0.05$) [Table 1].

Comparing survivors and non-survivors across total sample and gender subgroups

Basic characteristics

The comparison of basic characteristics between survivors and non-survivors showed that the mean age was significantly higher in non-survivors than survivors in the total sample (70.40 ± 13.23 vs 59.91 ± 18.14) and male subgroup (70.93 ± 10.25 vs 60.02 ± 18.79) ($P < 0.05$). The mean Charlson score was also significantly different between survivors and non-survivors in the total sample (3.51 ± 2.84 vs 6.33 ± 2.52) and gender subgroups (females: 3.58 ± 2.70 vs 5.50 ± 2.31, males: 3.46 ± 2.94 vs 6.75 ± 2.56) ($P < 0.05$). The non-survivors in the total sample (16.67% vs 3.64%) and the male subgroup (21.43% vs 2.36%) had a significantly higher prevalence of cancer compared with survivors ($P < 0.05$). Moreover, the prevalence of diabetes mellitus (50.00% vs 22.66%) was significantly higher in male non-survivors compared with survivors ($P < 0.05$). No significant difference was observed between non-survivors and survivors in the female subgroup regarding comorbidities ($P > 0.05$) [Table 2].

Signs/symptoms

The prevalence of diarrhea was significantly lower in non-survivors than survivors in the total sample (2.38% vs 14.3%) and male subgroup (0.00% vs 14.6%) ($P < 0.05$) [Table 2]. We did not find any significant differences between survivors and non-survivors regarding other sign and symptoms ($P > 0.05$).

Clinical variables

The prevalence of sepsis was significantly higher in non-survivors than survivors in the total sample and gender subgroups ($P < 0.05$). According to our data, the mean prevalence of intubation and severe COVID-19 disease was significantly higher in non-survivors than survivors in the total sample and gender subgroups ($P < 0.05$). The mean duration of ICU stay was also significantly higher in non-survivors than survivors in the total sample and gender subgroups ($P < 0.05$). We found a significantly lower mean value of SpO2 on admission in non-survivors than survivors in the total sample and gender subgroups ($P < 0.05$). However, the mean value of respiratory rate was significantly higher in non-survivors than survivors in the total sample and gender subgroups ($P < 0.05$). We did not find any significant difference between survivors and non-survivors regarding the type of administered medications except for the prevalence of administered antivirals in the female subgroup which was significantly lower in non-survivors than survivors [Table 2].

Biochemical and radiological variables

The comparison of biochemical variables between survivors and non-survivors showed that the mean values of white blood cells, serum creatinine, potassium, lactate dehydrogenase, creatinine phosphatase, and high sensitivity C-reactive protein was significantly higher in non-survivors than survivors in the total sample and gender subgroups ($P < 0.05$). Non-survivor females had a significantly lower mean value of calcium (8.02 ± 0.63 vs 8.68 ± 0.92) compared with non-survivors ($P < 0.05$). Moreover, the mean value of hemoglobin (12.48 ± 3.37 vs 13.82 ± 2.33) was significantly lower in non-survivors than survivors in the male subgroup ($P < 0.05$). We also found a significant difference between the two groups regarding radiological variables ($P < 0.05$) [Table 2].

Table 2: The comparison of basic, clinical, radiological, and biochemical characteristics between survivors and non-survivors across total sample and gender subgroups

Variables	Total (n=263)		P	Female (n=107)		P	Male (n=156)		P
	Survivors (n=221)	Non-survivors (n=42)		Survivors (n=93)	Non-survivors (n=14)		Survivors (n=128)	Non-survivors (n=28)	
Age (years)	59.91±18.14	70.40±13.23	<0.001	59.75±17.29	69.36±18.21	0.06	60.02±18.79	70.93±10.25	0.003
Smoking	11.76	16.67	0.44	3.22	7.14	0.43	17.97	21.43	0.79
Comorbidities									
Diabetes mellitus	30.77	42.86	0.15	41.93	28.57	0.40	22.66	50.00	0.005
Hypertension	20.36	26.19	0.41	22.58	35.71	0.32	18.75	21.43	0.79
Chronic obstructive pulmonary disease	7.24	9.52	0.54	6.45	21.43	0.09	7.81	3.57	0.69
Cardiovascular diseases	14.03	19.05	0.48	8.60	21.43	0.16	17.97	17.86	1.00
Cancer	3.64	16.67	0.004	5.38	7.14	0.58	2.36	21.43	0.001
Charlson comorbidity index	3.51±2.84	6.33±2.52	<0.001	3.58±2.70	5.50±2.31	0.01	3.46±2.94	6.75±2.56	<0.001
Signs/symptoms									
Fever	37.24±0.69	37.20±0.70	0.71	37.15±0.65	37.24±0.45	0.63	37.30±0.71	37.14±0.80	0.41
Cough	63.80	54.76	0.30	61.29	57.14	0.78	65.62	53.57	0.28
Shortness of Breath	71.49	69.05	0.71	65.52	64.29	1.00	76.56	71.43	0.63
Sputum	12.67	11.90	1.00	15.05	21.43	0.69	10.94	7.14	0.74
Fatigue	56.11	42.86	0.13	56.99	42.86	0.39	55.47	42.86	0.30
Headache	15.38	4.76	0.09	17.20	14.28	1.00	14.06	0.00	0.04
Nausea	19.00	11.90	0.38	24.732	21.43	1.00	14.84	7.14	0.37
Vomiting	13.57	14.28	1.00	16.13	35.71	0.13	11.72	3.57	0.31
Diarrhea	14.03	2.38	0.04	13.98	7.14	0.69	14.06	0.00	0.04
Abdominal pain	7.69	4.76	0.75	9.68	7.14	1.00	6.25	3.57	1.00
Loss of appetite	11.76	11.90	1.00	11.83	28.57	0.11	11.72	3.57	0.31
GI bleeding	1.36	2.38	0.50	0.00	7.14	0.13	2.34	0.00	1.00
Sepsis	0.90	33.33	<0.001	1.07	42.86	<0.001	0.78	28.57	<0.001
Clinical variables									
Oxygen Saturation at admission (%)	89.71±6.73	85.31±9.91	<0.001	90.01±7.41	84.21±7.53	0.008	89.50±6.22	85.86±11.00	0.02
Respiratory rate per minute	19.96±3.39	23.15±5.58	<0.001	20.24±3.28	26.21±4.26	<0.001	19.76±3.46	21.56±5.58	0.03
Mean duration of ICU stay (days)	2.47±6.12	6.63±7.61	<0.001	2.85±7.82	7.64±5.96	0.03	2.12±4.43	6.08±8.43	0.001
Intubation	7.24	78.57	<0.001	10.75	85.71	<0.001	7.24	78.57	<0.001
Severe COVID-19 infection	11.87	77.50	<0.001	11.96	78.57	<0.001	11.81	76.92	<0.001
Administered drugs									
Antibiotics	90.05	95.24	0.39	90.32	100	0.60	89.84	92.86	1.00
Antivirals	45.25	38.10	0.50	45.16	7.14	0.007	45.31	53.57	0.53
Corticosteroids	20.36	26.19	0.41	23.65	35.71	0.34	17.97	21.43	0.79
Interferons	17.65	9.76	0.26	20.43	14.29	0.73	15.63	7.41	0.37
Radiological variables									

Contd...

Table 2: Contd...

Variables	Total (n=263)		P	Female (n=107)		P	Male (n=156)		P
	Survivors (n=221)	Non-survivors (n=42)		Survivors (n=93)	Non-survivors (n=14)		Survivors (n=128)	Non-survivors (n=28)	
Ground Glass Opacity	76.92	52.38	<0.001	77.42	57.14	0.004	76.56	50.00	0.01
Bilateral subpleuretic consolidation	11.31	28.57		11.83	35.71		10.94	25.92	
Bilateral Ground Glass Opacity	0.00	4.76		0.00	7.14		0.00	3.70	
Biochemical variables									
White blood cells (10^3/µL)	7212.82±4288.50	10876.90±5766.09	<0.001	7124.41±3814.54	10822.86±7399.79	0.004	7277.56±4618.60	10903.93±4911.291	<0.001
Lymphocytes (10^3/µL)	1380.16±890.26	1389.721153.10	0.95	1350.60665.75	1222.69549.12	0.49	1401.80±1026.06	1473.24±1360.95	0.75
Hemoglobin (g/dl)	13.18±2.36	12.41±3.09	0.07	12.31±2.12	12.272.54	0.95	13.82±2.33	12.48±3.37	0.01
Platelet (10^3/µL)	184306.36±77094.94	180357.14±84754.69	0.77	202709.68±73018.55	183642.86±87639.65	0.38	170829.92±77489.13	178714.29±84861.92	0.63
Serum Creatinine (mg/dL)	1.38±0.78	2.95±2.19	<0.001	1.39±1.07	2.18±1.87	0.02	1.38±0.70	3.33±2.26	<0.001
Sodium (mEq/L)	138.27±4.97	137.67±8.55	0.53	138.5±55.38	136.212.67	0.11	138.06±4.67	138.39±10.29	0.80
Potassium (mEq/L)	4.28±0.60	4.89±0.97	<0.001	4.23±0.54	5.13±1.22	<0.001	4.32±0.64	4.76±0.82	0.002
Calcium (mg/dL)	8.68±0.86	8.46±1.14	0.21	8.68±0.92	8.020.63	0.02	8.68±0.81	8.67±1.27	0.97
Lactate dehydrogenase (U/L)	550.30±271.31	1164.94±744.40	<0.001	566.89±290.03	1001.04±752.02	0.001	537.02±256.43	1271.00±742.44	<0.001
Creatin phosphokinase (U/L)	186.30±247.73	592.96±561.68	<0.001	159.72±153.97	560.56±384.66	<0.001	210.18±308.18	609.17±641.91	0.001
Maximum Erythrocyte sedimentation rate (mm/h)	39.77±28.53	44.78±33.82	0.33	44.97±28.27	38.00±26.63	0.39	35.91±28.23	48.30±36.98	0.06
HS-C-reactive protein (mg/dL)	39.53±30.51	60.91±29.78	<0.001	42.13±28.16	62.83±32.61	0.01	37.68±32.07	59.91±28.80	0.001

Values in table are meanstandard deviation for continuous variables and percentage for categorical variables, P values were obtained from Student's t-test and the Mann-Whitney U-test for continuous variables with normal and non-normal distributions. *Variable was considered statistically significant different at a P<0.05

The association between CKD and risk of in-hospital mortality

Multiple logistic regression models of the association between CKD and in-hospital mortality for the total sample, males, and females are presented in Table 3. Our results showed that in the CRUD model, there was a significant positive association between CKD and in-hospital mortality in the total sample (OR = 8.64, CI: 3.67–20.35), female (OR = 4.77, CI: 1.38–16.40), and male subgroups (OR = 13.43, CI: 3.85–46.87) ($P < 0.05$). The association remained significant in the total sample and gender subgroups after adjustment for age (model I) ($P < 0.05$). Adjusting for sepsis, intubation, and the duration of ICU stay confounded the observed CRUD association between CKD and in-hospital mortality among males (OR = 2.00, CI: 0.3–13.17) ($P > 0.05$). Moreover, the association became insignificant across the total sample (OR = 1.70, CI: 0.35–8.19) and females (OR = 1.07 CI: 0.06–19.82) after additional adjustment for severe COVID-19 infection, and Charlson comorbidity score ($P > 0.05$). The association between CKD and in-hospital mortality become inverse among males after further adjustment for high sensitivity C-reactive protein (model IV) (OR = 0.87, CI: 0.07–10.33); however, the association was not statistically significant ($P > 0.05$).

Discussion

Infectious diseases are known as the most common CKD complications following cardiovascular diseases.[14] Some epidemiological studies have demonstrated that even mild to moderate reduction in eGFR is associated with increased risk of infectious diseases and hospitalization.[15,16] It has been suggested that a combination of various risk factors offers an increased risk of infectious diseases in CKD patients including, older age, comorbidities, and a weakened immune system.[17] Our results indicated that COVID-19 patients with CKD were more likely to die in the hospital compared with non-CKD patients. However, multivariable logistic regression revealed that CKD is not an independent predictor of in-hospital mortality. According to our results, the higher risk of mortality in COVID-19 patients with CKD is due to infection severity and Charlson comorbidity score. An association between CKD and a higher mortality rate has been suggested in several previous studies.[9-12] The results of a study on more than 4000 COVID-19 hospitalized patients demonstrated CKD as a predictor of increased mortality risk.[9] A systematic review and meta-analysis has also demonstrated an association between the risk of COVID-19 mortality and several comorbidities comprising chronic renal disease.[10] A multicenter study in Turkey by Ozturk *et al.*[12] reported a higher mortality rate in COVID-19 patients with CKD, stages 3 to 5, than patients without any kidney disease. However, the mediators of the association remained uninvestigated. Yamada *et al.*[11] reported a significantly increased risk of mortality in CKD patients with atrial fibrillation, ischemic heart disease, and heart failure hospitalized for COVID-19. Although, they have only assessed the prognostic effect of angiotensin-converting enzyme inhibitor as well as underlying disorders such as diabetes mellitus and cardiovascular disorders on mortality.

Older age has been demonstrated as a risk factor for severe disease and mortality in COVID-19 patients by previous studies.[18-20] On contrary, the results of our study refused to recognize age as a predictor of mortality in COVID-19 patients with CKD. The mean age was significantly different between cases and controls; however, the association between CKD and mortality remained significant after adjustment for age. It is possible that differences in the studied population, study design, and setting somewhat explain diverse results from various studies.

According to our results, the predictors of mortality in males were different from those in the total sample. Sepsis, intubation, and the duration of ICU stay were prognostic factors for mortality among males. We assume that less robust innate and adaptive immune responses to viral antigens among men increase the length of ICU stay and predispose them to the higher risk of sepsis and intubation as important determinants of in-hospital mortality.[21-24]

This study has several limitations that should be noted. First of all, our patient population was relatively small; thus, we could not stratify our patients based on various stages of CKD. Second, there was a lack of information regarding anthropometric variables of patients, which resulted in disregarding their potential confounding role. Finally, we only

Table 3: Summary of logistic regression of the association between chronic kidney disease and the risk of in-hospital mortality in the total sample and gender subgroups

	Crude model		Model I		Model II		Model III		Model IV		Model V	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Mortality in the total sample	8.64*	3.67-20.35	6.99*	2.79-17.55	4.15*	1.22-14.05	1.70	0.35-8.19	2.08	0.48-8.94	1.33	0.28-6.23
Mortality in females	4.77*	1.38-16.40	12.08*	3.09-47.30	7.13*	1.06-48.09	1.07	0.06-19.82	1.88	0.18-19.26	0.87	0.07-10.33
Mortality in males	13.43*	3.85-46.87	3.81*	1.05-13.78	2.00	0.3-13.17	1.32	0.10-17.78	1.85	0.16-21.81	1.21	0.09-16.57

Model 1 adjusted for age, model II adjusted for age, sepsis, intubation, and the duration of ICU stay, model III adjusted for age, sepsis, intubation, the duration of ICU stay, severe COVID-19 infection, and Charlson comorbidity score, model IV adjusted for age, sepsis, intubation, the duration of ICU stay, severe COVID-19 infection, Charlson comorbidity score, and high sensitivity C-reactive protein, and model V adjusted for age, sepsis, intubation, the duration of ICU stay, severe COVID-19 infection, Charlson comorbidity score, high sensitivity c-reactive protein, hemoglobin, and white blood cell.
*Variable was considered statistically significant different at a $P<0.05$

recorded the outcome and did not record the time to an event; accordingly, we could not be able to use Cox regression. As a result, further studies on CKD patients are warranted to explore the association between CKD and mortality risk plus related risk factors. In this observational case-control study, there was an indirect association between CKD and in-hospital mortality which was mediated by infection severity and comorbidities. Therefore, more intensive surveillance of COVID-19 patients with CKD is to be warranted.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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