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ORIGINAL RESEARCH

Clinical Presentation and Outcomes of Hospitalized Patients with Chronic Kidney Disease and COVID-19 Variant Omicron

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Purpose: To investigate the clinical characteristics of hospitalized patients with chronic kidney disease (CKD) and novel coronavirus (SARS-CoV-2) infection and identify potential risk factors that contribute to mortality.

Patients and Methods: This is a retrospective study, conducted on patients with CKD who were admitted to the First Medical Center of the People's Liberation Army General Hospital between December 1, 2022, and February 28, 2023. All patients were also infected with SARS-CoV-2. We analyzed the clinical characteristics of patients, and the patients were categorized into a survival group and a death group whose characteristics were compared. Cox regression analysis was used to identify risk factors that affected patient prognosis.

Results: A total of 406 patients were enrolled in this study, including 298 males (73.4%). The average age was 80.5 (67.0, 88.0) years, and the patients had an average estimated glomerular filtration rate (eGFR) of 50.3 (25.0–79.0) mL/min/1.73m². A total of 158 individuals died during hospitalization, resulting in a mortality rate of 38.9%. Renal function was worse in the death group than in the survival group ($P < 0.001$). Patients in the death group had more severe COVID-19 disease and higher CKD staging than those in the survival group (all P values < 0.001). Multivariate Cox regression analysis identified several risk factors that affected patient mortality, including being male, a higher resting heart rate (RHR) upon admission, dyspnea, a low lymphocyte count (Lym), a high international standardized ratio (INR), a high Acute Physiology and Chronic Health Evaluation II (APACHE II) score, heart failure, and the need for mechanical ventilation during the disease.

Conclusion: Hospitalized patients with CKD who were infected with SARS-CoV-2 (38.9%) had a relatively high mortality rate (38.9%). Furthermore, a marked correlation was observed between a reduced eGFR and an increased risk of mortality.

Keywords: SARS-CoV-2, estimated glomerular filtration rate, respiratory failure, mortality rate

Introduction

Coronavirus disease-19 (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus that set off a global pandemic with significant morbidity and mortality. COVID-19 patients with multiple co-morbidities, including chronic kidney disease (CKD), have a worse prognosis.[1] The worldwide prevalence of CKD is estimated to be 9–12%[2] and the condition is linked to a higher risk of hospitalization and outpatient pneumonia.[3] Patients with CKD have an approximately 10 times higher risk of mortality from pulmonary infections than the general population.[4] CKD is a significant risk factor for severe COVID-19[5] and is one of the most reliable predictors of prognosis among COVID-19 patients with severe and critical disease.[6] In a prospective cohort study[6] of 701 hospitalized patients with COVID-19, those with comorbid CKD had a two- to four-fold higher risk of death. A significant correlation between declining renal function and COVID-19-related mortality has also been demonstrated.[7] Specifically, patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2; *HR* = 2.5) have a higher risk of death from COVID-19 than other high-risk populations, including individuals with obesity, neoplasia, chronic heart disease, and lung disease. Thus, it is critical to accurately characterize

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the prognosis and clinical progression of CKD patients with COVID-19. However, most studies on COVID-19 and CKD assessed patients infected with the Alpha or Delta strains of SARS-CoV-2. Since the Omicron variant did not become prevalent until after November 9, 2021, few studies have specifically examined the association between SARS-CoV-2 Omicron infection and CKD.

Understanding the severity of COVID-19 disease in CKD patients studies is particularly important in China, which has been experiencing a nationwide epidemic since December 1, 2022. Thus, the current study focused on patients hospitalized in China with severe COVID-19 and CKD. Their clinical characteristics were explored, along with particular risk factors associated with in-hospital mortality. The findings provide valuable insight into how best to manage these conditions.

Material and Methods

Study Design

Hospitalized patients treated at the First Medical Center of the General Hospital of the Chinese People's Liberation Army from December 1, 2022, to February 28, 2023, who (1) met the diagnostic criteria for CKD,[8](2) had a confirmed diagnosis of SARS-CoV-2 using nasopharyngeal swab reverse transcription polymerase chain reaction (RT-PCR) testing or the detection of viral antigens using colloidal gold and immunofluorescence, (3) were ≥18 years of age, and (4) had well-developed medical records, were included in the study. Individuals who were <18 years of age, had acute kidney injury (AKI) on admission (without a previous history of CKD), and lacked discharge information or survival data, were excluded.

Research Methods

Data Collection

The following patient data were collected: (1) demographics, (2) vital signs, symptom presentation, and time from symptom onset to hospitalization at the time of admission, (3) laboratory tests conducted within 24 hours of admission, (4) estimated glomerular filtration rate calculated using the Collaborative Study of Epidemiology in Chronic Kidney Disease (CKD-EPI) equation,[9](5) any concomitant illnesses, (6) APACHE II and Sequential Organ Failure Assessment (SOFA) scores at the time of admission, (7) COVID-19 severity,[10] (8) treatment regimen, Vaccination status, and (9) clinical regression.

Related Definitions

(1) Diagnostic criteria for CKD[8] (according to the 2020 KDOQI Guidelines for CKD diagnostic criteria): renal injury or GFR <60 mL/(min-1.73m^2) for ≥3 months. Renal injury is defined as an abnormality of renal structure or function with at least one of the following: abnormal renal pathology, hematuria, or abnormalities observed on imaging. Hematuria and/or proteinuria (including microproteinuria) were considered abnormal on urinalysis. Hematuria is defined as fresh centrifuged urine with >3/HP erythrocytes on microscopic examination or glomerular hematuria (predominantly metastatic erythrocytes upon microscopic examination of the urine phase difference). Proteinuria is defined as a urine albumin creatinine ratio ≥30 mg/g or urine protein levels above microalbuminuria.

(2) CKD staging:[11] eGFR ≥90 mL/min/1.73m^2 was defined as CKD1 stage, 60≤ eGFR <90 mL/min/1.73m^2 was defined as CKD2 stage, 30≤ eGFR <60 mL/min/1.73m^2 was defined as CKD3 stage, 15≤ eGFR <30 mL/min/1.73m^2 was defined as CKD4 stage and eGFR <15 mL/min/1.73m^2 was defined as CKD5 stage.

(3) Patients were diagnosed with AKI[12] according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines: a serum creatinine (SCR) level that increased by >26.5 μmol/L (0.3 mg/dL) within 48 h, an SCR level that increased >1.5 times above the baseline level and was confirmed or speculated to occur within 7 days, and a urine volume <0.5 mL/kg·h for >6 h. It is important to note that when changes in urine volume are used as criteria, urinary tract obstructions and other causes of a drop in urine volume must be excluded.

(4) COVID-19 severity was determined according to the protocol for the diagnosis and treatment of novel coronavirus infections (10th edition) issued in China:[10](1) Mild disease was defined when a respiratory tract infection, including a dry pharynx, sore pharynx, cough, and fever was the primary manifestation; (2) Moderate disease was defined when there was a persistent high fever for >3 days and/or a cough or shortness of breath, but the respiratory rate (RR) was <30 breaths/minute and the finger oxygen saturation was >93% upon air intake at rest. In addition, characteristic pneumonia associated with a new coronavirus infection was observed on imaging; (3) Severe disease was defined when adult

patients met any of the following criteria that could not be explained by reasons other than a novel coronavirus infection: 1. shortness of breath (an RR ≥ 30 times/minute), 2. oxygen saturation ≤93% upon air intake at rest, 3. partial pressure of arterial blood oxygen (PaO_2)/ fractional inspired oxygen(FiO_2) ≤300 mmHg (1 mmHg = 0.133 kPa), and 4. progressive exacerbation of symptoms, including lung imaging showing significant progression of >50% of the lesions within 24–48 hours; (4) Critical disease was defined as 1. respiratory failure and need for mechanical ventilation, 2. shock and/or 3. other organ failure requiring ICU supervision and treatment.

Please note that, given that the patients participating in this study did not have a mild classification for COVID-19, we had to re-evaluate and adjust the classification criteria. Therefore, patients who were originally classified as having moderate COVID-19 were reassigned to the mild group, those with severe COVID-19 were reassigned to the moderate group, and critically ill patients with COVID-19 were placed in the severe group.

Prognostic Indicators

The prognosis of patients at discharge was categorized as survival or death.

Statistical Analysis

Normally distributed continuous variables were expressed as the mean ± standard deviation and non-normally distributed continuous variables were expressed as medians. Categorical data were expressed as n (%). The Student's *t*-test was used to compare normally distributed continuous variables between groups, the Mann–Whitney *U*-test was used to compare non-normally distributed continuous variables between groups, and the Pearson's $\chi 2$ test was used to compare ratios or composition ratios.

Preliminary screening was conducted using univariate COX regression analysis. To avoid potential collinear effects, secondary screening was performed on variables with $P<0.05$ in univariate analysis, and indicators with a variance inflation factor less than 5 were strictly selected to ensure mutual independence between variables. Finally, these strictly screened indicators were incorporated into the multivariate COX regression model, and a stepwise approach was adopted to more accurately assess the combined impact of various factors on prognosis.

SPSS software (v22.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. All tests were two-sided and P-values <0.05 were considered statistically significant.

Results

Demographic Characteristics, Comorbidities, and Medication

A total of 1139 patients were diagnosed with COVID-19 in our hospital from December 1, 2022, to February 28, 2023. Of these, 213 patients (18.7%) died. After applying the inclusion and exclusion criteria, 406 patients with COVID-19 and CKD were included in the study, of whom 158 patients (38.9%) died. Details of patient enrollment are shown in Figure 1.

The mean age of the enrolled patients was 80.5 (67.0, 88.0) years, and 73.4% were male. The mean arterial pressure(MAP) was 95.3 ± 14.10 mmHg, and the mean BMI was 23.7 ± 4.2. Additional information on the baseline parameters, comorbidities, and clinical characteristics of the patients at the time of admission is shown in Table 1.

The primary respiratory symptoms were fever (87.7%), cough (77.6%), and dyspnea (38.9%), and there was an average duration of 8.0 (3.3, 12.0) days from symptom onset to hospitalization.

The most prevalent concomitant disease among the enrolled patients was hypertension (273/406; 67.2%). This was followed by respiratory failure (201/406; 49.5%), diabetes mellitus (159/406; 39.2%), coronary heart disease (130/406; 32%), and heart failure (115/406; 28.3%).

Most patients had CKD3 stage (139/406; 34.2%), followed by CKD2 stage (95/406; 23.4%), CKD stage 5 (70/406; 17.2%), CKD1 stage (63/406; 15.5%), and CKD4 stage (39/406; 9.6%). Of the patients with CKD, 25.6% (94/367) developed AKI, 16.3% (66/406) required renal replacement therapy (RRT)., during the disease, and 27.2% (110/406) required mechanical ventilation.

Among the 406 patients, 28.3% (n=115) received the novel coronavirus vaccine. Of these vaccinated patients, 7.6% (n=31) received one dose, while 20.8% (n=84) received two or more doses.

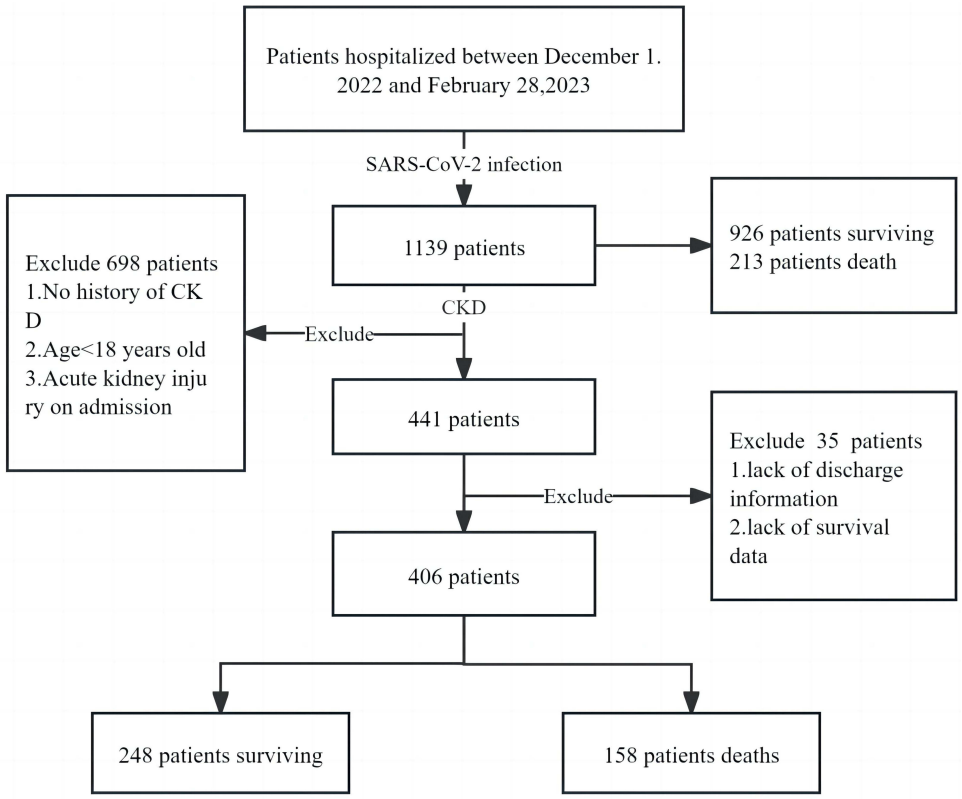


Figure 1 Flow chart of patient selection and grouping.

Paxlovid was administered for a median of 10.5 (7.0, 15.0) days after symptom onset in 34.5% (140/406) of patients and Azvudine was administered for a median of 9.0 (5.0, 11.5) days after symptom onset in 24.9% (101/406) of patients. Glucocorticoids were used to treat 66.3% (269/406) of patients.

Risk Factors for Death

Bivariate Analysis Comparing the Characteristics of Patients Who Survived and Died of COVID-19 Infection

The characteristics of the mortality group were distinct from those of the survivor group. The mortality group had a higher average age and a higher proportion of male patients. Patients in the mortality group also had a higher RHR on admission than those in the survivor group and a lower mean arterial pressure (Table 1).

Table 1 Demographic Characteristics, Comorbidities, and Medication Use in the Study Population: Comparison of the Patients Who Survived and Died in the Hospital

Project	Survival (N = 248)	Death (N = 158)	Total (N = 406)	P
Age (years)	77.0 (59.0, 86.8)	85.0 (70.0, 91.0)	80.5 (67.0, 88.0)	<0.001
Sex (male)	170 (68.5%)	128 (81.0%)	298 (73.4%)	0.006
RHR	80.0 (76.0, 89.0)	88.0 (79.5, 102.0)	83.0 (76.0, 96.0)	<0.001
RR	18.0 (18.0, 19.0)	18.0 (18.5, 20.0)	18.0 (18.0, 20.0)	0.082
MAP (mmHg)	97.6±12.8	91.5±15.2	95.3±14.1	<0.001
BMI (kg/m2)	23.9±4.2	23.4±4.2	23.7±4.2	0.265
Symptoms				
Cough (n, %)	182 (73.4%)	133 (84.2%)	315 (77.6%)	0.011
Fever (n, %)	213 (85.9%)	143 (90.5%)	356 (87.7%)	0.167
Dyspnea (n, %)	50 (20.2%)	108 (68.4%)	158 (38.9%)	<0.001
Time to hospitalization (days)	8.0 (3.5, 13.0)	7.0 (3.0, 12.0)	8.0 (3.3, 12.0)	0.489

(*Continued*)

Table 1 (Continued).

Project	Survival (N = 248)	Death (N = 158)	Total (N = 406)	P
Concomitant disease (n, %)				
Hypertension	157 (63.3%)	116 (73.4%)	273 (67.2%)	0.034
Diabetes	91 (36.7%)	68 (43.0%)	159 (39.2%)	0.202
Heart failure	30 (12.1%)	85 (53.8%)	115 (28.3%)	<0.001
Coronary heart disease	60 (24.42%)	70 (44.3%)	130 (32.0%)	<0.001
Tumor	41 (16.5%)	30 (19.0%)	71 (17.5%)	0.525
Chronic bronchitis	10 (4.0%)	8 (5.1%)	18 (4.4%)	0.623
COPD	9 (3.6%)	7 (4.4%)	16 (3.9%)	0.686
CKD stage (n, %)				<0.001
CKD1	47 (19.0%)	16 (10.1%)	63 (15.5%)	
CKD2	66 (26.6%)	29 (18.4%)	95 (23.4%)	
CKD3	90 (36.3%)	49 (31.0%)	139 (34.2%)	
CKD4	10 (4.0%)	29 (18.4%)	39 (9.6%)	
CKD5	35 (14.1%)	35 (22.2%)	70 (17.2%)	
AKI (n, %)	54 (21.8%)	50 (31.6%)	94 (25.6%)	0.026
RRT (n, %)	31 (12.5%)	35 (22.2%)	66 (16.3%)	0.010
Respiratory failure (n, %)	74 (29.8%)	127 (80.4%)	201 (49.5%)	<0.001
Mechanical ventilation (n, %)	9 (3.06%)	101 (63.9%)	110 (27.2%)	<0.001
Drinking (n, %)	58 (23.4%)	35 (22.2%)	93 (22.9%)	0.773
Smoking (n, %)				0.851
No	179 (72.2%)	115 (72.8%)	294 (72.4%)	
Previous	30 (12.1%)	21 (13.3%)	51 (12.6%)	
Now	39 (15.7%)	22 (13.9%)	61 (15.0%)	
Vaccination status (n, %)	77 (31.0%)	38 (24.1%)	115 (28.3%)	0.127
One does	19 (7.6%)	12 (7.6%)	31 (7.6%)	
≥ Two doses	58 (23.4%)	26 (16.5%)	84 (20.7%)	
Paxlovid (n, %)	92 (37.1%)	48 (30.4%)	140 (34.5%)	0.165
Initial use (days)	10.5 (6.3, 15.0)	10.5 (7.3, 12.8)	10.5 (7.0, 15.0)	0.683
Glucocorticoid (n, %)	156 (62.9%)	113 (71.5%)	269 (66.3%)	0.073
Azvudine (n, %)	59 (23.8%)	42 (26.6%)	101 (24.9%)	0.526
Initial use (days)	9.0 (6.0, 13.0)	9.0 (5.0, 11.0)	9.0 (5.0, 11.5)	0.228

Abbreviations: RHR, resting heart rate; RR, respiratory rate; MAP, mean arterial pressure; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; AKI, acute kidney injury; RRT, renal replacement therapy.

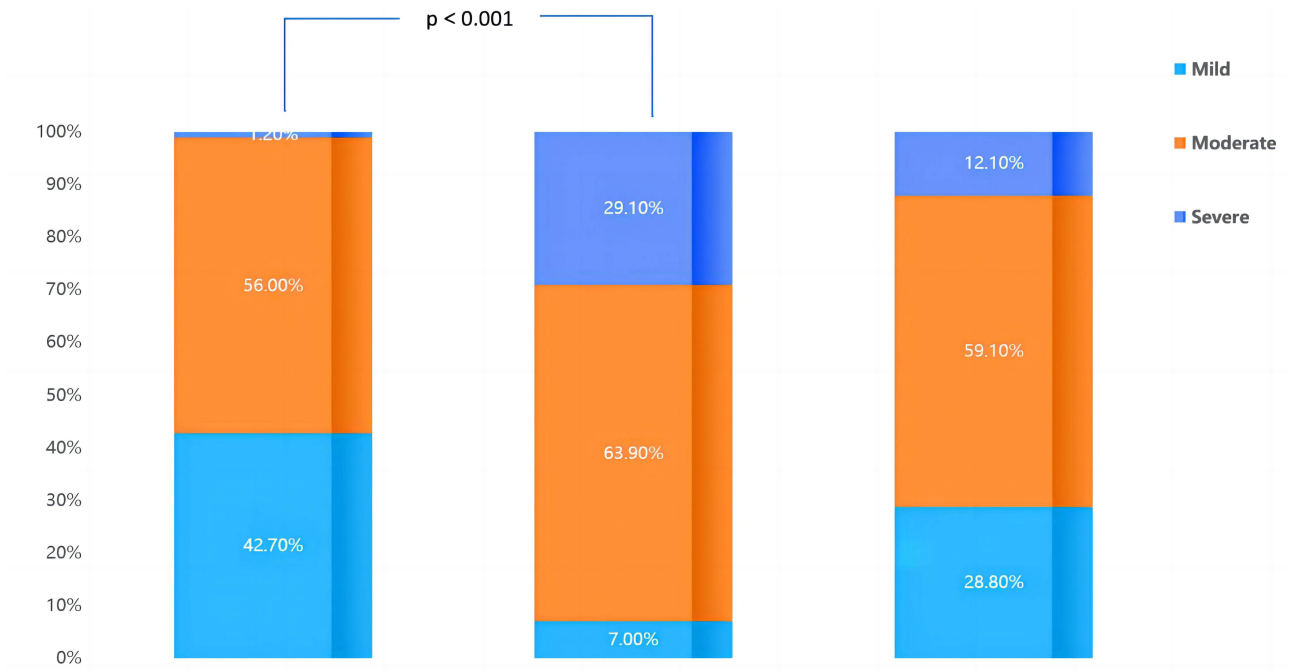
Coughing and dyspnea were more common in the death group than in the survivor group, while fever was similar between the two groups. The death group also had a higher proportion of hypertension, respiratory failure, cardiac failure, and coronary heart disease than the survivor group. However, other complications were similar between the groups.

The death group had poorer renal function than the survivor group. Patients in the death group, the most prevalent CKD stages were CKD3 stage (49/158; 31.0%), CKD5 stage (35/158; 22.2%), and CKD4 stage (29/158; 18.4%). In the survival group, the most common CKD stages were CKD3 stage (90/248; 36.3%), CKD2 stage (66/248; 26.6%), and CKD1 stage (47/248; 19.0%). It is worth noting that the proportions of patients with CKD5 and CKD4 stages were notably higher in the death group when compared to the survival group. In addition, more patients in the death group than in the survivor group had AKI and RRT during the disease course a higher proportion of patients in the death group also needed mechanical ventilation.

The vaccination status, medication situation, and initial medication time were similar between the two groups.

Association Between COVID-19 Severity and Patient Survival Prognosis and CKD Stage

Most of the COVID-19 patients had moderate disease (240/406; 59.1%), followed by mild (117/406; 28.8%), and severe disease (49/406; 12.1%) (Figure 2). Disease was more severe in the death group ($P < 0.001$), with 63.9% (101/158) of



	Suvival（N=248）	Death（N=158）	Total（n=406）	P
COVID--19 severity				<0. 001
Mild	106（42. 7%）	11（7. 0%）	117（28. 8%）	
Moderate	139（56. 0%）	101（63. 9%）	240（59. 1%）	
Severe	3（1. 2%）	46（29. 1%）	49（12. 1%）	

Figure 2 COVID-19 severity and survival prognosis.

cases having moderate and 29.1% (46/158) having severe disease. Meanwhile, 56.0% (139/248) of patients in the survivor group had moderate disease, 42.7% (106/248) had mild, and only 1.2% (3/246) had severe disease.

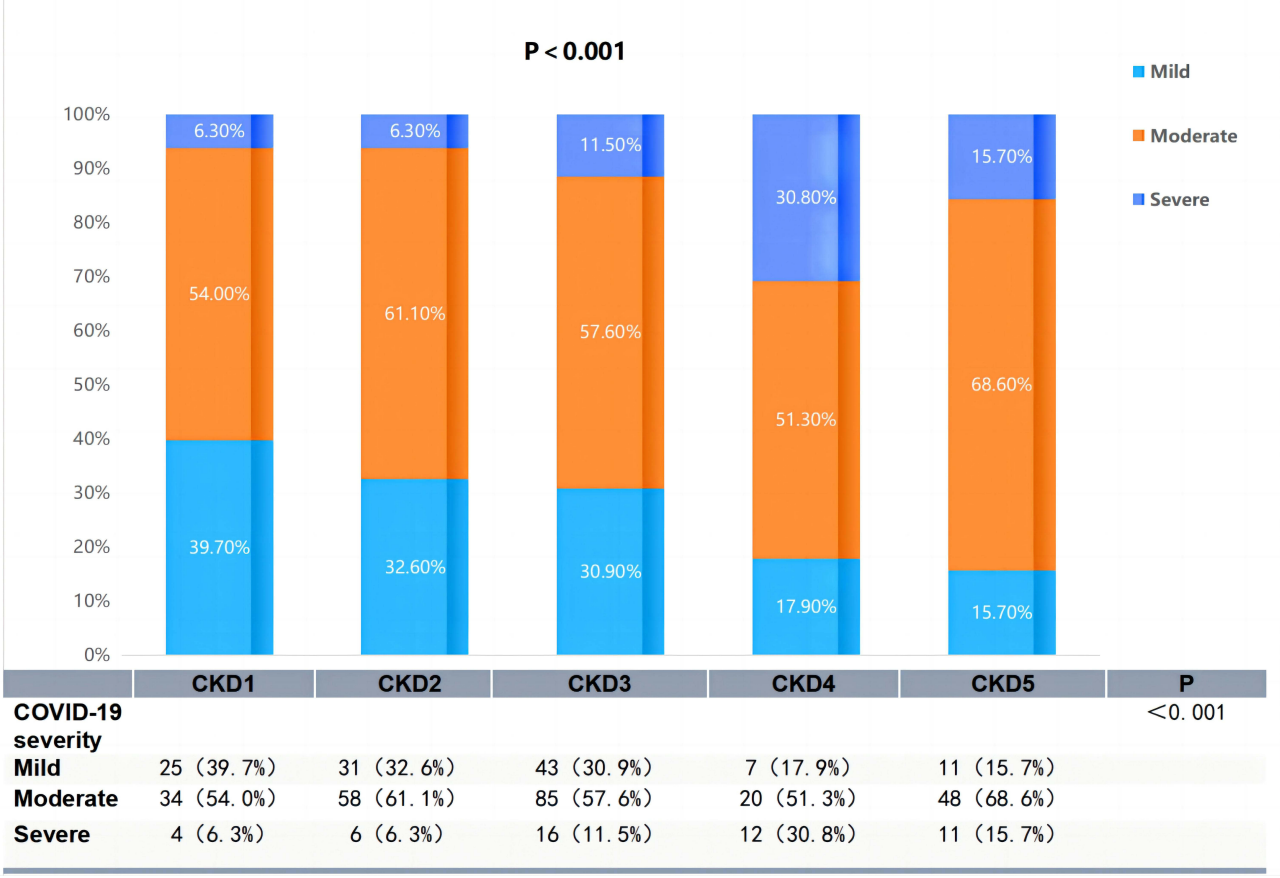
The COVID-19 clinical classification differed significantly by CKD stage ($P < 0.001$). As renal function declined, the proportion of patients with moderate and severe COVID-19 cases increased (Figure 3).

Bivariate Analysis of Laboratory Parameters in the Survivor and Mortality Groups

Patients in the death group had higher levels of inflammatory markers, including white blood cell (WBC) count, C-reactive protein (CRP) levels, and interleukin-6 (IL-6) levels than those in the survival group (Table 2). Lymphocyte count (Lym) and albumin (ALB) levels were lower in the death group, while several other markers, including aspartate transaminase (AST), direct bilirubin (DB), lactate dehydrogenase (LDH), glucose (Glu), uric acid (UA), sodium (Na), B-type natriuretic peptide (BNP), urinary protein (Upro), international normalized ratio (INR), and D-dimer, were higher. Renal function at admission was lower in the death group than in the survival group. Urea nitrogen (UN) and serum creatinine (Scr) levels were higher in the death group than in the survivor group, while eGFR was lower. Lower levels of PH, $P0_2/Fio_2$, and base excess (BE) were observed in the death group than in the survivor group.

Univariate Cox Regression Analysis of Risk Factors, Including Demographic Characteristics, Comorbidities, and Medication Use, Impacting Patient Mortality

Univariate Cox regression analysis identified several risk factors for COVID-19-related mortality. These included higher age, male gender, a faster RHR on admission, a faster respiratory rate(RR), low MAP, the presence of symptoms such as cough and dyspnea upon admission, the combination of respiratory failure and heart failure, coronary heart disease, a more severe stage of CKD, AKI, a requirement for mechanical ventilation, and more severe disease (Table 3).



	CKD1	CKD2	CKD3	CKD4	CKD5	P
COVID-19 severity						<0. 001
Mild	25 (39. 7%)	31 (32. 6%)	43 (30. 9%)	7 (17. 9%)	11 (15. 7%)	
Moderate	34 (54. 0%)	58 (61. 1%)	85 (57. 6%)	20 (51. 3%)	48 (68. 6%)	
Severe	4 (6. 3%)	6 (6. 3%)	16 (11. 5%)	12 (30. 8%)	11 (15. 7%)	

Figure 3 COVID-19 severity and CKD stages.

Univariate COX Regression Analysis of Laboratory Parameters Impacting Patient Mortality

Univariate COX regression analysis found that higher levels of inflammatory markers, including WBC, CRP, and IL-6, were associated with an increased risk of death. Conversely, a higher Lym was identified as a protective factor. Elevated levels of AST, ALT, Glu, LDH, Na, K, BNP, D-dimer, and INR on admission were also risk factors for death, while higher levels of ALB were associated with a lower risk of mortality. Poorer renal function, as indicated by higher levels of UN, UA, and a lower estimated eGFR, were identified as risk factors for death. Meanwhile, higher levels of pH, P02/FiO2, and BE in blood gas analysis upon admission were identified as protective factors for mortality (Table 4).

Table 2 Laboratory Parameters of the Study Population: Comparison of the Patients Who Survived and Died in the Hospital

Project	Survival (N=248)	Death (N=158)	Total (n=406)	P
Laboratory examination				
HB (g/L)	119.0 (101.0, 134.0)	113.0 (93.8, 131.3)	116.0 (97.0, 134.0)	0.095
WBC (10^9/L)	6.8 (4.9, 8.7)	9.1 (7.0, 13.0)	7.5 (5.4, 10.4)	<0.001
Lym	0.14 (0.07, 0.20)	0.05 (0.03, 0.10)	0.1 (0.05, 0.17)	<0.001
PLT (10^9/L)	170.0 (123.3, 224.0)	160.0 (108.8, 214.3)	166.0 (120.0, 222.3)	0.071
CRP (mg/dL)	3.6 (0.9, 7.1)	7.5 (3.8, 13.0)	5.2 (1.6, 7.7)	<0.001
IL-6 (pg/mL)	28.6 (10.5, 61.1)	70.9 (24.5, 176.7)	40.5 (16.0, 108.0)	<0.001
ALT (U/L)	19.9 (11.7, 32.7)	20.9 (12.1, 35.1)	20.0 (11.9, 33.2)	0.589
AST (U/L)	25.6 (18.3, 40.8)	34.8 (23.5, 57.3)	27.9 (20.1, 46.5)	<0.001
TP (g/L)	63.9±8.8	63.8±7.6	63.9±8.3	0.830
ALB (g/L)	33.1±5.3	30.2±4.4	32.0±5.2	<0.001

(*Continued*)

Table 2 (Continued).

Project	Survival (N=248)	Death (N=158)	Total (n=406)	P
TB (mmol/L)	7.6 (4.7, 10.9)	7.7 (4.8, 12.3)	7.6 (4.8, 11.2)	0.320
DB (mmol/L)	3,3 (2.1, 5.2)	4,2 (2.2, 6.5)	3.5 (2.1, 5.7)	0.036
LDH (U/L)	241.5 (202.3, 305.0)	388.5 (285.0, 529.0)	282.0 (214.8, 402.0)	<0.001
GLU (mmol/L)	6.6 (5.3, 9.4)	8.5 (6.4, 11.4)	7.4 (5.7, 10.5)	<0.001
UN (mmol/L)	8.3 (5.2, 12.6)	15.3 (9.7, 25.5)	10.2 (6.3, 18.7)	<0.001
SCR (umol/L)	102.5 (71.9, 142.7)	130.9 (88.3, 264.8)	109.5 (76.5, 188.5)	<0.001
UA (umol/L)	295.6 (203.4, 414.0)	393.0 (258.5, 566.0)	321.2 (220.4, 470.0)	<0.001
K (mmol/L)	4.0 (3.6, 4.4)	4.1 (3.7, 4.5)	4.0 (3.6, 4.5)	0.076
Na (mmol/L)	134.0 (132.0, 138.0)	138.0 (133.0, 143.0)	136.0 (132.0, 140.0)	<0.001
eGFR mL/min/1.73m2	57.0 (38.5, 83.6)	39.1 (17.5, 72.0)	50.3 (25.0, 79.0)	<0.001
BNP (pg/mL)	697.0 (263.3, 2491.0)	3405.0 (1383.5, 12,186.8)	1611.0 (434.3, 5070.0)	<0.001
UPR (mg/dl)	30.0 (20.0, 100.0)	70.0 (30.0, 100.0)	50.0 (30.0, 100.0)	0.003
INR	1.1 (1.0, 1.2)	1.2 (1.1, 1.4)	1.1 (1.0, 1.3)	<0.001
D-dimer (ug/mL)	1.3 (0.7, 2.5)	2.9 (1.5, 8.4)	1.8 (0.9, 4.5)	<0.001
PH	7.40 (7.37, 7.44)	7.39 (7.33, 7.43)	7.40 (7.36, 7.44)	0.007
P02/Fio2	254.5 (214.8, 322.5)	172.0 (114.0, 253.3)	230.0 (165.3, 300.7)	<0.001
PCO2	35.3 (31.3, 40.5)	36.9 (30.1, 42.6)	35.9 (31.0, 41.0)	0.273
BE	−1.7±4.3	−3.0±5.2	−2.2±4.7	0.01
APACHE II	8.0 (6.0, 11.0)	18.0 (14.8, 22.3)	11.0 (7.0, 17.0)	<0.001
SOFA	3 (2.0, 4.0)	7 (4.8, 11.0)	4.0 (2.0, 7.0)	<0.001

Abbreviations: HB, hemoglobin; WBC, white blood cell; Lym, lymphocyte count; PLT, platelets; CRP, C-reactive protein; IL-6, interleukin-6; ALT, alanine transferase; AST, aspartate transferase; TP, total protein; ALB, albumin; TB, total bilirubin; DB, direct bilirubin; LDH, lactate dehydrogenase; GLU, glucose; UN, urea nitrogen; SCR, serum creatinine; UA, uric acid; K, potassium; Na, sodium; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; Upro, urinary protein; INR, international normalized ratio; P02/FiO2, partial pressure of arterial blood oxygen /fluoro oxygen concentration; BE, base excess; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment.

Table 3 Cox Regression Analysis of Risk Factors, Including Demographic Characteristics, Comorbidities, and Medication Use, Impacting Patient Mortality

Univariate Cox regression analysis					Multivariate Cox regression analysis			
Influencing factors	**HR**	**95% CI Lower Limit**	**Upper Limit**	**P-value**	**HR**	**95% CI Lower Limit**	**Upper Limit**	**P-value**
Age (years)	1.025	1.014	1.037	<0.001				
Sex (male)	1.830	1.229	2.727	0.003	1.172	1.113	2.604	0.014
RHR	1.026	1.016	1.036	<0.001	1.012	1.002	1.023	0.020
RR	1.061	1.017	1.108	0.007				
MAP (mmHg)	0.970	0.959	0.982	<0.001				
Cough (n, %)	1.704	1.111	2.614	0.015				
Dyspnea (n, %)	4.502	3.210	6.315	<0.001	1.971	1.282	3.029	0.002
Respiratory failure (n, %)	4.704	3.175	6.969	<0.001				
Heart failure (n, %)	3.640	2.657	4.988	<0.001	1.575	1.087	2.281	0.016
Coronary heart disease (n, %)	1.855	1.354	2.541	<0.001				
CKD stage (n, %)	–	–	–	<0.001				
CKD1	–	–	–	–				
CKD2	0.936	0.507	1.726	0.832				
CKD3	1.349	0.767	2.373	0.299				
CKD4	3.940	2.136	7.268	<0.001				
CKD5	1.695	0.936	3.069	0.082				

(*Continued*)

Table 3 (Continued).

Univariate Cox regression analysis					Multivariate Cox regression analysis			
Influencing factors	**HR**	**95% CI Lower Limit**	**Upper Limit**	**P-value**	**HR**	**95% CI Lower Limit**	**Upper Limit**	**P-value**
AKI (n, %)	1.415	1.011	1.981	0.043				
Mechanical ventilation (n, %)	7.482	5.384	10.397	<0.001	2.001	1.283	3.122	0.002
COVID-19 severity (n, %)	–	–	–	0.001				
Mild	–	–	–	–				
Moderate	4.206	2.254	7.849	<0.001				
Sever	17.387	8.976	33.681	<0.001				

Abbreviations: RHR, resting heart rate; RR, respiratory rate; MAP, mean arterial pressure; CKD, chronic kidney disease; AKI, acute kidney injury.

Table 4 Cox Regression Analysis of Laboratory Parameters Impacting Influencing Patient Mortality

Univariate Cox regression analysis					Multivariate Cox regression analysis			
Influencing factors	**HR**	**95% CI Lower Limit**	**Upper Limit**	**P-value**	**HR**	**95% CI Lower Limit**	**Upper Limit**	**P-value**
WBC (10^9/L)	1.079	1.059	1.099	<0.001				
Lym	0.326	0.237	0.449	<0.001	0.032	0.001	0.734	0.031
CRP (mg/dL)	1.051	1.035	1.068	<0.001				
IL-6 (pg/mL)	1.001	1.000	1.001	<0.001				
ALT (U/L)	1.001	1.000	1.001	<0.001				
AST (U/L)	1.001	1.000	1.001	<0.001				
ALB (g/L)	0.934	0.907	0.963	<0.001				
Glu (mmol/L)	1.049	1.027	1.072	<0.001				
LDH (U/L)	1.001	1.000	1.001	<0.001				
UN (mmol/L)	1.034	1.024	1.045	<0.001				
UA (umol/L)	1.002	1.001	1.003	<0.001				
Na (mmol/L)	1.051	1.032	1.071	<0.001				
K (mmol/L)	1.311	1.039	1.652	0.022				
BNP	1.000	1.000	1.000	<0.001				
EGFR mL/min/1.73m^2	0.990	0.985	0.995	<0.001				
D-dimer (ug/mL)	1.066	1.043	1.090	<0.001				
INR	1.604	1.391	1.848	<0.001	1.512	1.260	1.815	<0.001
PH	0.029	0.005	0.179	<0.001				
PO2/FiO2	0.994	0.992	0.996	<0.001				
BE	0.955	0.923	0.988	0.008				
APACHE II	1.127	1.108	1.145	<0.001	1.056	1.029	1.082	<0.001
SOFA	1.198	1.162	1.236	<0.001				

Abbreviations: WBC, white blood cell; Lym, lymphocyte count; CRP, C-reactive protein; IL-6, interleukin-6; ALT, alanine transferase; AST, aspartate transferase; ALB, albumin; GLU, glucose; LDH, lactate dehydrogenase; UN, urea nitrogen; UA, uric acid; K, potassium; Na, sodium; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; P02/FiO2, partial pressure of arterial blood oxygen /fluoro oxygen concentration; BE, base excess; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment.

Multifactorial COX Regression Analysis of Risk Factors Impacting Patient Mortality

Covariate regression analysis was performed on variables with a P <0.05 in the univariate Cox regression analysis. Only variables with a VIF <5 were included in the multifactorial Cox regression analysis model. These included age, sex, RHR, RR, MAP, cough, dyspnea, respiratory failure, heart failure, coronary heart disease, acute kidney injury, mechanical ventilation, COVID-19 clinical stage, WBC, Lym, CRP, IL-6, ALT, ALB, Glu, LDH, UN, UA, Na, K, eGFR, BNP, D-dimer, INR, pH, $P0_2/FiO_2$, BE, APACHE II, and SOFA.

The multifactorial Cox regression revealed that male gender (*HR* = 1.172, 95% *CI* [1.113–2.604], P = 0.014), a faster RHR (*HR* = 1.012, 95% *CI* [1.002–1.023], P = 0.020), dyspnea (*HR* = 1.971, 95% *CI* [1.282–3.029], P = 0.002), a low Lym count (*HR* = 0.032, 95% *CI* [0.001–0.743], P = 0.031), a high INR (*HR* = 1.512, 95% *CI* [1.260–1.815], P < 0.001), a high APACHE II score (*HR* = 1.056, 95% *CI* [1.029–1.082], P < 0.001), heart failure (*HR* = 1.575, 95% *CI* [1.087–2.281], P = 0.016), and a requirement for mechanical ventilation (*HR* = 2.001, 95% *CI* [1.283–3.122], P = 0.002) were risk factors for death (Tables 3 and 4).

Discussion

A total of 1139 COVID-19 patients were admitted to our hospital between December 1, 2022, and February 28, 2023, of whom 213 (18.7%) died. After applying the inclusion and exclusion criteria, 406 patients were identified as having COVID-19 and CKD, of whom 158 (38.9%) died. Multifactorial Cox regression analysis revealed that being male, having an increased RHR upon admission, experiencing dyspnea, having a low lym, high INR, high APACHE II score, heart failure, and a requirement for mechanical ventilation were all identified as risk factors for an increased risk of death.

A total of 1139 patients were diagnosed with COVID-19 in this study, of whom 406 (35.6%) had CKD. This is higher than the average prevalence observed in the general population, which is typically 9–12%.[2] This may be because CKD is a highly prevalent risk factor for COVID-19.[5] Infection is more common in older adults and men with diabetes mellitus and other immunosuppressive disorders.[13] The prevalence of CKD also increases with age, with approximately 38% of patients being >65 years.[2] Furthermore, uremia is associated with an impaired T-cell response, increasing susceptibility to viruses and reducing vaccine responsiveness. Some autoimmune CKD patients receive immunosuppressive drugs, further increasing their vulnerability to infections. It is worth noting that patients requiring dialysis tend to be older and weaker than other COVID-19 patient groups.[14] In the current study, the mean age of enrolled patients was 80.5 (67.0, 88.0) years and 73.4% were male. Hypertension and other comorbidities were present in 67.2% of patients and 39.2% had diabetes mellitus. In addition, 16.3% of the patients were treated with RRT. Based on these characteristics, it is understandable that a high proportion of patients had comorbid CKD.

A prospective study says,[15] the hazard ratios for elevated SCr and previous CKD were 4.07 (95% *CI*: 3.07–5.39) and 4.17 (95% *CI*: 3.08–5.66), respectively. Based on these findings, the authors recommended mandatory screening for a history of CKD and assessment of renal function upon triage of patients diagnosed with COVID-19. Uribarri et al[16] reported that a deterioration in renal function during hospitalization was an independent factor for in-hospital death. Patients with an estimated eGFR of 30–60 mL/min/1.73 m^2 had a 2-fold HIGHER risk of death (*HR* 2.205, 95% *CI*: 1.573–3.091), while COVID-19 patients with an eGFR <30mL/min/1.73 m^2 had a nearly 5-fold increased risk of in-hospital death (*HR* 4.925, 95% *CI*: 2.152–5.244, P<0.001). In the current study, COVID-19 patients with CKD had a significantly higher mortality rate than the overall mortality rate of COVID-19 patients (38.9% vs 18.7%, respectively). These findings are consistent with a study conducted by Pilgram et al[17] in which 32.2% of the patients with CKD died, in Gur E's study,[18] this percentage was 32.2%. The association between lower eGFR levels and higher mortality highlights the importance of renal function in COVID-19 patient survival. In addition, some studies indicate CKD is itself associated with a pro-inflammatory state.[19] Thus, it is probable that patients with both chronic renal impairment and COVID-19 are at higher risk for a strong cytokine storm, severe systemic inflammation, and hypercoagulation that contribute to AKI, serious illness, and death.

Angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine-type 2 (TMPRSS2) receptors aid SARS-CoV-2 entry into cells.[20] Increased ACE2 expression is associated with a higher risk of SARS-CoV-2 infection. The presence of the ACE2 gene on the X chromosome in males explains why 66–75% of severe cases are male and why the disease prognosis is worse among males. TMPRSS2 is also more highly expressed in men and is associated with elevated levels of androgen, contributing to a higher risk of severe disease.[21,22] A total of 73.5% of the current study population was male and male gender was identified as a risk factor for death (*HR* = 1.172, 95% *CI* [1.113–2.604], P = 0.014), which is consistent with the studies described above.

SARS-CoV-2 infection is linked to various abnormalities in the autonomic control of cardiovascular function. The virus can activate the sympathetic cardiovascular drive and attenuate vagal cardiac influences, leading to severe imbalances in the autonomic system, and worse clinical outcomes.[23] One of the primary clinical signs of these autonomic alterations is an elevated RHR, which often presents as resting tachycardia. In this study, the RHR was identified as a risk factor for patient mortality, independent of comorbidities and APACHE II scores. Similar to some studies,[24,25] Vanoli et al[24] also identified a negative correlation between heart rate values and the prognosis of hospitalized patients with

COVID-19. Higher heart rates were associated with a worse prognosis. However, there is limited research on the prognostic value of the resting heart rate of COVID-19 patients with CKD and existing studies have primarily relied on a single assessment of heart rate at admission. Thus, more research is needed to fully understand the value of heart rate in prognostic assessment.

Dyspnea, or shortness of breath, can be caused by a variety factors,[26] and can be a symptom of respiratory failure. In the current study, 38.9% of patients reported dyspnea upon admission, 49.5% of whom had respiratory failure. This may be an underestimate given that some older COVID-19 patients may be less sensitive to their symptoms, have cognitive deficits, or even exhibit asymptomatic hypoxia.[27] These factors can contribute to delayed treatment and impact patient prognosis. Shi et al[28] conducted a meta-analysis involving 2091 cases from 11 studies and found a significant association between dyspnea and high mortality among patients with COVID-19 (*OR* = 4.34, 95% *CI* [2.68–7.05], P < 0.001). Indeed, dyspnea (*HR* = 1.971, 95% *CI* [1.282–3.029], P = 0.002) was identified as a risk factor for death in COVID-19 patients with CKD, supporting the results of prior studies.

Lymphocytes, essential components of the immune system responsible for antigen memory and recognition, play a critical role in adaptive immunity.[29] SARS-CoV-2 infection is associated with varying degrees of lymphocyte depletion and the number of peripheral blood lymphocytes and their subpopulations is significantly correlated with the prognosis of critically ill patients.[29] CKD is also associated with oxidative stress, immune dysregulation, and lymphocytopenia,[30] and a reduction in lymphocytes is associated with poor prognosis among COVID-19 patients with CKD.[19,29,31] The current study also found a correlation between low lymphocyte count (*HR* = 0.032, 95% *CI* [0.001–0.743], P = 0.031) and increased mortality.

COVID-19 infection promotes the release of pro-inflammatory and pro-oxidative cytokines, leading to multi-organ damage and coagulation dysfunction.[32] Elevated levels of D-dimer and fibrin degradation products, along with prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) at the time of patient admission are prognostic risk factors for COVID-19 patients[33,34] Zinellu et al[35] conducted a meta-analysis involving 38 studies and 9771 COVID-19 patients that identified a correlation between prolonged INR values and COVID-19 severity. Prolonged INR and elevated D-dimer levels were shown to reliably diagnose COVID-19-related coagulation disorders and predict clinical outcomes. The current study also identified prolonged INR as a risk factor for CKD in COVID-19 patients.

The APACHE II score is a clinical measure of disease severity in adult intensive care unit (ICU) patients, helping to predict the risk of death with reliable power.[36,37] The current study also showed that the APACHE II score *(HR* = 1.056, 95% *CI* [1.029–1.082], P < 0.001) has a strong predictive role. This study also found that elderly patients with COVID-19 and CKD who require mechanical ventilation face difficulties in weaning off the ventilator and have an extremely high mortality rate, similar to the findings reported by Lim et al.[38]

There are several limitations to this study. It was conducted at a single tertiary care hospital, which primarily admitted patients with more severe cases of COVID-19 and CKD, This led to a lack of representation of patients with mild cases of COVID-19. Additionally, the overall age of the patients was skewed toward older individuals due to an overwhelming surge of infections at the hospital and the inadequacy of healthcare resources. The COVID-19 vaccination rate among enrolled patients was low. Based on the above factors, the patients in the study contributed to the high mortality rate. And this retrospective study relies on existing medical records for data collection, which inherently carries the potential for limitations stemming from variations in record completeness and accuracy. Furthermore, the scope of our findings is constrained by the sample size and the specific data sources utilized, which may not offer a comprehensive representation of the overall COVID-19 patient population with CKD. It will be necessary to combine the findings of this study with those from multicenter studies to obtain more accurate data on the clinical manifestations and prognosis of COVID-19 patients with CKD.

Conclusion

Patients with COVID-19 and CKD have a higher mortality rate. More severe staging of CKD is also associated with increased mortality and is shown to be a risk factor for severe COVID-19. Multifactorial Cox regression analysis identified several risk factors that influence the risk of death in these patients. These include being male, higher RHR upon admission, dyspnea, low lymphocyte count, high INR, high APACHE II score, heart failure, and the requirement for mechanical ventilation during infection.

Abbreviations

RHR, resting heart rate; RR, respiratory rate; MAP, mean arterial pressure; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; AKI, acute kidney injury; RRT, renal replacement therapy, HB, hemoglobin; WBC, white blood cell; Lym, lymphocyte count; PLT, platelets; CRP, C-reactive protein; IL-6, interleukin-6; ALT, alanine transferase; AST, aspartate transferase; TP, total protein; ALB, albumin; TB, total bilirubin; DB, direct bilirubin; LDH, lactate dehydrogenase; GLU, glucose; UN, urea nitrogen; SCR, serum creatinine; UA, uric acid; K, potassium; Na, sodium; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; Upro, urinary protein; INR, international normalized ratio; P02/FiO2, partial pressure of arterial blood oxygen /fluoro oxygen concentration; BE, base excess; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment.

Data Sharing Statement

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

Ethics Approval and Informed Consent

This study was reviewed by the Medical Ethics Committee of the General Hospital of the People's Liberation Army of China (No. S2023-777-03). The requirement for written informed consent was waived by this institution due to the retrospective nature of the study. Decisions letter of Ethics Committee covered patient data confidentiality and compliance with the Declaration of Helsinki.

Consent for Publication

Consent to publish statements should confirm that the details of any images, videos, recordings, etc can be published, and that the person(s) providing consent have been shown the article contents to be published.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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