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Kidney damage in COVID-19 patients with or without chronic kidney disease: Analysis of clinical characteristics and related risk factors

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COVID-19 poses more risk to patients who already suffer from other diseases, particularly respiratory disorder. In this study, we analyzed the clinical characteristics and related risk factors during hospitalization of COVID-19 patients admitted with kidney damage. A total of 102 COVID-19 patients with kidney damage [irrespective of their chronic kidney disease (CKD) history] during hospitalization were included in this study. The patients were divided into a core group and a group who developed critical illness or death. Clinical data included age, gender, length of hospitalization, clinical manifestations, medical history, hypersensitive C-reactive protein (hs-CRP), high serum creatinine, low cardiac troponin I (cTnI), and hemoglobin. Univariate and multivariate logistic regression models were used to analyze the risk factors of patients' outcome. Among the outcomes, 75 patients (73.53%) were cured, 27 (26.47%) developed to critical illness or death, 20 (19.61%) of them died. A total of 36 (4.26%) out of 845 COVID-19 patients, developed acute kidney injury (AKI). Decreased oxygen saturation, elevated hs-CRP, elevated serum creatinine, elevated cTnI, and anemia were related factors for COVID-19 patients who developed to critical illness or death ($P < 0.05$). Decreased oxygen saturation, elevated hs-CRP and anemia were not independent factors, but elevated serum creatinine and elevated cTnI were independent factors for COVID-19 patients who developed to critical illness or death ($P < 0.05$). Among COVID-19 patients with or without CKD but with kidney damage during hospitalization, patients with elevated serum creatinine and elevated TnI, more likely to developed critical illness or death.

Keywords: Acute kidney injury (AKI), Anemia, CKD, Hypersensitive C-reactive protein, Serum creatinine, Cardiac troponin I

Since December 2019, an outbreak of novel coronavirus pneumonia (Coronavirus disease 2019, COVID-19) has developed into a global pandemic which has been declared by the World Health

Organization on March 11, 2020¹. COVID-19 is caused by a novel, enveloped single-stranded RNA virus, and is the 7th known coronavirus in humans and belongs to the same phylogenetic family as the 2002 SARS and the 2012 MERS-CoV-2². Coronaviruses can be divided into four genera: α , β , γ and δ . There are six coronaviruses that cause disease in humans, including 229E and NL63 of the α -genus and OC43, HKU1, SARS-CoV and MERS-CoV of the β genus, however, the human coronavirus infection is mainly related to the respiratory, intestinal and nervous systems³. The SARS-CoV-2 possesses high pathogenicity and transmissibility, hence, has challenged the global healthcare system⁴.

While containment and mitigation measures have intensified across the world, and various pharmacologic compounds are being tested to work against the deadly COVID-19, however, lack of information has made the task more intricate². However, various epidemiological studies carried out in past helps in understanding transmission dynamics, mortality trends and various models that may provide subsequent measures to control virus transmission⁵. Furthermore, epidemiological data helps in identification of predictive factors, risk stratification, management of hospital resource and guide public health experts⁶. Along with epidemiological history, clinical features and pathogen detection methods are important in the diagnosis of COVID-19. Timely and accurate diagnosis is necessary to control the outbreak⁴.

There are reports on hospitalization of COVID-19 patients with comorbid conditions such as CVD, hypertension, CKD, diabetes mellitus (DM), etc. and their impact on the disease outcomes when compared to patients with subclinical or mild symptoms of COVID-19. A pooling data from six studies (n=1527) revealed that prevalence rates of hypertension, CVD, and DM of 17.1, 16.4 and 9.7%, respectively, in COVID-19 patients⁷. It has been seen that patients with COVID-19 disease with comorbidities such as hypertension or DM, are more likely to develop a more severe course and progression of the COVID-19 disease, and such patients should take all necessary precautions to avoid getting infected⁸. A meta analysis of available data has shown CKD seems to be

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associated with enhanced risk of severe COVID-19 infection, and shall be regarded as an important factor in future risk stratification models for COVID-19⁶. Among CKD patients, the markedly altered immune system and immuno-suppressed condition may predispose them to COVID-19 infection. Published data shows that risk for severe COVID-19 is 3-fold higher in CKD patients CVD⁹.

By early May, 2020, COVID-19 showed >4 million confirmed cases and 0.33 million fatalities from 214 countries with US in lead. People with respiratory disorders were more susceptible to COVID-19 who suffered multiple organ failure¹. The clinical manifestations and prognosis of different individuals after COVID-19 infection varied greatly. Studies have shown that patients with chronic kidney disease (CKD) have a worse prognosis after infection with COVID-19¹⁰ and the mortality rate of COVID-19 patients with acute kidney injury (AKI) was extremely high^{11,12}. At present, there are few studies on the clinical outcome and prognosis of COVID-19 patients of kidney damage with or without CKD. In the present study, we retrospectively analyzed the general condition of COVID-19 patients with kidney damage with or without CKD and the risk factors developing into critical illness or death thereby provide reference for the prognosis judgment and clinical treatment of COVID-19 patients with kidney damage.

Materials and Methods

Study design and participants

Data for this single-center, retrospective, observational study was obtained from the electronic medical records of HIS system of Wuhan No. 1 Hospital. A total of 845 patients were infected with SARS-CoV-2, among them 107 cases had kidney damage but with or without CKD during hospitalization from December 31, 2019 to March 20, 2020. Among all, 5 patients with incomplete laboratory data were excluded from the study. Statistical analysis was performed on the clinical data of 102 patients, and according to the outcome, the patients were divided into a cure group and a group of patients who developed critical illness or death.

The study was approved by the Institutional Ethics Board of Wuhan No.1 Hospital [No. (2020) 8]. Although the retrospective study was exempted from written informed consent, however, verbal consent obtained from all patients included in the study.

Diagnostic criteria

According to the New Coronavirus Pneumonia Diagnosis and Treatment Program (*Trial Version 7*) issued by the National Health Commission of the People's Republic of China, the diagnostic standard included:

Epidemiological history

(i) Patients who had history of travel or residence in Wuhan and surrounding areas or other communities with reported cases within 14 days before the onset; (ii) Had a history of contact with COVID-19 patients (positive nucleic acid test) within 14 days before onset; (iii) Had contacted patients with fever or respiratory symptoms from Wuhan and surrounding areas, or from communities with case reports within 14 days before onset; and (iv) Patients who are from clusters of disease;

Clinical manifestations

(i) Fever and/or respiratory symptoms; (ii) Pneumonia manifestations of COVID-19 in radiologic imaging; and (iii) Whether the total number of white blood cells/ lymphocyte was normal or decreased in the early stage of onset;

Etiology or serology

(i) Real-time fluorescent RT-PCR detects the positive nucleic acid of the COVID-19 coronavirus; (ii) Sequencing of viral genes, highly homologous to the known COVID-19 coronavirus; and (iii) Positive for serum novel coronavirus-specific IgM antibody and IgG antibody, or serum novel coronavirus-specific IgG antibody changed from negative to positive or the recovery period was 4 times or more higher than the acute period.

Suspected cases

In case of clear or non-clear epidemiological evidences, two and three clinical manifestations must be met, respectively. A suspected case with one of the etiological or serological evidence can be diagnosed easily for the disease. In this study, clinical outcome endpoint was monitored up to May 5, 2020.

Clinical classification

As per the established guidelines, the following criteria must be met to decide whether the case is mild, moderate, severe or critical type: *Mild type*: Patients with mild clinical symptoms but with no viral pneumonia manifestations on chest CT scans; *Moderate type*: Patients with fever, respiratory tract infections, other symptoms and have pneumonia manifestations on chest CT scans; *Severe type*: Patients with shortness of breath, respiratory rate

(RR) >30 breaths/min, oxygen saturation <93% at rest state, arterial blood oxygen partial pressure (PaO₂)/oxygen concentration (FiO₂) ≤300 mmHg (1.0 mmHg = 0.133 kPa). At high altitude (over 1000 meters above sea level), PaO₂/FiO₂ should be corrected according to the following formula:

$$PaO_2/FiO_2 \times \frac{\text{Atmospheric pressure (mmHg)}}{760}$$

Furthermore, pulmonary lesion progression >50% within 24–48 h on radiologic imaging were treated as severe cases. *Critical type*: Patients with episodes of respiratory failure requiring mechanical ventilation, presence of shock, and other organ failure that requires monitoring and treatment in the intensive care unit are treated as critical type.

As per established guidelines, CKD includes kidney damage or glomerular filtration rate of <60 mL/min/1.73 m², time >3 months. Besides, it includes abnormal kidney pathology or abnormal kidney damage markers in blood and urine and abnormal renal imaging examination. While as AKI has a diagnostic criteria of the 2012 KDIGO (Kidney Disease Global Outcomes) guidelines which includes: Blood creatinine increased by more than 26.5 μmol/L (0.3 mg/dL) within 48 h, increased blood creatinine > 1.5 times of the baseline, confirmed or speculated within 7 days; and urine output of <0.5 mL/(kg·h) for more than 6 h. Thus, a patient is diagnosed with AKI if one of the three above guidelines is met.

Data collection

Clinical data was retrospectively collected through the electronic medical record HIS system of Wuhan No. 1 Hospital, which includes age, gender, length of hospitalization, clinical manifestations, past medical history and laboratory examination results during hospitalization, such as value of hs -CRP, serum creatinine, cTnI and hemoglobin.

Statistical analysis

SPSS24.0 software was used for statistical description and analysis of the data. The measurement data conforming to the normal distribution was expressed by $\bar{x} \pm s$, and the independent sample *t*-test was used for comparison between groups. The measurement data of non-normal distribution was represented by the median *M* (*P*₂₅, *P*₇₅), and Mann-Whitney *U*-test was used for comparison between groups. Count data was expressed in frequency (%), and Pearson chi-square test was used for comparison between groups. Univariate and multivariate logistic regression analysis was used to analyze the related

factors of the 102 patients with COVID-19 outcomes (critical illness or death). The *P* <0.05 was considered statistically significant.

Results and Discussion

General situation

A total of 845 patients were diagnosed and were found to be infected with SARS-CoV-2, among them 91 patients had CKD while as 16 patients were non-CKD but had kidney damage during hospitalization. In 107 cases, 5 patients with incomplete laboratory data were excluded from the study. The statistical analysis outcomes for clinical data of 102 patients are presented by Fig. 1.

The median age of the 102 patients was 73.5 years (61 males and 41 females) with an average hospital stay of 25.74 days. Among them, 72 patients had hypertension (70.59%), 29 patients had diabetes (28.43%), 26 patients had cardiovascular disease (CVD) history (25.49%), 67 patients had fever (65.68%) and 21 patients (20.59%) had a degree of decline oxygen saturation. There were 75 patients (73.53%) with elevated hs-CRP, 58 patients (56.86%) with elevated serum creatinine, 33 patients (32.35%) with elevated cTnI, and 76 patients (74.51%) with anemia, 22 patients (21.56%) were mild and common confirmed COVID-19 cases, 2 cases (1.96%) developed to critical illness or death, 80 (78.43%) patients were severe and critical confirmed COVID-19 cases, and 25 cases (24.51%) developed critical

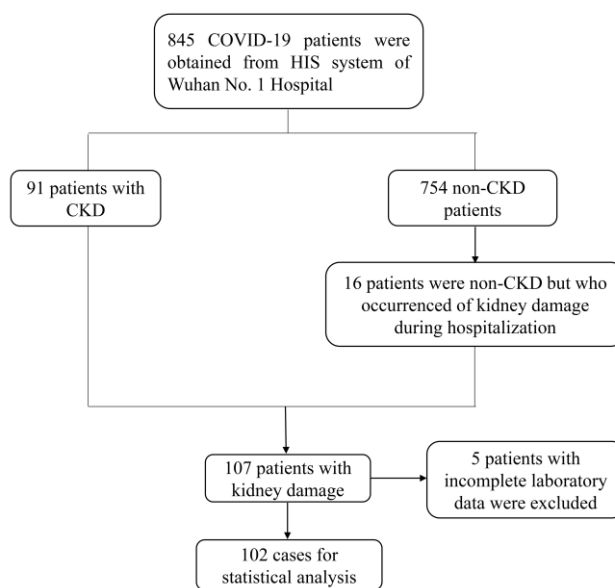


Fig. 1 — COVID-19 patients (102) with or without CKD but had kidney damage during hospitalization were included for statistical analysis

illness or death. Among the medical interventions, 75 patients (73.53%) got cured, however, 27 (26.47%) were developed critical illness or death, and 20 (19.61%) of them died (Table 1). Furthermore, out of 845 COVID-19 patients, a total of 36 (4.26%) developed AKI condition.

Univariate logistic regression analysis of factors associated with COVID-19 patients who developed critical illness or death

Univariate logistic regression analysis showed that decreased O₂ saturation, elevated hs-CRP, elevated serum creatinine, elevated cTnI, and anemia were related factors for COVID-19 patients who developed critical illness or death ($P < 0.05$). Specifically, the probability of COVID-19 patients with no decrease in O₂ saturation developed critical illness or death was 18.52%, and those with aerobic saturation decreased developed critical illness or death was 57.14% ($P < 0.001$); COVID-19 patients with no elevated in hs-CRP had a probability of 3.70% who developed critical illness or death, and those with elevated in hs-CRP had a probability of 34.67%, who developed to critical illness or death ($P = 0.002$). COVID-19 patients with no elevated serum creatinine had a probability of 6.82% who developed critical illness or death, and those with elevated serum creatinine had a probability of 41.38% to develop to critical illness or death ($P < 0.001$).

Furthermore, COVID-19 patients with no elevated cTnI, had a probability of 8.70% to develop to critical illness or death, and those with elevated cTnI had a

probability of 63.64% to develop to critical illness or death ($P < 0.001$). The COVID-19 patients without anemia had probability of 11.54% to develop critical illness or death, and those with anemia developed critical illness or death at rate of 31.58% ($P = 0.046$). Results of univariate logistic regression analysis are presented in Table 2.

Multivariate logistic regression analysis of factors associated with COVID-19 patients who developed critical illness or death

Factors with significant ($P < 0.05$) outcomes in univariate analysis were further subjected to multivariate logistic regression analysis. The results showed that decreased O₂ saturation, elevated hs-CRP and anemia were not independent factors for COVID-19 patients who developed critical illness or death ($P > 0.05$). However, elevated serum creatinine was independent factor development of critical illness or death ($P = 0.040$). Results suggested that the probability of developing critical illness or death among patients without elevated serum creatinine was 22.2% and those with elevated serum creatinine included COVID-19 patients of kidney damage with or without CKD, which means that elevated serum creatinine is an independent risk factor for development of critical illness or death.

Furthermore, elevated cTnI was also an independent factor that led to development of critical illness or death ($P = 0.001$). Probability of developing critical illness or death among patients without elevated cTnI was 12.1% as compared to patients with

Table 1 — Baseline characteristics of 102 patients with COVID-19 infection

Characteristics	Total (n=102)	Cure (n=75)	Developed critical illness or death (n=27)	Chi-square /Z	P- value
Age [year, <i>M</i> (P25, P75)]	73.50 (65.75, 82.00)	73 (65-81)	77 (70-86)	-1.897 ^{##}	0.058
Sex				1.705	0.192
Male <i>n</i> (%)	61 (59.80)	42 (41.18)	19 (18.62)		
Female <i>n</i> (%)	41 (40.19)	33 (32.35)	8 (7.84)		
Length of hospital stay (days, $\bar{x} \pm s$)	25.74±11.063	25.55±8.229	26.26±16.803	-0.286 [#]	0.776
Hypertension, <i>n</i> (%)	72 (70.59)	54 (52.94)	18 (17.65)	0.272	0.602
Diabetes, <i>n</i> (%)	29 (28.43)	22 (21.57)	7 (6.86)	0.113	0.736
Cardiovascular disease, <i>n</i> (%)	26 (25.49)	16 (15.69)	10 (9.80)	2.578	0.108
Fever, <i>n</i> (%)	67 (65.68)	51 (50.00)	16 (15.68)	0.673	0.412
Decreased oxygen saturation, <i>n</i> (%)	21 (20.59)	9 (8.82)	12 (11.77)	12.782*	<0.001
Elevated hs-CRP, <i>n</i> (%)	75 (73.53)	49 (48.04)	26 (25.49)	9.779*	0.002
Elevated serum creatinine, <i>n</i> (%)	58 (56.86)	34 (33.33)	24 (23.53)	15.354*	<0.001
Elevated cTnI, <i>n</i> (%)	33 (32.35)	12 (11.76)	21 (20.59)	34.620*	<0.001
Anemia, <i>n</i> (%)	76 (74.51)	52 (50.98)	24 (23.53)	3.997*	0.046
Clinical Classification, <i>n</i> (%)					
Mild	10 (9.80)	10 (9.80)	0	28.229*	<0.001
Moderate	12 (11.76)	10 (9.80)	2 (1.96)		
Severe	46 (45.10)	41 (40.20)	5 (4.90)		
Critical	34 (33.33)	14 (13.72)	20 (19.61)		

[* $P < 0.05$; [#] data was conforms to normal distribution by SK normality test, ^{##} data is non-normally distributed by SK normality test. hs-CRP: hypersensitive C-reactive protein, cTnI: cardiac troponin I]

Table 2 — Univariate logistic regression analysis of factors associated with COVID-19 patients who developed critical illness or death

Factors associated with COVID-19		Cure	Outcome Development of critical illness or death	% who developed critical illness or death	Chi-square /Z	P-value
Sex	Male	42	19	31.15	1.705	0.192
	Female	33	8	19.51		
Hypertension (yes vs. no)	No	21	9	30.00	0.272	0.602
	Yes	54	18	25.00		
Diabetes (yes vs. no)	No	53	20	27.40	0.113	0.736
	Yes	22	7	24.14		
Cardiovascular disease (yes vs. no)	No	59	17	22.37	2.578	0.108
	Yes	16	10	38.46		
Fever (yes vs. no)	No	24	11	31.43	0.673	0.412
	Yes	51	16	23.88		
Decreased oxygen saturation (yes vs. no)	No	66	15	18.52	12.782*	<0.001
	Yes	9	12	57.14		
Elevated hs-CRP (yes vs. no)	No	26	1	3.70	9.779*	0.002
	Yes	49	26	34.67		
Elevated serum creatinine (yes vs. no)	No	41	3	6.82	15.354*	<0.001
	Yes	34	24	41.38		
Elevated cTnI (yes vs. no)	No	63	6	8.70	34.620*	<0.001
	Yes	12	21	63.64		
Anemia (yes vs. no)	No	23	3	11.54	3.997*	0.046
	Yes	52	24	31.58		
Age ^{###}		73 (65^81)	77 (70^86)		-1.897	0.058
Length of hospital stay [#]		25.55±8.229	26.26±16.803		-0.286	0.776

[*P <0.05; # data was conforms to normal distribution by SK normality test, ### data is non-normally distributed by SK normality test. hs-CRP: hypersensitive C-reactive protein, cTnI: cardiac troponin I]

Table 3—Multivariate logistic regression analysis of factors associated with COVID-19 patients who developed critical illness or death

Factors associated with COVID-19	B	Standard Error	Wald statistics	Degrees of freedom	Significance	OR	95% confidence interval for OR		
							Lower limit	Upper limit	
Decreased oxygen saturation (yes vs. no)	no	-0.746	0.707	1.116	1	0.291	0.474	0.119	1.894
	yes	0					1		
Elevated hs-CRP (yes vs. no)	no	-1.087	1.133	0.921	1	0.337	0.337	0.037	3.105
	yes	0					1		
Elevated serum creatinine (yes vs. no)	no	-1.505	0.734	4.204	1	0.040*	0.222	0.053	0.936
	yes	0					1		
Elevated cTnI (yes vs. no)	no	-2.113	0.632	11.183	1	0.001*	0.121	0.035	0.417
	yes	0					1		
Anemia (yes vs. no)	no	-0.725	0.867	0.700	1	0.403	0.484	0.089	2.647
	yes	0					1		
Constant		1.435	0.621	5.340	1	0.021	4.200		

[*P <0.05. hs CRP: hypersensitive C-reactive protein; cTnI: cardiac troponin I]

elevated cTnI COVID-19 patients with kidney damage but with or without CKD. Based on the above conclusions, the CKD or non-CKD COVID-19 patients with kidney damage, the prediction accuracy is 73.5% if selected serum creatinine and cTnI were used to predict the outcome of the patients, indicating that the above conclusions have significant practice application value. Results of multivariate logistic regression analysis are presented in Table 3.

The virus responsible for COVID-19 was named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by World Health Organization (WHO) on February 11, 2020. The invasion of SARS-

CoV-2 into human cells is mainly mediated by cellular receptors angiotensin enzyme-2 (ACE2)¹³ and high expression of ACE2 in kidney suggests that it is the main target organ of SARS-CoV-2¹⁴. A number of studies have shown that patients with COVID-19 infection had hematuria, proteinuria and elevated serum creatinine on admission were significantly associated with poor outcomes. Patients who developed AKI had a higher mortality risk as compared to patients without AKI^{12,15}.

This study shows that the probability of developing critical illness or death in patients without elevated serum creatinine was 22.2%, as compared to CKD or

non-CKD COVID-19 patients with elevated serum creatinine having kidney damage. This means that elevated serum creatinine is an independent risk factor of developing critical illness or death. Thus, the kidney damage is of great significance for the screening, prevention, condition judgment and prognosis of the COVID-19 epidemic. Hence, it is advisable that more attention be paid to the COVID-19 patients with kidney damage when they are admitted to the hospitals. Kidney function must be closely monitored during the course of treatment and different measures of kidney protection be adopted according to the specific conditions of the COVID-19 patients.

AKI caused by coronavirus infection is not uncommon and the main manifestation is renal tubular injury. Studies indicated that the incidence of AKI was 6.7% in SARS-CoV and 75% in MERS-CoV infection patients, respectively¹⁶⁻¹⁸. Our results showed 36 of 845 COVID-19 patients (4.26%) developed to AKI as compared to previous report that showed the rate of AKI ranged widely between 0.5 - 29%. Such wide differences may be related to sample size and patient bias, and the overall incidence of AKI in COVID-19 patients seems to be lower than that in SARS and MERS cases. However, the exact incidence of AKI remains to be confirmed by larger sample data in the future. Continuous renal replacement therapy has been proved to be an effective in treatment of SARS-CoV in 2003 and MERS-CoV in 2012. SARS-CoV-2, like SARS-CoV and MERS-CoV, belongs to β -coronavirus¹⁹, which may have similarities in pathogenicity. Therefore, it can be speculated that if CRRT is used in time for progression of AKI among COVID-19 patients with kidney damage, the mortality rates might be significantly reduced.

Reports suggest that the mortality of COVID-19 patients with CVD and other risk factors is high^{20,21}. Our results showed that elevated cTnI, a sensitive myocardial injury marker, was an independent risk factor of development of critical illness or death among CKD or non-CKD COVID-19 patients having kidney damage. However, COVID-19 patients with or without CVD is not a related factor of developing critical illness or death. An increase in cTnI is an important clinical feature of critical patients with COVID-19²². SARS-CoV-2 infection can cause cytokine storm syndrome (CSS), which has a series of effects on the cardiovascular system, and can promote thrombosis and myocardial infarction. At the same

time, virus or inflammation itself can also directly lead to myocardial damage^{23,24}. Therefore, the monitoring of cTnI is very important for condition assessment and prognosis judgment of patients with COVID-19.

A study pointed out that the inflammation biomarkers in plasma samples of COVID-19 patients increased significantly, and the levels of related inflammatory factors in severe patients were significantly higher than those in mild patients²⁴, which suggested that there is a correlation between cytokine storm and the severity of infection. In this study, 63 cases (61.76%) of severe and critical patients and 12 cases (11.76%) of mild and common patients with elevated hs-CRP were found, which indicated that there was obvious inflammatory reaction among them, especially in the severe and critical cases. The results of univariate logistic regression analysis showed that the probability of developing critical illness or death was 3.70% in patients without increased hs-CRP, and 34.67% in patients with increased hs-CRP ($P = 0.002$), and the difference was statistically significant. However, multivariate logistic regression analysis outcomes showed that the increase of hs-CRP was not an independent factor for developing critical illness or death, which needs further studies. It is suggested more attention be paid to adopt anti-infection and anti-inflammatory regimes for COVID-19 patients with CSS.

Conclusion

Our study found that the elevated serum creatinine and cTnI were more likely to develop critical illness or death in CKD or non-CKD COVID-19 patients having kidney damage and the two biomarkers can help in predicting the outcomes of such patients. Moreover, patients with CKD had a higher probability of developing critical illness or death after AKI, and the inflammatory storm reaction was more obvious in severe and critical cases. Therefore, it is suggested that more attention should be paid to early intervention of basic kidney disease, monitoring of cardiovascular related indicators and anti-inflammatory treatment in COVID-19 patients in order to improve outcome and prognosis of the disease and reduce the mortality rate.

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Conflict of interest

The authors declare no conflict of interests.

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