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Original Article

Association of acute kidney injury and clinical outcomes in patients with COVID-19 in Shenzhen, China: a retrospective cohort study

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Abstract: Background: Acute kidney injury (AKI) was found in some patients with COVID-19 pneumonia and accompanied with poor outcomes. The objective of this study was to investigate the association of AKI with clinical outcomes in COVID-19 patients. Methods: In this cohort study, we reviewed electronic medical data from patients with COVID-19 in Shenzhen from January 11 to February 19, 2020. Clinical features and clinical outcomes in COVID-19 patients with and without AKI were analyzed. Further, we evaluated the association between AKI development and clinical outcomes. Results: In this study, 9.6% patients developed AKI during hospitalization. Those with AKI presented older age, severer pneumonia, more comorbidity and lower lymphocyte count. Totally, more patients (77.5%) had primary composite outcomes (intensive care unit (ICU) admission, use of high-flow nasal cannula (HFNC) and mechanical ventilation) in AKI group compared to non-AKI group (2.9%) during the observation period. The median length of stay (LOS) and ICU stay were longer among those with AKI. After adjusted for related covariates, AKI development was independently correlated with LOS (β (95% CI): 9.16 (3.87-14.46)), rather than primary outcomes (HR (95% CI): 1.34 (0.56-3.21)) in COVID-19 patients. Conclusions: The development of AKI was not one of the reasons for ICU admission, use of HFNC and mechanical ventilation, but a kind of manifestation of severe illness in COVID-19 hospitalized patients.

Keywords: Acute kidney injury, ICU admission, mechanical ventilation, length of stay, COVID-19

Introduction

Since December 2019, a novel coronavirus, designated as acute respiratory syndrome coronavirus 2 (SARS-CoV-2), induced pandemic rapidly around global [1-3]. The World Health Organization finally coined the disease as coronavirus disease 2019 (COVID-19). As of July 2020, this disease has spread 215 countries and regions and infected more than 10 million people, resulting in over 500,000 deaths worldwide [4]. Although the lungs were the main target organ of COVID-19, other organs (e.g. kidney) were also involved during the progression of the disease [5]. A recent report from China found that more than 40% patients had abnormal kidney function during their hospital stay [6]. An upswing in-hospital mortality (33.7%) was found in patients with elevated baseline serum creatinine. Patients developed with acute kidney injury (AKI) had increased the probability of other adverse events (e.g. cardiovascular events) [7]. Thus, determining the association of AKI occurrence and clinical outcomes in COVID-19 patients is helpful for early implementing preventative measures and improving the prognosis.

AKI developed in about 0.5% to 36.6% patients infected with SARS-CoV-2 from the reports of China and other western countries [8, 9]. Different incidences may be ascribed to the study

populations and the criteria of AKI. Among these studies diagnosed AKI was mostly based only on the changes of serum creatinine, which was probably underestimated the incidence in clinical practice. So, it was urgently warranted that adding the records of urine volume to monitor the development of AKI during the hospitalization, especially for the patients admitted to intensive care unit (ICU). Chao *et al.* found that patients developing AKI intended to ICU admission, prolonged length of stay (LOS) and the use of mechanical ventilation [10]. Patients undergoing these events above were usually surged expenditure and worse prognosis. In light of the enormous economic and disease burden of these patients, it is therefore vital to focus on the association of AKI with these outcomes in newly onset COVID-19 patients.

In this retrospective cohort study, we totally recruited 417 patients confirmed with COVID-19 in a designated local tertiary hospital in Shenzhen. The demographic, clinical features, laboratory findings and clinical outcomes were described in detail. Then, we analyzed to determine the association between AKI with clinical outcomes, including ICU admission, administration of high-flow nasal cannula (HFNC) and mechanical ventilation and LOS.

Patients and methods

Participants and data collection

In this study, we enrolled consecutive patients with COVID-19 admitted to the Third People's Hospital of Shenzhen from January 11 to February 19, 2020, which was the only designated hospital for the treatment of patients with COVID-19 in Shenzhen, China. The study was approved by the Ethics Committee of the Third People's Hospital of Shenzhen. The clinical outcomes of the patients were monitored up to April 24, 2020. The confirmed diagnosis of COVID-19 was based on the criteria issued by the Chinese National Health Commission. The demographical features, clinical characteristics and laboratory data were collected from electronic medical records. The clinical characteristics were mainly consisted of the types of COVID-19 pneumonia, blood pressure and comorbidities. The laboratory investigation included blood routine indices, liver, myocardial, coagulation and kidney function tests and blood gas analysis. Besides these, the levels of serum creatinine and urine output were monitored intermittently during hospitalization. The thresholds of these biochemical parameters were set by laboratory medicine in hospital.

The primary composite outcome was ICU admission, the use of high-flow nasal cannula oxygen therapy and mechanical ventilation. These outcomes were also applied in H7N9 infection to assess the severity of infectious disease [11]. The secondary outcomes were the duration of ICU stay and LOS during follow up.

Definitions

The severity of COVID-19 patients was staged into four types: mild, moderate, severe and critical severe, according to the guidelines for diagnosis and treatment of COVID-19 issued by Chinese National Health Commission (trial fifth edition). AKI was defined as the 2012 Kidney Disease: Improving Global Outcomes criterion [12]. The urine output was recorded as 24 hours for the sake of convenience in clinical practice. Simultaneously, patients with urine output reached the criteria just on the first day of hospitalization were designated as non-AKI because of uncertain of record time. The baseline Scr was the first value after admission. The stages of AKI were classified using the Acute Kidney Injury Network criteria [13].

Statistical analyses

Continuous variables were presented as mean ± standard deviation or median (interquartile range); categorical variables were performed as percentages in the descriptive data. Independent samples t test and Wilcoxon rank-sum test were used to compare means and median between groups, respectively. Rate comparisons were expressed by chi-square test or Fisher's exact test as appropriate. The missing data were used multiple imputation when the missing percentage less to 20%. The cumulative rates of AKI and primary composite outcomes were calculated using the Kaplan-Meier method. The log-rank test was used to compare the cumulative rates of composite out-

Table 1. Demographical and clinical features of patients with COVID-19

Variables	All (n = 417)	AKI (n = 40)	Non-AKI (n = 377)	*P* value	Missing
Age, yr	45.2 ± 17.7	60.1 ± 12.5	43.7 ± 17.4	< 0.001	0
Male	198 (47.3)	26 (65.0)	172 (45.6)	0.020	0
Days from illness onset to admission, d	3 (1-6)	4 (2-8)	3 (1-5)	0.026	0
The COVID-19 type of admission				< 0.001	0
Mild	39 (9.4)	1 (2.5)	38 (10.1)		
Moderate	351 (84.2)	25 (62.5)	326 (86.5)		
Severe	23 (5.5)	11 (27.5)	12 (3.2)		
Critical	4 (1.0)	3 (7.5)	1 (0.3)		
The severest COVID-19 type during hospitalization				< 0.001	0
Mild	16 (3.8)	0 (0.0)	16 (4.2)		
Moderate	309 (74.1)	5 (12.5)	304 (80.6)		
Severe	53 (12.7)	7 (17.5)	46 (12.2)		
Critical	39 (9.4)	28 (70.0)	11 (2.9)		
Fever on admission	277 (66.4)	30 (75.0)	247 (65.5)	0.227	3
Systolic blood pressure, mmHg	125 (116-137)	136 (125-144)	125 (115-136)	0.159	11
Diastolic blood pressure, mmHg	80 (74-88)	81 (77-89)	80 (73-88)	0.999	11
BMI (kg/m^2)	23.1 (21.0-25.4)	25.6 (22.6-27.5)	22.9 (20.8-25.1)	0.403	3
Any Comorbidity	100 (24.0)	19 (47.5)	81 (21.5)	< 0.001	9
COPD	16 (3.8)	5 (12.5)	11 (2.9)	0.003	9
Hypertension	55 (13.2)	15 (37.5)	40 (10.6)	< 0.001	0
Diabetes	19 (4.6)	5 (12.5)	14 (3.7)	0.011	0
Coronary heart disease	26 (6.2)	10 (25.0)	16 (4.2)	< 0.001	0
Cerebrovascular disease	3 (0.7)	1 (2.5)	2 (0.5)	0.161	0
Chronic liver disease	13 (3.1)	1 (2.5)	12 (3.2)	0.813	9
Tumor	6 (1.4)	0 (0.0)	6 (1.6)	0.438	9
In-hospital mortality	3 (0.7)	3 (100)	0 (0.0)	< 0.001	0

AKI, acute kidney injury; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

comes over time between AKI and non-AKI group. The association of AKI and primary composite outcomes was determined by Cox proportional hazard regression analysis, respectively. In multivariable regression model, covariates were age, gender, the severest type of disease during hospitalization, any comorbidities and lymphocyte count. Statistical analyses were used the SAS software (version 9.4, SAS Institute, Cary, NC).

Results

Demographical and clinical features

In total, 417 patients with confirmed COVID-19 were admitted to the Third People's Hospital of Shenzhen. Among these patients, the mean age of patients was 47.3 years and 47.3% (26 of 417) patients was male (**Table 1**). 6.4% patients were severe and critical cases at admission and the percentage increased to 21.1% during the hospitalization. 24.0% patients were recorded to have at least one kind of comorbidity. Forty patients (9.6%) were diagnosed as having AKI during hospitalization. The median time from admission to the development of AKI was 5 days (range, 2-11 days, **Figure 1**). Those patients with AKI were older, male-preponderant and were more severely illness compared with those without AKI. The percentage of patients fulfilled with the admission diagnoses of severe and critical case was sharply increased from 35.0% to 87.5% in AKI during follow-up. Meanwhile, patients with AKI were more likely to have comorbidity than patients without AKI (47.5 *vs.* 21.5%, $P < 0.001$). All three death cases occurred in AKI group, the median time to death was 32 days (range, 29-34 days).

Laboratory findings

Among the 417 patients infected with COVID-19, both lymphocyte and platelet counts were

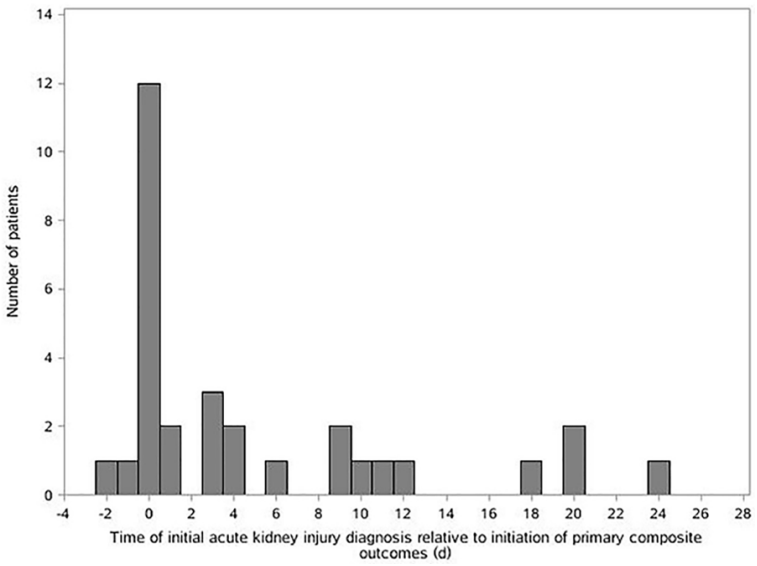

Figure 1. The frequency distribution of AKI diagnosis relative to time of primary composite outcomes in COVID-19 patients. The median of initial AKI diagnosis relative to initiation of primary composite outcomes 0 (IQR: 1-9) days. Of these who occurred AKI and primary composite events (n = 31), 38.7% patients happened AKI and primary outcome events at the same day. 54.8% and 6.5% patients developed AKI after and before primary outcome events.

significantly declined, especially in those with AKI (**Table 2**). In addition, the proportions of cases with abnormal liver, coagulation and myocardial functions were much higher in patients with AKI patients ($P < 0.05$). From the first kidney function test after admission, patients with AKI demonstrated apparently higher Scr, blood urea nitrogen, β_2-microglobulin and cystatin C levels. Besides, more than half patients presented higher erythrocyte sedimentation rate and high-sensitivity C-reactive protein level, which was particularly higher in AKI patients (95% *vs.* 69.5%, $P < 0.001$; 87.5% *vs.* 51.2%, $P < 0.001$).

Primary and secondary outcomes

Totally 42 patients occurred primary composite outcomes (either admission ICU, use of HFNC or mechanical ventilation) during the observation period. The incidence of primary composite outcome in AKI group was nearly 25 times as high as the non-AKI group, especially in the use of mechanical ventilation (62.5% *vs.* 2.7%, $p < 0.001$, **Table 3**). Furthermore, the severer AKI stage was usually accompanied with higher percentage of primary composite events (Supplementary Table 1). **Figure 1** shows the time sequence of AKI and primary composite outcomes during follow-up period. Of patients who had AKI and primary outcomes, 38.7% (12/31) had the onset of AKI within one day of primary outcome events. 54.8% (17/31) patients had AKI after primary endpoint events. The median time from initial AKI to primary outcomes was 0 (IQR: 1-9) days. The baseline characteristics of AKI 1 (AKI occurred before the primary composite events or at the same time) and AKI 2 (AKI occurred after the primary composite events patients) were presented in Supplementary Table 2.

As for the secondary outcomes, median of the LOS and ICU stay were 28 days and 11 days in all COVID-19 patients, respectively. LOS was significantly longer among AKI patients. However, there were no significant difference of ICU stay, duration of HFNC, invasive mechanical ventilation (IMV) and non-invasive mechanical ventilation between those two groups. The LOS, ICU stay and duration of IMV were much longer when patients developed severer AKI (**Table 3**).

Cumulative incidence of AKI and primary outcomes

Because the onset of AKI was usually acute and duration was short, we examined the relatively short-term outcomes of development of AKI (e.g. 28 days). Thirty-eight (9.1%) AKI cases were identified after admission 28 days. The cumulative risk curve of developing AKI in this cohort study is shown in **Figure 2**. Over 30 AKI cases (78.9%) were appeared in the first 9 days after admission. **Figure 3** presents the cumulative risk of primary composite outcomes between AKI and non-AKI group. Overall, there was distinct difference of increasing trend between these two groups. The cumulative incidence of primary composite outcomes (73.7%) in patients developed AKI was increased sharply at the beginning 9 days, whereas the proportion in patients without AKI was just 2.4%.

Table 2. Laboratory data of patients with COVID-19 on admission

Variables	All	AKI	Non-AKI	*P* value	Missing
Blood cell counts					
White blood cells ($\times 10^9$/L)	5.0 ± 1.9	5.0 ± 2.0	5.0 ± 1.9	0.934	80
Lymphocyte ($\times 10^9$/L)	1.5 ± 0.7	1.0 ± 0.4	1.5 ± 0.8	< 0.001	70
Hemoglobin, g/L	138 ± 16	139 ± 18	138 ± 16	0.666	80
Platelet ($\times 10^9$/L)	189 ± 59	164 ± 54	192 ± 58	0.004	80
Liver functional indices					
AST > 40 U/L	90 (21.6)	20 (50.0)	70 (18.6)	< 0.001	119
ALT > 40 U/L	60 (14.4)	11 (27.5)	49 (13.0)	0.013	84
Total bilirubin > 20 mmol/L	29 (7.0)	5 (12.5)	24 (6.4)	0.180	115
Albumin < 35 g/L	5 (1.2)	5 (100.0)	0 (0.0)	< 0.001	137
Myocardial functional indices					
Creatinine kinase > 60 U/L	87 (20.9)	13 (32.5)	74 (19.6)	0.057	75
CK-MB > 18 U/L	1 (0.2)	1 (2.5)	0 (0.0)	0.096	311
D-dimer > 0.5 mg/L	56 (13.4)	20 (50.0)	36 (9.5)	< 0.001	282
cTnI > 1.5 ng/mL	132 (31.7)	30 (75.0)	102 (27.1)	< 0.001	278
Coagulation functional indices					
PT > 14.5 s	3 (0.7)	0 (0.0)	3 (0.8)	1.000	281
APTT > 42 s	15 (3.6)	6 (15.0)	9 (2.4)	0.001	282
Blood Electrolytes					
Sodium	138 ± 3.0	139 ± 2.7	138 ± 3.0	0.111	35
Potassium	3.9 ± 0.4	3.9 ± 0.4	3.9 ± 0.4	0.474	35
Blood gas analysis					
pH	7.42 ± 0.03	7.43 ± 0.04	7.42 ± 0.03	0.571	102
PCO_2, mmHg	26.0 (24.5-28.6)	23.3 (22.9-26.1)	26.3 (24.6-28.6)	0.012	308
PO_2, mmHg	96.0 (82.2-110.7)	99.0 (87.0-114.4)	95.3 (82.0-110.4)	0.210	96
Oxygenation index, < 300 mmHg	72 (17.3)	10 (25.0)	62 (16.5)	0.174	100
Kidney function					
Creatinine, umol/L	63.0 (52.0-77.0)	68.5 (54.5-96.5)	62 (52-76)	0.024	2
BUN, mmol/L	3.91 (3.18-4.80)	5.43 (3.69-6.51)	3.84 (3.17-4.67)	< 0.001	2
β_2-MG, umol/L	2.94 (2.32-3.56)	3.76 (2.77-4.42)	2.89 (2.31-3.43)	< 0.001	77
CysC, mg/L	0.79 (0.67-0.92)	1.04 (0.86-1.21)	0.77 (0.68-0.89)	< 0.001	77
Inflammation-related indices					
ESR > 15 mm/h	300 (71.9)	38 (95.0)	262 (69.5)	< 0.001	119
High-sensitivity C-reactive protein > 10 mg/L	228 (54.7)	35 (87.5)	193 (51.2)	< 0.001	84
Procalcitonin > 0.5 ng/mL	17 (4.1)	4 (10.0)	13 (3.5)	0.046	115
LDH, U/L	311 ± 205	492 ± 359	292 ± 171	0.001	137

AKI, acute kidney injury; AST, aspartate transaminase; ALT, alanine transaminase; CK-MB, creatine kinase isoenzyme MB; cTnI, cardiac troponin I; PT, prothrombin time; APTT, activated partial thromboplastin time; BUN, blood urea nitrogen; β_2-MG, β_2-microglobulin; CysC, cystatin C; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase.

Association of AKI with primary and secondary outcomes

On invariable analysis, AKI development had nearly 32-fold hazard odds (95% CI, 16.27 to 65.04) of occurrence of primary adverse outcomes in Cox proportion hazard regression. AKI was still positively associated with primary outcomes (HR (95% CI): 2.40 (1.09-5.31)) after adjusted for age, sex, the severest type of disease, any comorbidity and lymphocyte count (**Table 4**). After excluded the cases that AKI developed after primary outcomes, the independent association between AKI and primary events was absent (HR (95% CI): 1.34 (0.56-3.21)). Additionally, no interaction was found between AKI and age or sex, so we did not further stratify by age or sex in regression analysis (*p* for interaction = 0.057, 0.807).

During follow up, patients with AKI had 1.7-folds LOS compared with non-AKI patients,

Table 3. Primary and secondary outcomes in patients with COVID-19

Outcomes	All	AKI	Non-AKI	*P* value	Missing
Primary outcomes					
Composite	42 (10.1)	31 (77.5)	11 (2.9)	< 0.001	0
Admission to ICU	34 (8.2)	26 (65.0)	8 (2.1)	< 0.001	0
HFNC	26 (6.2)	19 (47.5)	7 (1.9)	< 0.001	0
Any administration of mechanical ventilation	35 (8.4)	25 (62.5)	10 (2.7)	< 0.001	0
IMV	17 (4.1)	15 (37.5)	2 (0.5)	< 0.001	0
NIV	33 (7.9)	23 (57.5)	10 (2.7)	< 0.001	0
Secondary outcomes					
Length of stay, d	28 (15-28)	34 (21-54)	20 (15-26)	< 0.001	8
ICU stay, d	11 (5-26)	15 (6-32)	6.5 (4.5-11.0)	0.084	3
Duration of HFNC, d	2 (1-6)	2 (1-5)	2 (1-6)	0.848	0
Duration of IMV, d	17 (10-23)	17 (10-28)	8 (6-10)	0.073	0
Duration of NIV, d	5 (3-7)	5 (3-7)	7 (5-7)	0.299	0

AKI, acute kidney injury; IMV, invasive mechanical ventilation; NIV, non-invasive mechanical ventilation; HFNC, high-flow nasal cannula; ICU, intensive care unit.

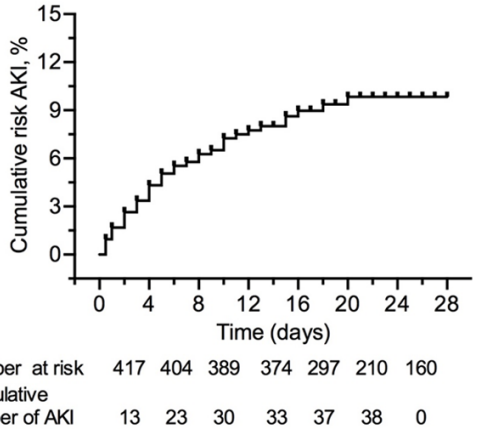

Figure 2. Cumulative incidence of acute kidney injury of patients with COVID-19. AKI, acute kidney injury.

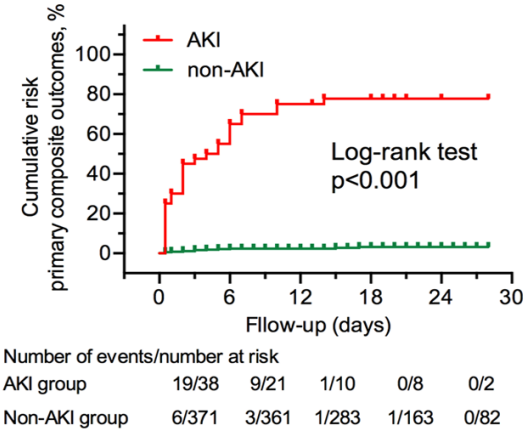

Figure 3. Time-dependent risk of reaching to the composite endpoints between patients with (red curve) or without AKI (green curve). AKI, acute kidney injury.

respectively. **Table 5** shows the results of the invariable and multivariable linear regression analysis of AKI associated with LOS. The development of AKI after admission prolonged LOS both in invariable (β (95% CI): 19.71 (15.37-24.05), $p < 0.001$) and multivariable (β (95% CI): 9.16 (3.87-14.46), $p < 0.001$) results.

Sensitivity analysis

To further ascertain the association between AKI with primary outcomes, we made serial sensitivity analyses in different condition. Based on only the changes in serum creatinine levels or urine output, 13 and 32 cases were identified as AKI during hospitalization, respectively. AKI occurring during hospitalization was not associated with primary composite outcomes in patients diagnosed AKI with only urine output (HR (95% CI): 2.11 (0.97-4.59)) rather than with serum creatinine levels (HR (95% CI): 0.90 (0.97-4.59), Supplementary Table 3). Before multiple imputation, AKI remained increased nearly 2-folds risk of reaching primary composite outcomes.

Discussion

COVID-19 is a new contagious disease already caused global pandemic with high morbidity.

Table 4. Cox regression analysis for association of AKI with primary composite outcomes of patients with COVID-19 at different conditions[1]

AKI	Primary composite outcomes		Primary composite outcomes 1	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Model 1[a]	32.53 (16.27-65.04)	< 0.001	16.98 (7.82-36.86)	< 0.001
Model 2[b]	19.00 (8.94-40.38)	< 0.001	9.28 (3.99-21.54)	< 0.001
Model 3[c]	2.40 (1.09-5.31)	0.030	1.34 (0.56-3.21)	0.506

[1]Primary composite outcomes 1, only recognized the cases that AKI occurred before the primary composite events or at the same time as positive cases, the rest cases were negative cases. [a]Univariable regression analysis; [b]adjusted for age and sex; [c]adjusted for age, sex, the severest type of admission, any comorbidity, and lymphocyte count. AKI, acute kidney injury.

Table 5. Linear regression analysis for association of AKI with length of stay in patients with COVID-19

AKI	β	95% CI	*P*-value
Length of stay			
Model 1[a]	19.71	15.37-24.05	< 0.001
Model 2[b]	17.94	13.45-22.43	< 0.001
Model 3[c]	9.16	3.87-14.46	< 0.001

[a]Univariable linear regression analysis; [b]adjusted for age and sex; [c]adjusted for age, sex, the severest type of admission, any comorbidity, and lymphocyte count. AKI, acute kidney injury.

Multiple studies found that many other organs were often affected including the kidneys rather than lung. More than 75.4% patients with SARS-CoV-2 had evidence of renal abnormalities, which was consistent with the findings in patients with other critical illness [14, 15]. Although the incidence of AKI varied greatly among different studies related to COVID-19, they all found that the occurrence of AKI and the stage of AKI were closely related to poor prognosis [9, 16, 17]. It has been reported that the development of AKI in COVID-19 patients increased the 29-folds odds of presence of composite primary end point, including ICU admission, use of invasive mechanical ventilation and in-hospital death, compared to the patients without the occurrence of AKI [2]. However, the causal relationship of AKI on the ICU admission, the administration of mechanical ventilation and length of stay in patients infected with SARS-CoV-2 was rare. Therefore, we focused on causal correlation of the incurrence of AKI with those adverse outcomes in this cohort study deeply.

As described, SARS-CoV-2 mainly facilitated the virus entry into host cells via angiotensin-converting enzyme-2 (ACE-2) [18]. The surface of kidney tubular cells abundantly distributed ACE-2, so the infection of SARS-CoV-2 may stimulate the local immune response and further induced occurrence of AKI. From the findings of SARS-CoV-2 infected postmortem revealed that varying degrees of acute tubular necrosis, luminal brush border sloughing and hyaline casts in kidney tissues, which was identical with the development of AKI [19]. The etiology of AKI in COVID-19 patients was also required fully elucidated. First, SARS-Cov 2 may exert destructive effects on kidney tissue via angiotensin converting enzyme 2-dependent pathway [20]. Also, the formation of thrombus in COVID-19 patients probably is another related factor could be attributed to AKI, which may reduce the blood perfusion of kidney and then cause the tubular cells necrosis [21]. Recently, it has been shown that SARS-Cov 2 could stimulate cytokine storm, which induce the release of circulating substances and then deposited in the kidneys [22]. The immune complexes located in kidneys may further caused varying degrees of acute tubular necrosis, including luminal brush border sloughing, casts formation and microthrombi [23]. Therefore, multiple biological mechanisms have reported during the process of COVID-19-induced AKI.

Several studies found that higher proportion of comorbidities in patients infected with SARS-Cov 2, including diabetes, COPD and other chronic diseases. Gao et al. illustrated the increase susceptibility to ischemia-induced renal dysfunction in diabetes animal model, manifesting that TNF-α and Toll-like receptor 4 mRNA involved this process [11]. Our recent study also demonstrated the independent association of diabetic mellitus and failed renal recovery in AKI patients used a cross-sectional survey in China (unpublished data). As for the COPD, a kind of common chronic lung disease, AKI occurred in 21% patients with acute exacerbation of COPD (AECOPD). What's more, AECOPD with AKI patients presented higher in-

hospital mortality, longer ICU stay and longer hospitalization. And, AKI might be a poor prognostic predictor of COPD patients' survival [24]. In total, patients with chronic comorbidities were susceptible with AKI patients. The susceptibility probably also found in patients with COVID-19.

The incidence of AKI was 9.6% according to the serum creatinine and urine output in our cohort study, which was slightly higher than the results from other perspective cohort study (5.1%, based only on the serum creatinine levels) [6]. In our analysis, AKI mostly developed in 9 days after admission that coincided with other two COVID-19 related studies [17, 25]. It should be noted that, Jamie et al. determined 53.6% AKI patients required invasive mechanic ventilation and the proportion in no AKI patients was only 3.5% [3]. The ratios in our cohort study were 57.5% and 2.7%, respectively. To consider more adverse events, we composited primary outcomes into analysis (ICU admission, administration of HFNC and mechanical ventilation) and the incidence of this composite outcomes was much higher in AKI patients compared with no AKI (77.5% vs. 10.8%). The time sequence and causal relationship between AKI and primary composite events in COVID-19 was not fully evaluated in previous studies. In our study, 93.5% (29/31) had the AKI development after primary outcome events or at the same day, so we could speculate that AKI development was a part of severe manifestations, rather than one of the reasons of primary outcome events.

The development of AKI was independently associated with prolonged the hospital stay (3.6 days) in patients undergone percutaneous coronary intervention in the United State [26]. This relation was also found in the COVID-19 patients group after adjusted for relative confounders. However, the difference in our analysis turned out to be even bigger (14 days), suggesting that more serious impact on SARS-CoV-2 infected patients induced by AKI occurrence. The other reason for this phenomenon might the more AKI patients with onset of mild or moderate on admission progressed to the severe cases during the hospitalization than non-AKI patients (80.0% vs. 12.3%). In critically ill children, the presence of AKI and severe AKI stages were persistently associated with longer ICU length of stay and mechanical ventilation [27], the results almost identical with our findings in COVID-19 patients. The possible pathophysiology reasons for this great difference were fluid imbalance, acid-basic disturbance and cytokine storm after infected with SARS-CoV-2 [28, 29], especially in patients occurred AKI. However, the underlying mechanism of AKI deteriorated prognosis and prolonged hospital stay need further investigation.

Although the study demonstrated the association of AKI with poor outcomes in COVID-19 patients, it still has several limitations in this single center cohort study. First, the number of patients in this research is limited, but we already enrolled 98.6% patients with COVID-19 in Shenzhen up to June 29, 2020. Second, repeated measurements of blood creatinine and urine volume records were not completed for all patients, which will cause the incidence of AKI to be underestimated. Third, AKI identified in this study should be more serious than the missed cases, so the overestimation of the strength of the exposure-outcome association cannot be ruled out. However, such limitations also presented in other similar studies, and this study has done better than other studies at this point. Fourth, we could not observe the long-term prognosis of all patients in this study that was constrained by the duration of follow-up. Fifth, although we adjusted for the relative covariates in Cox regression analyses, the unknown and immeasurable confounders might also play a role.

Conclusion

In summary, there was no apparently causal relationship between AKI development and ICU admission, use of HFNC and mechanical ventilation in COVID-19. AKI was just a kind of manifestation of severe illness during hospitalization.

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Disclosure of conflict of interest

None.

Abbreviations

AKI, acute kidney injury; ICU, intensive care unit; HFNC, high-flow nasal cannula; LOS, length of stay; SARS-CoV-2, acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; ACE-2, angiotensin-converting enzyme-2; BMI, body mass index; COPD, chronic obstructive pulmonary disease; AST, aspartate transaminase; ALT, alanine transamina; CK-MB, creatine kinase isoenzyme MB; cTnI, cardiac troponin I; PT, prothrombin time; APTT, activated partial thromboplastin time; BUN, blood urea nitrogen; β_2-MG, β_2-microglobulin; CysC, cystatin C; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; IMV, invasive mechanical ventilation; NIV, non-invasive mechanical ventilation.

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References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF and Tan W; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-733.

[2] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY and Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708-1720.

[3] Moran K. Task force for 2019-nCoV: epidemiologic characteristics of early cases with 2019 novel coronavirus (2019-nCoV) disease in Korea. Epidemiol Health 2020; 42: e2020007.

[4] Johns Hopkins University. Coronavirus 2019-nCoV global cases by Johns Hopkins CSSE. Available at: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. Accessed 30.06.2020.

[5] Wang T, Du Z, Zhu F, Cao Z, An Y, Gao Y and Jiang B. Comorbidities and multi-organ injuries in the treatment of COVID-19. Lancet 2020; 395: e52.

[6] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S and Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020; 97: 829-838.

[7] James MT, Bhatt M, Pannu N and Tonelli M. Long-term outcomes of acute kidney injury and strategies for improved care. Nat Rev Nephrol 2020; 16: 193-205.

[8] Liu YF, Zhang Z, Pan XL, Xing GL, Zhang Y, Liu ZS and Tu SH. The chronic kidney disease and acute kidney injury involvement in COVID-19 pandemic: a systematic review and meta-analysis. MedRxiv 2020.

[9] Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazzan AD, Fishbane S and Jhaveri KD; Northwell COVID-19 Research Consortium; Northwell Nephrology COVID-19 Research Consortium. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020; 98: 209-218.

[10] Chao CT, Hou CC, Wu VC, Lu HM, Wang CY, Chen L and Kao TW. The impact of dialysis-requiring acute kidney injury on long-term prognosis of patients requiring prolonged mechanical ventilation: nationwide population-based study. PLoS One 2012; 7: e50675.

[11] Gao HN, Lu HZ, Cao B, Du B, Shang H, Gan JH, Lu SH, Yang YD, Fang Q, Shen YZ, Xi XM, Gu Q, Zhou XM, Qu HP, Yan Z, Li FM, Zhao W, Gao ZC, Wang GF, Ruan LX, Wang WH, Ye J, Cao HF, Li XW, Zhang WH, Fang XC, He J, Liang WF, Xie J, Zeng M, Wu XZ, Li J, Xia Q, Jin ZC, Chen Q, Tang C, Zhang ZY, Hou BM, Feng ZX, Sheng JF, Zhong NS and Li LJ. Clinical findings in 111 cases of influenza A (H7N9) virus infection. N Engl J Med 2013; 368: 2277-2285.

[12] Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, Herzog CA, Joannidis M, Kribben A, Levey AS, MacLeod AM, Mehta RL, Murray PT, Naicker S, Opal SM, Schaefer F, Schetz M and Uchino S. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012; 2: 1-138.

[13] Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG and Levin A; Acute Kidney Injury Network. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11: R31.

[14] Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, Ma Z, Huang Y, Liu W, Yao Y, Zeng R and Xu G. Renal involvement and early prognosis in patients with COVID-19 pneumonia. J Am Soc Nephrol 2020; 31: 1157-1165.

[15] Han SS, Ahn SY, Ryu J, Baek SH, Chin HJ, Na KY, Chae DW and Kim S. Proteinuria and hematuria are associated with acute kidney injury and mortality in critically ill patients: a retrospective observational study. BMC Nephrol 2014; 15: 93.

[16] Li Z, Wu M, Yao JW, Guo J, Liao X, Song SJ, Li JL, Duan GJ, Zhou YX, Wu XJ, Zhou ZS, Wang TJ, Hu M, Chen XX, Fu Y, Lei C, Dong HL, Xu C, Hu YH, Han M, Zhou Y, Jia HB, Chen XW and JN Y. Caution on kidney dysfunctions of COVID-19 patients. MedRxiv 2020.

[17] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H and Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-1062.

[18] Letko M, Marzi A and Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol 2020; 5: 562-569.

[19] Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, Yi F, Yang HC, Fogo AB, Nie X and Zhang C. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020; 98: 219-227.

[20] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF and Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-273.

[21] Connors JM and Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020; 135: 2033-2040.

[22] Henderson LA, Canna SW, Schulert GS, Volpi S, Lee PY, Kernan KF, Caricchio R, Mahmud S, Hazen MM, Halyabar O, Hoyt KJ, Han J, Grom AA, Gattorno M, Ravelli A, De Benedetti F, Behrens EM, Cron RQ and Nigrovic PA. On the alert for cytokine storm: immunopathology in COVID-19. Arthritis Rheumatol 2020; 72: 1059-1063.

[23] Diao B, Wang CH, Wang RS, Feng ZQ, Tan YJ, Wang HM, Wang CS, Liu L, Llu Y, Liu YP, Wang G, Yuan ZL, Ren L, Wu YZ and Chen YW. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. MedRxiv 2020.

[24] Wan X, Chen D, Tan Y, Ma MQ, Zhang F, Liu ZH, Chen Y, Shao W and Cao CC. Incidence, risk factors, and prognostic implications of acute kidney injury in patients with acute exacerbation of COPD. Int J Chron Obstruct Pulmon Dis 2020; 15: 1085-1092.

[25] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S and Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475-481.

[26] Amin AP, McNeely C, Spertus JA, Bach RG, Frogge N, Lindner S, Jain S, Bradley SM, Wasfy JH, Goyal A, Maddox T, House JA, Kulkarni H and Masoudi FA. Incremental cost of acute kidney injury after percutaneous coronary intervention in the United States. Am J Cardiol 2020; 125: 29-33.

[27] Alkandari O, Eddington KA, Hyder A, Gauvin F, Ducruet T, Gottesman R, Phan V and Zappitelli M. Acute kidney injury is an independent risk factor for pediatric intensive care unit mortality, longer length of stay and prolonged mechanical ventilation in critically ill children: a two-center retrospective cohort study. Crit Care 2011; 15: R146.

[28] Matthay MA, Aldrich JM and Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. Lancet Respir Med 2020; 8: 433-434.

[29] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS and Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395: 1033-1034.

Supplementary Table 1. The clinical outcomes of COVID-19 patients stratified by AKI staging

Outcomes	AKI stage 1 (n=27)	AKI stage 2+3 (n=13)	*P* value
Primary outcomes			
Composite, n (%)	20 (74.1)	11 (84.6)	< 0.001
Admission to ICU, %	15 (55.6)	11 (84.6)	< 0.001
High-flow nasal cannula, %	12 (44.4)	8 (61.5)	< 0.001
Any administration of mechanical ventilation, %	15 (55.6)	11 (84.6)	< 0.001
IMV	7 (25.9)	7 (58.3)	< 0.001
NIV	13 (48.2)	11 (84.6)	< 0.001
Secondary endpoint events			
Length of stay, d	30 (20-49)	42 (33-81)	0.020
ICU stay, d	4.0 (3.0-5.5)	7 (4-15)	0.446
Duration of HFNC, d	1.5 (1.0-6.0)	1.2 (1.5-2)	0.872
Duration of IMV, d	11 (8-20)	23 (17-49)	0.084
Duration of NIV, d	5 (3-7)	5 (3-11)	0.579

ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, non-invasive mechanical ventilation; HFNC, high-flow nasal cannula.

Supplementary Table 2. Demographical and clinical features of patients with COVID-19 in different groups

Variables	Non-AKI (n=377)	AKI 1 (n=16)	AKI 2 (n=15)	*P* value[1]	*P* value[2]
Age, yr	43.7 ± 17.4	61.3 ± 10.8	62.6 ± 10.8	< 0.001	< 0.001
Male	172 (45.6)	10 (62.5)	12 (80.0)	0.185	0.009
Days from illness onset to admission, d	3 (1-5)	4.5 (2.0-8.0)	4 (2-8)	0.125	0.086
The COVID-19 type of admission				< 0.001	< 0.001
Mild	38 (10.1)	0 (0.0)	0 (0.0)		
Moderate	326 (86.5)	8 (50.0)	9 (60.0)		
Severe	12 (3.2)	7 (43.8)	4 (26.7)		
Critical	1 (0.3)	1 (6.3)	2 (13.3)		
The severest COVID-19 type during hospitalization				< 0.001	< 0.001
Mild	16 (4.2)	0 (0.0)	0 (0.0)		
Moderate	304 (80.6)	0 (0.0)	0 (0.0)		
Severe	46 (12.2)	3 (18.8)	1 (6.7)		
Critical	11 (2.9)	13 (81.3)	14 (93.3)		
Fever on admission	247 (65.5)	13 (81.3)	12 (80.0)	0.186	0.238
Systolic blood pressure, mmHg	125 (115-136)	129.0 (122.5-140.5)	138 (127-142)	0.182	0.004
Diastolic blood pressure, mmHg	80 (73-88)	80.0 (76.0-85.5)	85 (79-90)	0.801	0.108
BMI (kg/m^2)	22.9 (20.8-25.1)	24.2 (21.9-27.20)	26.6 (22.1-28.4)	0.116	0.001
Any Comorbidity	81 (21.5)	9 (56.3)	7 (46.7)	0.002	0.018
COPD	11 (2.9)	2 (12.5)	1 (6.7)	0.093	0.378
Hypertension	40 (10.6)	8 (50.0)	4 (26.7)	< 0.001	0.075
Diabetes	14 (3.7)	2 (12.5)	3 (20.0)	0.134	0.022
Coronary heart disease	16 (4.2)	6 (37.5)	4 (26.7)	< 0.001	0.005
Cerebrovascular disease	2 (0.5)	0 (0.0)	1 (6.7)	1.000	0.111
Chronic liver disease, n (%)	12 (3.2)	0 (0.0)	1 (6.7)	1.000	0.403
Tumor, n (%)	6 (1.6)	0 (0.0)	0 (0.0)	1.000	1.000
In-hospital mortality, n (%)	0 (0.0)	1 (6.3)	2 (13.3)	0.041	0.001

AKI 1, only recognized the cases that AKI occurred before the primary composite events or at the same time as AKI 1 cases; AKI 2, only recognized the cases that AKI occurred after the primary composite events as AKI 2 cases; [1]AKI 1 *vs.* non-AKI; [2]AKI 2 *vs.* non-AKI. AKI, acute kidney injury; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Supplementary Table 3. Sensitivity analysis on the association of AKI with composite endpoints in patients with COVID-19[1]

AKI	Sample size (events)	Cox regression		
		HR	95% CI	*P* value
Composite endpoints[A]				
Model[a]	417 (13)	0.90	0.36-2.20	0.808
Composite endpoints[B]				
Model[a]	417 (32)	2.11	0.97-4.59	0.060
Composite endpoints[C]				
Model[a]	338 (42)	2.04	0.88-4.71	0.096

[1]composite endpoints concluded ICU admission, any administration of mechanical ventilation and HFNC. [A]based on serum creatinine levels; [B]based on urine volume change; [C]before multiple imputation. [a]adjusted for age, sex, the severest type during hospitalization, any comorbidity, and lymphocyte count.