Research Article

Acute Kidney Injury in Patients with the Coronavirus Disease 2019: A Multicenter Study

Xiaoyang Cui^a Xin Yu^a Xiaojing Wu^a Linna Huang^a Ye Tian^a
Xu Huang^a Zeyu Zhang^a Zhenshun Cheng^b Qiang Guo^c Yi Zhang^a
Ying Cai^a Qingyuan Zhan^a

^aDepartment of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, Institute of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, PR China; ^bDepartment of Pulmonary and Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan, PR China;

^cDepartment of Critical Care Medicine, The First Affiliated Hospital of Soochow University, Suzhou, PR China

Keywords

Acute kidney injury · Coronavirus disease 2019 · Extrapulmonary complications

Abstract

Introduction: Severe acute respiratory viral infections are frequently accompanied by multiple organ dysfunction, including acute kidney injury (AKI). In December 2019, the coronavirus disease 2019 (COVID-19) outbreak began in Wuhan, Hubei Province, China, and rapidly spread worldwide. While diffuse alveolar damage and acute respiratory failure are the main features of COVID-19, other organs may be involved, and the incidence of AKI is not well described. We assessed the incidence and clinical characteristics of AKI in patients with laboratory-confirmed COVID-19 and its effects on clinical outcomes. **Methods:** We conducted a multicenter, retrospective, observational study of patients with COVID-19 admitted to two general hospitals in Wuhan from 5 January 2020 to 21 March 2020. Demographic data and information on organ dysfunction were collected daily. AKI was defined according to the KDIGO clinical practice guidelines. Early and late AKI were defined as AKI occurring within 72 h after admission or after 72 h, respectively. **Results:** Of the 116 patients, AKI developed in 21 (18.1%) patients. Among them, early and late AKI were found in 13 (11.2%) and 8 (6.9%) patients, respectively. Compared with patients without AKI, patients with AKI had more severe organ dysfunction, as indicated by a higher level of disease severity status, higher sequential organ failure assessment (SOFA) score on admission, an increased prevalence of shock, and a higher level of respiratory support. Patients with AKI had a higher SOFA score on admission (4.5 ± 2.1 vs. 2.8 ± 1.4 , OR 1.498, 95% CI 1.047–2.143) and greater hospital mortality (57.1% vs. 12.6%, OR 3.998,

Qingyuan Zhan
Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, Institute of Respiratory Medicine, China-Japan Friendship Hospital, No. 2 Yinghua East Road Chaoyang District, Beijing 100029 (PR China)
drzhanqy@163.com

95% CI 1.088–14.613) than patients without AKI in both the univariate and multivariate analyses. Patients with late AKI, but not those with early AKI, had a significantly prolonged length of stay (19.6 vs. 9.6 days, $p = 0.015$). **Conclusion:** Our findings show that admission SOFA score was an independent risk factor for AKI in COVID-19 patients, and patients with AKI had higher in-hospital mortality. Moreover, AKI development after 72 h of admission was related to prolonged hospitalization time.

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Introduction

In December 2019, an outbreak of a pneumonia of unknown cause occurred in Wuhan, Hubei Province, China. By 7 January 2020, Chinese scientists isolated a novel coronavirus, named SARS-CoV-2, previously known as 2019-nCoV [1], from human airway epithelial cells. On 30 January 2020, the World Health Organization (WHO) officially declared the coronavirus disease 2019 (COVID-19) epidemic as a public health emergency of international concern. The clinical symptoms of COVID-19 patients include fever, cough, and fatigue, and a small population of patients exhibit gastrointestinal symptoms. The elderly and people with underlying diseases are susceptible to infection and prone to serious outcomes, which may be associated with acute respiratory distress syndrome and cytokine storm [2, 3]. Previous studies have demonstrated that severe acute respiratory viral infections are accompanied by multi-organ dysfunction, which may contribute to death [4]. In particular, acute kidney injury (AKI) is a common, serious complication in critically ill patients, which may result in increased mortality, longer hospital stays, and higher medical costs [5]. Studies of patients with COVID-19 also demonstrated that, in addition to pneumonia, nonpulmonary organ impairment can be seen, including impairment of the liver, cardiovascular system, and kidneys. The aim of this study was to evaluate the incidence, risk factors, and impact on mortality of AKI in critically ill patients with COVID-19.

Materials and Methods

Study Design and Data Collection

We conducted a retrospective multicenter study enrolling two cohorts of adult inpatients (>18 years of age) from Zhongnan Hospital of Wuhan University and Tongji Hospital of Huazhong University of Science and Technology Sino-French New City Branch from 5 January 2020, (i.e., when the first patient was admitted) to 21 March 2020. The two hospitals, located in Wuhan, Hubei Province, are teaching and general hospitals. In early January, these two hospitals were designated to treat COVID-19 patients. We continuously enrolled patients diagnosed with COVID-19 by respiratory specimens using real-time RT-PCR methods.

Two physicians (Y.C. and Y.Z.) extracted the epidemiological, demographic, clinical, laboratory, treatment, and outcome data from the electronic medical records system using a standard case report form. After finishing the form, a researcher (Y.T.) adjudicated any differences in interpretation between the two primary reviewers. Patients without the laboratory confirmation of SARS-CoV-2 infection were excluded.

Laboratory Procedures

Throat swab specimens for SARS-CoV-2 RNA were detected by health institutions using real-time RT-PCR before or soon after admission to the hospital. All patients completed routine blood examinations, coagulation profiles, and serum biochemical tests (including

renal and liver function, and electrolytes) on admission or the next morning. Myocardial enzymes, creatine kinase, lactate dehydrogenase, interleukin-6, serum ferritin, erythrocyte sedimentation rate, and high-sensitivity C-reactive protein were tested according to the patient condition. The upper limit of normal for serum creatinine was 104 $\mu\text{mol/L}$. The frequency of examination was daily or second daily, as determined by the treating physician.

Definitions

Respiratory comorbidities included chronic obstructive lung disease or asthma, pleural effusion, tuberculosis infection or nontuberculous mycobacteria infection, bronchiectasis, and lung cancer. Cardiovascular comorbidities included coronary heart disease, hypertension, arrhythmia, heart failure, and pericardial effusion. The immunosuppressed state included the following: corticosteroid or immunosuppressant use within 90 days unrelated to COVID-19, seropositive for human immunodeficiency virus, malignant tumor, and patients receiving radiation therapy or chemotherapy for an underlying malignancy within 90 days. Fever was defined as an axillary temperature of at least 37.3 °C. AKI was diagnosed according to the KDIGO clinical practice guidelines [6]. If the patient had not previously had a history of chronic kidney disease (CKD) and the serum creatinine on admission was 26.5 $\mu\text{mol/L}$ more than the upper limit (104 $\mu\text{mol/L}$), the patient was considered to have AKI. The stage of AKI was determined using the peak serum creatinine level after AKI detection, with increases of 1.5–1.9, 2.0–2.9, and 3 or more times baseline being defined as AKI stage 1, 2, and 3, respectively.

Early AKI was defined as AKI occurring within 72 h of hospital admission. Patients who developed AKI later than 72 h after hospital admission were classified into the late AKI group. The illness severity of COVID-19 was defined according to the Chinese management guideline for COVID-19 (version 7.0) [7]. Each patient was assigned the sequential organ failure assessment (SOFA) score on admission [8]. Shock was defined as arterial systolic blood pressure less than 90 mm Hg, mean arterial pressure less than 60 mm Hg, or use of norepinephrine at any dosage to maintain systolic blood pressure at 90 mm Hg or more or mean arterial pressure at 60 mm Hg or more. Fluid balance was calculated as the difference between fluid input and fluid output. Fluid input included all fluids infused by intravenous or enteral routes. Fluid output included urine output, volume of fecal matter, and fluid loss from drains.

Statistical Analysis

Clinical data were compared between patients with and without AKI, as well as between patients with early and late AKI. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, and continuous variables were analyzed using Student's *t* test or the Mann-Whitney U test. After testing the distribution of continuous variables, normally distributed variables were presented as the mean $\pm$ SD, and non-normally distributed variables were presented as the median (interquartile range). Multivariate analysis was performed to evaluate risk factors for AKI and clinical outcomes, which were expressed as the odds ratio (OR) and its 95% confidence interval (CI). A two-sided *p* value less than 0.05 was considered statistically significant. SPSS 18.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

General Characteristics

During the observation period, 158 patients were continuously admitted to the two centers. Forty-two patients were excluded because of a clinical diagnosis without nucleic acid test results. The characteristics of the 116 patients included are shown in Table 1.

Table 1. Patient characteristics and clinical outcomes of patients with COVID-19

	AKI (n = 21)	Non-AKI (n = 95)	p value
<i>Prehospital information</i>			
Age, years	61.05±12.9	58.58±14.6	0.477
Sex (male)	12 (57.1)	54 (56.8)	0.122
BMI	23.9±6.5	23.1±2.5	0.449
Comorbidity			
Respiratory diseases	4 (19.0)	10 (10.5)	0.475
Cardiovascular disease	10 (47.6)	38 (40)	0.692
Hypertension	9 (42.9)	29 (30.5)	0.405
Diabetes mellitus	2 (9.5)	26 (27.4)	0.202
Chronic kidney disease	1 (4.8)	4 (4.2)	1
Time from symptom onset to hospital admission, days	10.81±12.30	10.44±7.85	0.894
Immunosuppressed	2 (9.5)	5 (5.3)	0.814
Antiviral use before admission to the hospital	8 (38)	45 (47.4)	0.596
<i>In-hospital situation</i>			
Symptoms			
Fever	21 (100)	78 (82.1)	0.062
Cough	17 (81)	62 (65.3)	0.163
Myalgia	5 (23.8)	24 (25.3)	0.889
Diarrhea	4 (19)	26 (27.4)	0.431
Laboratory findings			
WBC, ×10 ⁹ /L	6.88 (4.83–8.59)	5.43 (4.03–6.83)	0.448
LYM, ×10 ⁹ /L	0.77 (0.49–0.92)	0.83 (0.55–1.27)	0.224
CK, U/L	165.15 (70.75–1,004.5)	81.00 (47.75–160.00)	0.002*
NT-proBNP, pg/mL	471.5 (231.00–1,836.27)	253.0 (91.00–633.00)	0.683
D-Dimer, µg/L	0.53 (0.21–2.58)	0.53 (0.26–1.56)	0.912
hs-CRP, mg/L	57.50 (35.90–144.33)	57.90 (15.00–104.60)	0.500
ESR, mm/h	37.00 (13.75–73.25)	39.00 (22.00–60.00)	0.975
Ferritin, µg/L	515.40 (372.58–2,639.23)	618.40 (321.34–1,486.95)	0.669
IL-6, pg/mL	46.46 (12.20–89.04)	22.10 (5.88–52.18)	0.938
Disease severity status			
General	4 (19)	37 (38.9)	0.084
Severe	6 (28.6)	31 (32.6)	0.718
Critical	11 (52.4)	26 (27.4)	0.026*
SOFA score	4.5±2.1	2.8±1.4	0.002*
Respiratory support			
Ambient air	1 (4.8)	22 (23.2)	0.107
Nasal cannula	6 (28.6)	47 (49.5)	0.134
HFNC	3 (14.3)	6 (6.3)	0.433
NPPV	2 (9.5)	8 (8.4)	1
IPPV	6 (28.6)	7 (7.4)	0.016*
ECMO	3 (14)	4 (4.2)	0.056
Shock	10 (47.6)	24 (25.3)	0.042*
<i>Outcomes</i>			
Mortality	12 (57.1)	12 (12.6)	0.000*
Time from admission to death or discharge, days	14.06±9.12	16.97±9.64	0.243

Data are presented as mean ± SD, median (IQR), or n (%), as appropriate. WBC, white blood cell count; LYM, lymphocyte count; CK, creatine kinase; NT-proBNP, N-terminal B-type natriuretic peptide; hs-CRP, high-sensitive C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; HFNC, high-flow nasal cannula oxygen therapy; NPPV, noninvasive positive pressure ventilation; IPPV, invasive positive pressure ventilation; ECMO, extracorporeal membrane oxygenation. Antivirus medications included umifenovir, ganciclovir, interferon, lopinavir with ritonavir, oseltamivir, and ribavirin. * *p* < 0.05 was considered significant.

Table 2. Multivariate analysis of variables and outcomes associated with AKI in patients with COVID-19

	OR (95% CI)	p
SOFA score	1.498 (1.047–2.143)	0.027*
Mortality	3.988 (1.088–14.613)	0.037*
Critical		0.338
Shock		0.224
IPPV		0.795

* $p < 0.05$ was considered significant.

Of the 116 patients evaluated in this study, the mean age was 59 years, 55 (47.4%) were under 60 years of age, and 66 (56.9%) were male. Fourteen (12%) of them had underlying respiratory diseases (6 COPD or asthma, 2 pleura effusion, 3 tuberculosis or nontuberculous mycobacteria infection, 2 lung cancer, and 1 bronchiectasis), 48 (41.4%) had circulatory system diseases (14 coronary heart disease, 38 hypertension, 3 arrhythmia, 1 heart failure, and 1 pericardial effusion), 28 (24.1%) had diabetes mellitus, and 5 (4.3%) had CKD. The disease severity status of the patients was as follows: 48 (41.4%) general, 47 (40.5%) severe, and 20 (17.2%) critical. Twenty-three (19.8%) patients did not need oxygen therapy, 53 (45.7%) patients used nasal oxygen inhalation, and 9 (7.76%) patients needed high-flow nasal cannula oxygen therapy. Mechanical ventilation was used in 23 (19.8%) patients; among them, 10 patients needed noninvasive mechanical ventilation, and 13 patients needed invasive mechanical ventilation. Moreover, 7 (6%) of the 116 included patients needed extracorporeal membrane oxygenation (ECMO) support because of severe respiratory failure. Eighteen patients died, a mortality rate of 15.5%, and the median time from admission to discharge or death was 14 days (IQR 10–22).

Acute Kidney Injury

AKI developed in 21 (18.1%) of the 116 patients with COVID-19. The demographic information, prevalence of different comorbidities, time from onset to hospital admission, immunosuppressed state, and symptoms were not significantly different between AKI and non-AKI patients. Compared with patients without AKI, patients with AKI had higher creatine kinase (165.15 vs. 81 U/L, $p = 0.002$) and more severe organ dysfunction, as indicated by a higher level of disease severity status (critical: 52.4 vs. 27.4%, $p = 0.026$), higher SOFA score on admission (4.5 ± 2.1 vs. 2.8 ± 1.4 , $p = 0.002$), a greater presence of shock (47.6 vs. 25.3%, $p = 0.042$), and a higher level of respiratory support (mechanical ventilation: 38.1 vs. 15.8%, ECMO: 14 vs. 4.2%). Patients with AKI had higher hospital mortality than patients without AKI in both the univariate and multivariate analyses (57.1 vs. 12.6%, $p = 0.000$) (Table 2).

Early versus Late AKI

Early AKI was found in 13 patients (11.2% of all patients), and late AKI was found in 8 patients (6.9%) (Table 3).

A male predominance was more obvious in the early AKI group (69.2 vs. 37.5%, $p = 0.331$). The BMI of the late AKI patients was higher than that of early AKI patients, but the difference was not statistically significant (25.6 ± 3.43 vs. 22.5 ± 8.15 , $p = 0.326$). The comorbidities and laboratory findings were not different between the two groups. Regarding the disease severity status, the patients' condition in the early AKI group was worse than that in the late AKI group (critical: 61.5 vs. 37.5%, $p = 0.534$), they had a higher SOFA score on admission (5.00 ± 1.96 vs. 3.63 ± 2.07 , $p = 0.142$), and needed a higher level of respiratory

Table 3. Subgroup analysis of early and late AKI in patients with COVID-19

	Early AKI (<i>n</i> = 13)	Late AKI (<i>n</i> = 8)	<i>p</i> value
<i>Prehospital information</i>			
Age, years	60.69±14.19	61.63±11.30	0.877
Sex (male)	9 (69.2)	3 (37.5)	0.331
BMI	22.5±8.15	25.6±3.43	0.326
<i>Comorbidity</i>			
Respiratory diseases	2 (15.4)	2 (25)	1
Cardiovascular disease	7 (53.8)	3 (37.5)	0.781
Hypertension	6 (46.2)	3 (37.5)	1
Diabetes mellitus	1 (7.7)	1 (12.5)	1
Chronic kidney disease	0	1	
Immunosuppressed	2 (15.4)	0 (0)	0.505
Antiviral use before admission to the hospital	6 (46.2)	2 (25)	0.612
<i>In-hospital situation</i>			
<i>Laboratory findings</i>			
WBC, ×10 ⁹ /L	6.67 (5.04–12.99)	7.23 (3.97–7.87)	0.280
LYM, ×10 ⁹ /L	0.77 (0.42–0.88)	0.78 (0.54–0.99)	0.898
D-Dimer, µg/L	0.53 (0.28–2.89)	0.56 (0.19–2.74)	0.667
ESR, mm/h	35.00 (13.50–63.00)	66.00 (19.00–82.00)	0.387
IL-6, pg/mL	40.17 (7.64–73.43)	94.07 (31.92–169.35)	0.067
<i>Disease severity status</i>			
General	2 (15.4)	2 (25.0)	1
Severe	3 (33.3)	3 (37.5)	1
Critical	8 (61.5)	3 (37.5)	0.534
<i>Respiratory support</i>			
Ambient air	1 (7.7)	0 (0)	1
Nasal cannula	2 (15.4)	4 (50)	0.227
HFNC	1 (7.7)	2 (25)	0.647
NPPV	2 (15.4)	0 (0)	0.505
IPPV	5 (38.5)	1 (12.5)	0.434
ECMO	2 (15.4)	1 (12.5)	1
Shock	5 (38.5)	3 (37.5)	1
<i>Outcomes</i>			
Mortality	7 (53.8)	5 (62.5)	1.000
Time from admission to death or discharge, days	9.60±4.14	19.63±10.78	0.015*

Data are presented as mean ± SD, median (IQR), or *n* (%), as appropriate. WBC, White blood cell count; LYM, Lymphocyte count; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; HFNC, high-flow nasal cannula oxygen therapy; NPPV, noninvasive positive pressure ventilation; IPPV, invasive positive pressure ventilation; ECMO, extracorporeal membrane oxygenation. Antivirus medications included in umifenovir, ganciclovir, interferon, lopinavir with ritonavir, oseltamivir, and ribavirin.

* *p* < 0.05 was considered significant.

support (mechanical ventilation: 53.9 vs. 12.5%, ECMO: 15.4 vs. 12.5%). As for the severity stage of AKI between the two groups, the majority of patients in the early AKI group were in stage 1 (*n* = 9, 69.5%) whereas half of the patients in the late AKI group were in stage 3 (*n* = 4, 50%). The mean peak serum creatinine was similar in both groups (early vs. late AKI groups: 233 ± 170 vs. 204 ± 109 µmol/L, *p* = 0.66). Compared with patients with early AKI, patients with late AKI had a significantly prolonged hospital length of stay (19.63 ± 10.78 vs. 9.6 ± 4.14 days, *p* = 0.015) and higher mortality (62.5 vs. 53.8%, *p* = 1.000). Among the 13 patients with early AKI, 6 patients' renal function improved before discharge or death, while 7 patients' renal function did not improve.

Table 4. Fluid balance of AKI and non-AKI patients

	AKI	Non-AKI	<i>p</i>
Fluid balance, mL/24 h	457.2±123.6	182.1±78.9	0.07
Urine output, mL/kg/h	0.8±0.7	1.2±0.4	0.18

Data are presented as mean ± SD. Fluid balance was calculated as the difference between the daily fluid input and fluid output.. *p* < 0.05 was considered significant.

Fig. 1. Daily fluid balance of the AKI and non-AKI patients. Fluid balance was calculated as the difference between the daily fluid input and fluid output. Data are expressed as mean ± SEM.

Fluid Balance and AKI

In our study, 10 AKI patients and 14 non-AKI patients had daily fluid balance recorded. AKI patients had more fluid accumulation than non-AKI patients (457.2 ± 123.6 vs. 182.1 ± 78.9 mL/24 h, *p* = 0.07) and lesser urine output (0.8 ± 0.7 vs. 1.2 ± 0.4 mL/kg/h, *p* = 0.18) (Table 4; Fig. 1). This trend was more prominent in the early and late AKI subgroups. Late-onset AKI patients had significantly more fluid accumulation than early-onset AKI patients (-157.5 ± 278.9 vs. 769.4 ± 125.2 mL/24 h, *p* = 0.007) and more severe kidney damage (urine output: 1.0 ± 0.9 vs. 0.7 ± 0.5 mL/kg/h, *p* = 0.48) (Table 5; Fig. 2).

Discussion

The present study found an incidence of AKI of 18.1% among patients admitted with COVID-19 in Hubei Province, China. AKI was generally diagnosed in sicker patients. Most of the patients in the AKI group were critical (52.4%), had a higher admission SOFA score (4.5 ± 2.1), and had combined shock (47.6%), while in the non-AKI group only a quarter of patients were critical (27.4%), the mean admission SOFA score was 2.8 ± 1.4 , and the incidence of shock was significantly lower (25.3%). The incidence of AKI in COVID-19 patients varies in published studies. Huang et al. [3] reported 41 COVID-19 patients, among whom 10% had elevated creatinine (>133 μmol/L) on admission and 7% had AKI. For critically ill patients in the ICU, the incidence was 23%. Zhou et al. [2] found that AKI occurred in 15% of patients, of which 50% occurred in nonsurvivors and 1% occurred in survivors. A retrospective single-center study of 138 hospitalized patients in Zhongnan Hospital of Wuhan University from 1 January 2020 to 28 January 2020 indicated that the incidence of AKI was 3.6% in total patients and 8.3% in ICU patients [9]. As our study indicated, the admission SOFA score of the patients

Table 5. Fluid balance of early AKI and late AKI patients

	Early AKI	Late AKI	<i>p</i>
Fluid balance, mL/24 h	-157.5±278.9	769.4±125.2	0.007*
Urine output, mL/kg/h	1.0±0.9	0.7±0.5	0.48

Data are presented as mean ± SD. Fluid balance was calculated as the difference between the daily fluid input and fluid output. * *p* < 0.05 was considered significant.

Fig. 2. Daily fluid balance of the early AKI and late AKI patients. Fluid balance was calculated as the difference between the daily fluid input and fluid output. Data are expressed as mean ± SEM.

was an independent risk factor for AKI in COVID-19 patients. We speculated the fundamental reason for the different incidence of AKI in the studies was the difference in the severity of the patients included.

The reason why AKI occurs in COVID-19 patients may be, at least in part, related to the mechanism of SARS-CoV-2 entry into target cells. The first step in SARS-CoV-2 infection is to bind to the host cell receptor and enter the cells. Studies have verified that SARS-CoV-2 uses the SARS-CoV ACE2 receptor for entry [10, 11]. Therefore, cells with ACE2 expression, such as type II alveolar cells (AT2) in the lung, may act as target cells and may be susceptible to COVID-19 infection. However, it should be noted that ACE2 protein has abundant expression in many different cell types, such as respiratory epithelial cells, myocardial cells, renal tubular epithelial cells, urothelial cells, and gastrointestinal epithelial cells [12]. A clinical implication of this is that, in addition to the lungs, organs expressing ACE2 should be regarded as potentially susceptible to SARS-CoV-2 infection, which may explain the nonrespiratory symptoms observed in COVID-19 patients. Moreover, Farkash et al. [13] offered confirmatory evidence that direct renal infection occurs in the setting of AKI in COVID-19. They performed an autopsy on a single patient who died of COVID-19 and found viral particles in the renal tubular epithelium that were morphologically identical to SARS-CoV-2, and with viral arrays and other features of virus assembly which provided evidence of a direct infection of the kidney by SARS-CoV-2.

Our study revealed that admission SOFA score was independently associated with the development of AKI in COVID-19 patients. This result was consistent with that of a previous study on pandemic influenza A (H1N1) [14]. SOFA score indicates the level of organ dysfunction and illness severity [15], which accounts for its association with AKI in the present study. In our study, AKI patients had a significant higher mortality rate after adjusting for admission SOFA score, severity status, respiratory support method, and shock. A previous prospective

cohort study of 701 patients with COVID-19 also showed that AKI stage 1 (OR 1.90, 95% CI 0.76–4.76), stage 2 (OR 3.51, 95% CI 1.49–8.26), and stage 3 (OR 4.38, 95% CI 2.31–8.31) were independent risk factors for hospital death [16]. Similar phenomena were observed in SARS patients in 2003, and the mortality rate was significantly higher among patients with SARS and acute renal impairment than among those with SARS and no renal impairment (91.7 vs. 8.8%, $p < 0.0001$) [17]. Because of the high homology of SARS-CoV-2 and SARS-CoV, the results of this study were similar and consistent with the presentation of renal function injury in SARS.

Previous studies suggested that patients with early and late AKI had different prognosis and may have different pathogenesis [14, 18, 19]. In our subgroup analysis, we also found that the time of onset of AKI characterized two different populations. Patients with late AKI (onset 72 h after admission) had a higher mortality rate and significantly longer hospitalization time than patients with early AKI. This result is consistent with that presented in the previous study of the 2009 influenza A (H1N1) pandemic. Nin et al. [19] found that patients with early AKI had only slightly and insignificantly higher mortality rates than patients without AKI, whereas patients with late AKI had significantly higher mortality rates than either non-AKI or early AKI patients. This result may be due to early AKI probably being determined, to some extent, by direct cytopathic effects of the virus [10, 12, 20], virus-induced specific immunological effector mechanisms [17], virus-induced cytokines or mediator effects [21], and hypovolemic organ hypoperfusion, whereas late AKI generally appeared in combination with sepsis, multiple organ failure, and the use of nephrotoxic agents. In our study, 69.2% of patients in the early AKI group were in AKI stage 1, as opposed to 25% of patients in the late AKI group. This may be another reason for the better prognosis of the early-onset AKI group. However, we should also consider that most of the included patients had no prior baseline serum creatinine record. Therefore, the first serum creatinine level on admission was considered the baseline value. If the patient had no previous history of CKD and the serum creatinine on admission was 26.5 $\mu\text{mol/L}$ more than the upper limit (104 $\mu\text{mol/L}$), the patient was considered to have AKI. This may cause the severity of AKI to be underestimated.

In our study, AKI patients had a trend towards more fluid accumulation and lower urine output than non-AKI patients, with late-onset AKI patients having significantly more fluid accumulation than early-onset AKI patients. There is growing evidence that fluid administration beyond the correction of hypovolemia is associated with AKI [22], longer periods of hospital stay, increased mortality [23], organ dysfunction, and worse clinical outcomes [24]. However, the optimal hydration strategy for patients with COVID-19 cannot be determined from the present data.

Our research was conducted in the early stage of the outbreak in Wuhan, and it has several limitations. First, the two centers (Zhongnan Hospital of Wuhan University and Tongji Hospital of Huazhong University of Science and Technology Sino-French New City Branch) in our study were general and teaching hospitals and they were assigned responsibility by the government for the treatment of patients with severe COVID-19 in January 2020. The patients had relatively severe illness and comorbidities were common, which is likely to have contributed to the high frequency of AKI in this cohort. Second, the small study size limited the capacity for meaningful subgroup analysis. Third, an accurate baseline serum creatinine was not available, which may have led to an overestimate of AKI. Fourth, owing to the lack of data, we could not comment on concomitant medications, urine sediment, or longer-term patient outcomes.

Conclusion

The incidence of AKI in COVID-19 patients in our study was 18.1%. Admission SOFA score was an independent risk factor for AKI in COVID-19 patients, and patients with AKI had higher in-hospital mortality. The development of AKI later in the course of disease was associated with longer hospitalization time.

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Statement of Ethics

The study protocol was approved by the Ethics Committee of the China-Japan Friendship Hospital and was conducted in full accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

In the study, X.C., X.Y., and L.H. designed the research project. X.C., X.Y., L.H., Y.T., X.H., Z.Z., X.W., Z.C., Q.G., Y.Z., and Y.C. performed the study and collected the clinical data. X.C. and L.H. analyzed the data. X.C. and X.Y. drafted the manuscript. X.C. and Q.Z. revised and approved the final version of the manuscript.

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