Brief Report

Clinical Characteristics and Risk Factors for Acute Kidney Injury in COVID-19

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Objective: The objective of the study is to describe the clinical characteristics, risk factors, and prognosis for acute kidney injury (AKI) among patients with coronavirus disease (COVID-19). Methods: Retrospective study of 456 consecutive patients with confirmed COVID-19 infection at the whole hospital from January 1 to March 1, 2020 was enrolled. Demographic, clinical characteristics, the risk factors, and prognosis were collected and analyzed. Results: Of 456 patients with COVID-19, 38 patients developed AKI. Patients with AKI were older and predominantly male sex and were more likely to have comorbidities such as hypertension, cardiovascular, and cerebrovascular diseases. Among patients with AKI, the white blood cell count, neutrophil count, neutrophil-to-lymphocyte ratio, alanine aminotransferase, and C-reaction protein were increased, and lymphocyte and platelet count were decreased. Multivariate analysis showed that age, hypertension, and lymphocyte count were independent risk factors for AKI. The overall mortality rate of 456 patients was 9.9%, and the mortality rate of patients with AKI was 23.7%. In particular, increasing AKI severity was associated with increased risk. Conclusions: The risk of AKI was high in patients with COVID-19. Older age, hypertension, and lower lymphocyte count were independent risk factors for AKI. COVID-19-associated AKI was associated with higher risk of death in patients with COVID-19.

Keywords: COVID-19, kidney injury, pneumonia, risk factors

Introduction

Coronavirus disease-19 (COVID-19) caused by the novel severe acute respiratory syndrome (SARS) COV-2 coronavirus has been spread to more than 200 countries and regions since its outbreak in December 2019 and has infected more than ten million people.[1,2] Several studies have shown that in addition to common respiratory symptoms such as cough and fever, patients with COVID-19 may have other symptoms, including liver and kidney damage.[3] It has reported that patients with pneumonia, especially the elderly patients, have a high risk of acute kidney injury (AKI) during hospitalization.[4] A multicenter study has shown that about 10% of patients with COVID-19 have renal dysfunction.[5] Pneumonia-related AKI can increase the risk of poor prognosis,[6] time, and cost of hospitalization.[7] In addition, the application of drugs will become more complicated due to the impact of AKI, which makes the rehabilitation of patients more difficult.[8] The risk factors of AKI in patients with COVID-19 during hospitalization were not clear. The present study collected the relevant case data and investigated the characteristics, the risk factors of COVID-19 combined with AKI and its relationship with fatal outcome.

Access this article online

Website: www.tccmjournal.com

DOI: 10.4103/2665-9190.330535

How to cite this article: Zhang J, Rao X, Chen L, Jiang X, Yang C, Wang F, et al. Clinical Characteristics and Risk Factors for Acute Kidney Injury in COVID-19. J Transl Crit Care Med 2021;3:12.

Submission: 10-07-2021 Review: 23-09-2021
Accepted: 27-09-2021 Published: 16-11-2021

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METHODS

Study design and participants
This study was conducted in Zhongnan Hospital of Wuhan university and Wuhan fourth Hospital from January 1 to March 18, 2020, and was approved by the institutional ethics board in each participating hospital (20200202 to Zhongnan Hospital of Wuhan University and 2020-020-01 to Wuhan Fourth Hospital). Informed consent was obtained from patients or their legal representatives. All patients with COVID-19 enrolled in this study were diagnosed according to the World Health Organization (WHO) interim guidance.[9] Reverse transcriptase-polymerase chain reaction (RT-PCR) was used as a gold standard to diagnose COVID-19 in multiple and different clinical specimens when necessary.

Data collection
Demographics, laboratory values, treatment strategies, complications, and clinical outcomes of patients were abstracted from the medical records using a standardized report form designed for this study. The clinical symptoms and laboratory findings at hospital admission and complications and clinical outcomes throughout the hospitalization were collected. AKI was identified according to the diagnostic criteria of Kidney Disease Improving Global Outcomes.[9] During data collection, the patient's real name was replaced by numbers and individual information was hidden.

Statistical analysis
SPSS 23.0 (Statistical Product and Service Solutions, IBM, Armonk, New York, USA) statistical software was used to analyze the data. For the measurement data meeting the normal distribution, the mean ± standard deviation was used; for the measurement data not meeting the normal distribution, the median and quartile were used. The independent sample t-test was used to compare the normal distribution between the two groups, and the Satterthwaite approximate t-test was used when the variance was uneven. The measurement data of abnormal distribution were compared by Mann–Whitney U test. χ² test was used for counting data. Logistic regression was used to calculate odds ratio (OR), and Cox proportional hazard regression was used to calculate hazard ratio (HR). The statistical significance level was set at a two-sided (P < 0.05).

RESULTS

Characteristics of the patients
Of the 456 patients enrolled in this study, 38 patients developed AKI (8.3%) [Table 1]. In addition, 16 patients had a maximum AKI Stage 1, 5 patients had AKI Stage 2, and 17 patients had AKI Stage 3 [Table 2]. Patients in the AKI group were older. Male patients were more likely to develop AKI. In terms of comorbidities, patients with hypertension, diabetes, cardiovascular diseases, and cerebrovascular diseases were more likely to develop AKI. There was no difference in the proportion of patients with chronic obstructive pulmonary disease, chronic liver disease, and malignancy between AKI group and non-AKI group. In particular, the long-term use of antihypertensive and hypoglycemic drugs by overall patients before admission was not discontinued after admission. There was no significant difference in the use of ACEI and ARB between the AKI group and non-AKI group.

There was no difference in admission temperature, heart rate, and respiratory rate between the two groups. The median temperature was 37.2°C, and the median heart rate was 85 beats per min. The median respiratory rate was 20 breaths/min.

In addition to the significant differences in serum creatinine and urea, the white blood cell count, neutrophil count, neutrophil-to-lymphocyte ratio, alanine aminotransferase, and C reaction protein of AKI group were significantly high, while the lymphocyte count and platelet count were low.

In the radiology examination, 85.1% of the patients had bilateral lung lesions, but only 38 patients had infiltrated more than 50%. In addition, 12 patients developed hydrothorax.

Multivariate analysis of risk factors of acute kidney injury
The factors with statistical significance in the results of single factor analysis were included in the logistic regression model as covariates. Multivariate analysis showed that age, hypertension and lymphocyte count were the independent risk factors of AKI in patients with COVID-19. The adjusted OR of age was 1.045 and 95% confidence interval (CI) was 1.015–1.076. The adjusted OR of hypertension was 2.188 and 95% CI was 1.015–4.715. The adjusted OR of lymphocyte count was 0.293 and 95% CI was 0.112–0.771 [Table 3].

Mortality of patients in COVID-19 with or without acute kidney injury
Of the 456 patients included in this study, 411 were discharged and 45 died. The overall mortality rate was 9.9%, 23.7% in AKI group and 8.6% in normal group. Kaplan–Meier survival curve showed that the survival rate of AKI group was lower than that of normal group (P = 0.003) [Figure 1]. Cox proportional hazard regression also showed that the HR of AKI was 2.882 and 95% CI was 1.383–6.004 (P = 0.005). In addition, increasing AKI severity was associated with increased mortality [Table 2]. Cox regression showed that the HR...
Table 1: Characteristics of the patients with coronavirus disease-2019 between neonatal acute kidney injury and acute kidney injury

| Factors                          | All (n=456) | Non-AKI (n=418) | AKI (n=38) | P       |
|----------------------------------|-------------|-----------------|------------|---------|
| Age (IQR)                        | 57 (45-68)  | 56 (44-66)      | 70 (62-78) | <0.001  |
| Gender, n (%)                    |             |                 |            |         |
| Male                             | 229 (50.2)  | 204 (48.8)      | 25 (65.8)  | 0.045   |
| Female                           | 227 (49.8)  | 214 (51.2)      | 13 (34.2)  | 0.045   |
| Comorbidities, n (%)             |             |                 |            |         |
| Hypertension                     | 169 (37.1)  | 144 (34.4)      | 25 (65.8)  | <0.001  |
| Diabetes                         | 72 (15.8)   | 58 (13.9)       | 14 (36.8)  | <0.001  |
| Cardiovascular disease           | 56 (12.3)   | 46 (11.0)       | 10 (26.3)  | 0.006   |
| Cerebrovascular disease          | 26 (5.7)    | 20 (4.8)        | 6 (15.8)   | 0.005   |
| Chronic obstructive pulmonary disease | 6 (1.3)  | 5 (1.2)         | 1 (2.6)    | 0.457   |
| Chronic liver disease            | 12 (2.6)    | 12 (2.9)        | 0 (0)      | 0.290   |
| Malignancy                       | 28 (6.1)    | 25 (6.0)        | 3 (7.9)    | 0.638   |
| ACEI and ARB use history         | 56 (13.4)   | 51 (12.9)       | 5 (20.0)   | 0.315   |
| Temperature (IQR)                | 37.2 (36.5‑38.2) | 37.1 (36.5‑38.2) | 37.6 (36.8‑38.6) | 0.114   |
| Hear rate (IQR)                  | 85 (78‑94)  | 85 (78‑94)      | 84 (77‑95) | 0.854   |
| Respiratory rate (IQR)           | 20 (19‑22)  | 20 (19‑22)      | 20 (20‑25) | 0.061   |
| Laboratory data                  |             |                 |            |         |
| White blood cell count, ×10⁹/L (IQR) | 4.89 (3.68‑6.89) | 4.83 (3.65‑6.72) | 6.56 (4.14‑9.59) | 0.005   |
| Neutrophil count, ×10⁹/L (IQR)   | 3.27 (2.30‑5.34) | 3.24 (2.26‑4.98) | 5.46 (2.99‑9.10) | 0.001   |
| Lymphocyte count, ×10⁹/L (IQR)   | 0.87 (0.59‑1.23) | 0.89 (0.61‑1.24) | 0.55 (0.33‑0.94) | <0.001  |
| Neutrophil-to-lymphocyte ratio (IQR) | 3.91 (2.23‑7.49) | 3.62 (2.13‑7.08) | 6.31 (4.22‑26.79) | <0.001  |
| Platelet count, ×10⁹/L (IQR)     | 177.5 (133.0‑224.0) | 178 (135.5‑226.5) | 173.5 (113.0‑194.0) | 0.035   |
| Alanine aminotransferase, U/L (IQR) | 26.0 (17.0‑41.0) | 25.0 (16.0‑40.0) | 34.0 (25.0‑47.0) | 0.031   |
| Aspartate aminotransferase, U/L (IQR) | 31.0 (23.0‑47.0) | 30.0 (23.0‑46.0) | 40.1 (26.0‑64.0) | 0.061   |
| Creatinine, μmol/L (IQR)         | 67.8 (55.8‑81.7) | 66.4 (55.2‑79.5) | 86.7 (69.0‑131.0) | <0.001  |
| Urea, mmol/L (IQR)               | 4.59 (3.66‑6.33) | 4.50 (3.56‑6.08) | 7.28 (4.95‑9.94) | <0.001  |
| C reaction protein (IQR)         | 29.3 (15.5‑53.4) | 28.1 (15.0‑50.7) | 51.2 (32.7‑63.1) | 0.013   |
| Radiology                         |             |                 |            |         |
| Bilateral distribution, n (%)    | 353 (85.1)  | 327 (84.7)      | 26 (89.7)  | 0.472   |
| Lesion range (>50%), n (%)       | 38 (17.7)   | 36 (17.5)       | 2 (22.2)   | 0.761   |
| Hydrothorax, n (%)               | 12 (4.9)    | 12 (5.1)        | 0          | 0.489   |
| Outcome                          |             |                 |            |         |
| Death, n (%)                     | 45 (9.9)    | 36 (8.6)        | 9 (23.7)   | 0.003   |
| Hospital stay (IQR)              | 13 (10‑18)  | 13 (10‑18)      | 13 (7‑26)  | 0.722   |

AKI: Acute kidney injury, IQR: Interquartile range, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker

of severe AKI (Stage 2 or 3) was 5.080 and 95% CI was 2.355‑10.960 (P < 0.001).

**DISCUSSION**

COVID-19 has been declared a “pandemic” by the WHO.[11] The pandemic of COVID-19 is causing substantial morbidity and mortality.[12‑14] This study showed that the proportion of COVID-19 patients developing AKI was 8.3%. Recent studies have shown that 2019-nCoV can bind to ACE2 protein on the surface of human cells.[15] ACE2 expresses quite highly in renal cells, particularly in tubular cells.[5] Therefore, patients with COVID-19 have a high potential risk of AKI.

Multivariate analysis showed that age, hypertension, and lymphocyte count were independent risk factors for AKI in patients with COVID-19. This was consistent with a study involving 3464 patients that found age-dependent changes to be independent risk factors for AKI.[16] The structure of the kidney may change with age, such as vascular sclerosis, weight loss, and sclerotic glomerulus, and the kidney function may also change with age, such as the decrease of glomerular filtration rate, the decrease of ultrafiltration coefficient with the increase of glomerular capillary pressure, and changes in renal sensitivity to vasoconstrictors and vasodilators. Thus, the structural and functional changes associated with aging increase risk for AKI.[17] Hypertension has been reported as an independent risk factor for AKI in a study of 60 hospitals.[18] Persistent hypertension can increase glomerular capillary pressure, lead to glomerular fibrosis and renal arteriosclerosis, and cause renal parenchymal ischemia and renal unit failure, which increases the risk of AKI.[19] In addition, it has reported that the decrease of lymphocyte count is an independent risk...
factor of AKI in SARS patients. Lymphocytes played an important role in regulating the appropriate inflammatory response. The decrease of lymphocyte count, to a certain extent, represented the suppression of immune system and the release of inflammatory factors. Inflammation was an important part of the pathophysiological process of AKI. In particular, the present study showed that C reaction protein in patients with AKI was significantly higher than that in patients without AKI, which meant that inflammation played an important role in the process of COVID-19-associated AKI.

The mortality rate of patients in the AKI group was 23.7%, which was significantly higher than that in the non-AKI group (8.6%). The mortality rate was worsened with the severity of AKI. This was in line with previous findings that patients with impaired renal function had a high risk of death in hospital. It has reported that AKI may increase the mortality of SARS patients through secondary multiple organ failure and unstable hemodynamics. Therefore, it is very important to research the clinical characteristics and risk factors of COVID-19-associated AKI. The use of ACEI and ARB in patients with COVID-19 remains controversial.

In this study, ACEI and ARB had no significant risk for AKI. Although a large number of patients are included in this study, there were still some limitations in this study. First, as a retrospective study, this study may lack some data of baseline. Second, the sample size of AKI patients is not enough, and some associations will be attenuated, or even fail to reach statistical significance. Third, the long-term outcome of patients was not followed up, especially the incidence of chronic kidney disease. Fourth, drug-induced AKI cannot be ruled out.

**Conclusions**

The incidence of COVID-19-associated AKI was high, and the mortality of patients was significantly increased by COVID-19-associated AKI. Age, hypertension, and lymphocyte count were independent risk factors for AKI in patients combined with COVID-19. Clinicians should raise their awareness of COVID-19-associated AKI in patients.

**Ethics approval and consent to participate**

The local institutional review boards approved this study (2020-020 to Zhongnan Hospital of Wuhan University and 2020-020-01 to Wuhan Fourth Hospital), and informed consent was obtained from patients or their legal representatives.
Financial support and sponsorship
This work was supported by the National Natural Science Foundation (grant No. 81772046 and No. 81971816 to Dr. Peng, and grant No. 82102298 to Dr. Su), the Special Project for Significant New Drug Research and Development in the Major National Science and Technology Projects of China (grant No. 2020ZX09201007 to Dr. Peng), Innovation Cultivation Foundation of Wuhan University/Zhongnan Hospital (grant No. 413000345/CXPY20200017 to Dr. Su) and Research Project Foundation of Zhongnan Hospital (grant No. ZNYB2020013 to Dr. Su).

Conflicts of interest
There are no conflicts of interest.

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