Coronavirus Disease 19 Infection Does Not Result in Acute Kidney Injury: An Analysis of 116 Hospitalized Patients from Wuhan, China

Luwen Wang\textsuperscript{a}, Xun Li\textsuperscript{a}, Hui Chen\textsuperscript{c}, Shaonan Yan\textsuperscript{a}, Dong Li\textsuperscript{b}, Yan Li\textsuperscript{b}, Zuojiong Gong\textsuperscript{a}

\textsuperscript{a}Department of Infectious Diseases, Renmin Hospital of Wuhan University, Wuhan, China; \textsuperscript{b}Department of Laboratory Medicine, Renmin Hospital of Wuhan University, Wuhan, China; \textsuperscript{c}Institute of Infectious Diseases, Hubei Provincial Center for Disease Control and Prevention, Wuhan, China

Keywords
Severe acute respiratory syndrome-CoV-2 · Coronavirus disease 19 · Acute kidney injury · Chronic kidney disease · Continuous renal replacement therapy

Abstract

Background: Whether the patients with coronavirus disease 19 (COVID-19) infected by severe acute respiratory syndrome (SARS)-CoV-2 would commonly develop acute kidney injury (AKI) is an important issue worthy of clinical attention. This study aimed to explore the effects of SARS-CoV-2 infection on renal function through analyzing the clinical data of 116 hospitalized COVID-19-confirmed patients.

Methods: One hundred sixteen COVID-19-confirmed patients enrolled in this study were hospitalized in the Department of Infectious Diseases, Renmin Hospital of Wuhan University from January 14 to February 13, 2020. The recorded information includes demographic data, medical history, contact history, potential comorbidities, symptoms, signs, laboratory test results, chest computer tomography scans, and treatment measures. SARS-CoV-2 RNA in 53 urine sediments of enrolled patients was detected by real-time reverse transcription-polymerase chain reaction. Results: Twelve (10.8\%) patients showed mild increase of blood urea nitrogen or creatinine (<26 μmol/L within 48 h), and 8 (7.2\%) patients showed trace or 1+ albuminuria in 111 COVID-19-confirmed patients without chronic kidney disease (CKD). All these patients did not meet the diagnostic criteria of AKI. In addition, 5 patients with CKD who were undergone regular continuous renal replacement therapy (CRRT) before admission were confirmed infection of SARS-CoV-2 and diagnosed as COVID-19. In addition to therapy for COVID-19, CRRT was also applied 3 times weekly during hospitalization for these 5 patients with CKD. In the course of treatment, the renal function indicators showed stable state in all 5 patients with CKD, without exacerbation of CKD, and pulmonary inflammation was gradually absorbed. All 5 patients with CKD were survived. Moreover, SARS-CoV-2 RNA in urine sediments was positive only in 3 patients from 48 cases without CKD, and 1 patient had a positive for SARS-CoV-2 open reading frame 1ab from 5 cases with CKD.

Conclusion: AKI was uncommon in COVID-19. SARS-CoV-2 infection does not result in AKI, or aggravate CKD in the COVID-19 patients.
Introduction

In December 2019, an acute respiratory infectious disease caused by a novel coronavirus occurred in Wuhan, Hubei Province, China, which is now officially named as "coronavirus disease 19 (COVID-19)" by the WHO [1–3]. The disease has spread rapidly from Wuhan to other regions in China. As of March 17, 2020, a total of 80,881 COVID-19-confirmed cases were reported in China [4]. Internationally, confirmed cases have been reported in >150 countries and regions around the world at present [5]. On January 3, 2020, a novel coronavirus was identified in a bronchial alveolar lavage fluid sample from a patient in Wuhan and confirmed to be the cause of COVID-19 [6]. Whole genome sequencing and systematic analysis showed that this novel coronavirus is a distinct clade from beta coronavirus associated with human severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome [6], which was officially named "SARS-CoV-2" by WHO now. Although the origin of SARS-CoV-2 is still being investigated, current evidence suggests it was transmitted to humans through the spread of wild animals illegally sold in Huanan Seafood Wholesale Market [7]. Case reports have confirmed the interpersonal transmission of SARS-CoV-2 [8]. Currently, there are no specific treatments or vaccines for COVID-19. Huang et al. [9] first reported 41 COVID-19 cases, most of whom had a history of exposure to Huanan Seafood Wholesale Market. The patient’s clinical manifestations included fever, unproductive cough, dyspnea, myalgia, fatigue, normal or decreased white blood cell count, and imaging evidence of pneumonia [9]. Wang et al. [10] reported in 138 hospitalized COVID-19-confirmed cases, presumed hospital-related transmission of SARS-CoV-2 was suspected in 41% of patients, 26% of patients received intensive care unit (ICU) care, and mortality was 4.3%. In this study, the clinical data of 116 hospitalized COVID-19-confirmed patients were analyzed, and the effects of SARS-CoV-2 infection on renal function were explored.

Materials and Methods

Study Design and Participants

Renmin Hospital of Wuhan University is located in Wuhan City, Hubei Province, an area where COVID-19 is endemic. It is one of the city’s major tertiary teaching hospitals and the designated COVID-19-treatment hospital by the Wuhan Municipal Government. In this study, 116 COVID-19-confirmed patients were enrolled, who were hospitalized in the Department of Infectious Diseases, Renmin Hospital of Wuhan University from January 14 to February 13, 2020 (before January 20, they were diagnosed as unknown origin viral pneumonia). Oral consent was obtained from all patients. A confirmed diagnosis of all COVID-19 patients participating in this study was made according to the WHO’s interim guidelines [11]. This study was approved by the Institutional Ethics Committee of Renmin Hospital of Wuhan University (IRB number is WDRY2020-K115).

Nucleic Acid Detection of SARS-CoV-2

All COVID-19 patients enrolled in this study were laboratory-confirmed cases, which were identified with nucleic acid detection of SARS-CoV-2 from a throat swab samples using reverse transcription-polymerase chain reaction (RT-PCR). The criteria for the confirmed diagnosis of SARS-CoV-2 were that at least one gene site was amplified to be positive for nucleocapsid protein (NP) gene and open reading frame (ORF) 1ab gene. In brief, the throat swab was put into a collection tube containing 150 μL viral preservation solution, and the total RNA was extracted within 2 h with the respiratory sample RNA separation Kit (Zhongzhi, Wuhan). The suspension was used for RT-PCR assay of SARS-CoV-2 RNA. Two target genes, including NP and ORF1ab, were simultaneously amplified and tested during the real-time RT-PCR assay. Target 1 (NP): forward primer GGGGAACCTTCTCGTC-TAGAAT; reverse primer CAGACATTTTGCTCTCAAGCTG; and the probe 5′-FAM-CTGTCTGCTTACAGATT-TAMRA-3′. Target 2 (ORF1ab): forward primer CCTGGTTGGTTT-TAGACTTAA; reverse primer AGGATTGTGC ATCAGCTGA; and the probe 5′-VIC-CCGTCTCGGTATGTAAGAGTT- TATGG-BHQ1–3′. The real-time RT-PCR assay was performed using a 2019-nCoV nucleic acid detection kit according to the manufacturer’s protocol (Shanghai bio-germ Medical Technology Co Ltd). Specific primers and probes for SARS-CoV-2 RNA detection were based on the recommendation by the National Institute for Viral Disease Control and Prevention (China; http://ivdc.chinacdc.cn/kyyz/202001/t20200121_211337.html).

Data Collection

Epidemiological, clinical, laboratory, and radiological characteristics were recorded. The patients’ medical history as well as treatment and outcome data was also obtained through data collection tables in electronic medical records. Data were reviewed by a team of specialists. The recorded information includes demographic data, medical history, contact history, potential comorbidities, symptoms, signs, laboratory test results, chest computer tomography (CT) scans and treatment measures (i.e., antiviral therapy, glucocorticoid usage, breathing support, kidney replacement therapy). The onset date was defined as the date on which symptoms appear. Different clinical categories were defined for all COVID-19 patients participating in the study according to the WHO’s interim guidelines, including mild pneumonia, severe pneumonia, and acute respiratory distress syndrome (ARDS) [11].

Standard Definitions of Acute Kidney Injury and Chronic Kidney Disease Diagnosis

Acute kidney injury (AKI) was identified according to Kidney Disease: Improving Global Outcomes [12]. The standard definition of AKI in adults is one of the following: an increase in serum creatinine (SCr) by ≥26 μmol/L (0.3 mg/dL) within 48 h, or an increase in SCr to >1.5 times baseline within the previous 7 days, or urine volume <0.5 mL/kg/h for >6 h. Moreover, the minimum value of preadmission SCr was used as the baseline of renal func-
SARS-CoV-2 Infection Does Not Result in AKI

SARS-CoV-2 Infection Does Not Result in AKI

345

Am J Nephrol 2020;51:343–348
DOI: 10.1159/000507471

Am J Nephrol 2020;51:343–348
DOI: 10.1159/000507471

tion, so that more AKI cases could be found according to a relevant research report [13]. When baseline outpatient SCr was not available, SCr GFR-75 as surrogate for the baseline SCr was used to diagnose AKI [14].

The standard definition of chronic kidney disease (CKD) according to Kidney Disease: Improving Global Outcomes is glomerular filtration rate of < 60 mL/min/1.73 m², or markers of kidney damage (such as albuminuria, urine sediment abnormalities, electrolyte, and other abnormalities due to tubular disorders, Abnormalities detected by histology, Structural abnormalities detected by imaging, history of kidney transplantation), or both, of at least 3 months duration, regardless of the underlying cause [15].

Statistical Analysis

Categorical variables were described as frequency and percentage, and continuous variables were described as using mean, median, and interquartile range (IQR) values. When the data were normally distributed, independent t tests were used to compare the mean of continuous variables. Otherwise, the Mann-Whitney test is used. Although Fisher’s exact test was used with limited data, the χ² test was used to compare the proportion of categorical variables. Analysis of covariance was used to compare the clinic characteristics of the patients. Age, gender, and comorbidities were used as covariate variables in the analysis of covariance. All statistical analyses were performed using SPSS version 13.0 software. A p value of <0.05 is statistically significant.

Results

Presenting Characteristics

In this study, the median age of 116 COVID-19-confirmed patients was 54 years (IQR 38–69; range 20–95 years), of which 67 (57.8%) were male. In these patients, 59 (50.8%) were mild pneumonia and 46 (39.7%) were severe pneumonia, who entered the isolation ward, while 11 (9.5%) were ARDS, who were transferred to ICU (Table 1). In these patients, 51 (43.9%) cases had one or more comorbidities. Hypertension (43 [37.1%]), diabetes (18 [15.5%]), malignant tumors (12 [10.3%]), cerebral infarction (7 [6.0%]), and CKD with long-term hemodialysis (5 [4.3%]) were the common coexisting diseases.

Changes of Kidney-Related Clinical Data

As shown in Table 2, 111 COVID-19-confirmed patients without CKD did not develop obvious abnormal renal function after infection with SARS-CoV-2 and during the treatment of pneumonia. Twelve (10.8%) patients without CKD showed a mild increase in blood urea nitrogen (BUN) or SCr after infection with SARS-CoV-2 and during the treatment of pneumonia. However, the increase values of SCr were all < 26 μmol/L within 48 h. In addition, 8 (7.2%) patients without CKD showed trace or 1+ albuminuria in the detection of urine routine during the treatment of pneumonia. All these patients did not meet the diagnostic criteria of AKI and gradually returned to normal after a follow-up without receiving special treatment for the kidneys. At present, none of the patients exhibited acute renal failure. In addition, the patients with CKD were still undergoing regular continuous renal replacement therapy (CRRT) except for the treatment of COVID-19. In the course of treatment, the monitoring of renal function indicators showed stable state,
without exacerbation of CKD, and reexamination of CT showed that pulmonary inflammation was gradually absorbed.

**Detection Data of SARS-CoV-2 RNA in Urine Sediment**

SARS-CoV-2 RNA in urine sediments of COVID-19-confirmed 53 patients, including 5 CKD cases, enrolled in this study was examined by real-time RT-PCR. The results showed that SARS-CoV-2 RNA in urine sediments was positive in 3 patients without CKD (3/48), except 1 patient with CKD had a positive for SARS-CoV-2 ORF 1ab (1/5). There was no significant difference in the characteristics and clinical course between those with and without positive SARS-CoV-2 RNA in urine sediments.

**Mortality of 116 COVID-19-Confirmed Patients**

As of February 13, 2020, 7 (6.03%) ARDS patients transferred to ICU died of respiratory failure. All the 7 dead patients with ARDS were over 60 years old, and the maximum age was 95 years old. None of the 7 patients exhibited AKI, but all of them had other comorbidities, including 4 patients with advanced malignant tumor, 2 patients with hypertension and coronary heart disease, and 1 patient with diabetes and cerebral infarction. All of the 7 patients had pulmonary consolidation and hypoxemia which was difficult to correct. Even if invasive ventilation was used, they still died from respiratory failure. It is worth noting that all of 5 patients with CKD were survived, who did not develop to ARDS or CKD deterioration.

**Discussion**

The first step in SARS-CoV-2 infection is to bind to the host cell receptor and enter the cells. Recent a study shows that the common ancestor of SARS-CoV-2 and SARS-CoV is similar to bat coronavirus HKU9–1 [16]. These coronaviruses have a 3-dimensional structure of spike protein, which is closely bound to human cell receptor angiotensin converting enzyme 2 (ACE2). Therefore, the cells with ACE2 expression may act as target cells and be susceptible to COVID-19 infection, such as type II alveolar cells (AT2) in the lung [17]. It should be noted that ACE2 protein has been proved to have an abundant expression in many kinds of cells, such as intestinal epithelial cells, renal tubular epithelial cells, alveolar epithelial cells, heart, artery smooth muscle cells, and gastrointestinal system [18]. Therefore, it is reasonable to speculate that SARS-CoV-2 may invade the lung, upper respiratory tract, ileum, heart, and kidney, which may lead to dyspnea, diarrhea, acute heart injury, and AKI, especially in the case of viremia.

Recently, a medRxiv preprint study on kidney functions in 59 patients infected by SARS-CoV-2 was reported [19]. It was found that 63% (32/51) of the patients exhibited proteinuria, 19% (11/59) and 27% (16/59) of the patients had an elevated level of plasma creatinine and urea nitrogen, respectively. Moreover, the CT scan showed radiographic abnormalities of the kidneys in 100% (27/27) of the patients. Therefore, it was concluded that renal impairment is common in COVID-19 patients,
which may be one of the major causes of the illness by the virus infection and also may contribute to multiorgan failure and death eventually.

In this study, the effects of SARS-CoV-2 infection on renal function were explored through analyzing the clinical data of 116 hospitalized COVID-19-confirmed patients. However, the results of common renal impairment in COVID-19 patients were not observed in this study. Although 12 patients (10.8%) without CKD showed mild increase of BUN or SCr (<26 μmol/L within 48 h), and 8 patients (7.2%) showed trace or 1+ albuminuria after infection with the virus and during the treatment of pneumonia, all these patients did not meet the diagnostic criteria of AKI. Moreover, these patients gradually returned to normal after a follow-up without receiving special treatment for the kidneys. The temporary abnormal renal function is probably supposed as secondary injury due to hypoxemia in these patients.

In this study, 116 patients with COVID-19 hospitalized in the Department of Infectious Diseases were included. Except 5 patients with CKD were treated by long-term dialysis before hospitalization, the other 111 patients were all without CKD before. There were no predialysis patients with significant CKD in this study, which prevented the observation for these patients because they are indeed at high risk of AKI. This is just a chance, which made us regret that we could not observe whether these predialysis patients with CKD would develop to AKI and worsen the original CKD after infection with SARS-CoV-2. The issue resulted in one of the limitations of the study, but it did not affect the observation for the patients without CKD. We did observe that there was no AKI in these patients without CKD, which is the main purpose of this study to conclude that AKI was uncommon in COVID-19.

A previous study, Wang et al. [10] reported the clinical characteristics of 138 hospitalized COVID-19-confirmed cases in a study. The data showed that the value of both BUN (4.4 [3.4–5.8] mmol/L [median (IQR)]) and creatinine (72 [60–87] μmol/L [median (IQR)]) were within the normal range. Guan et al. [20] presented also the data of clinical characteristics of 1,099 patients confirmed with COVID-19 from 552 hospitals in 31 provinces/provincial municipalities in a study. From this study, the renal function showed that the patients’ number of Creatinine ≥133 μmol/L were 12/752 (1.6%). Data from above 2 studies suggested that AKI was uncommon in COVID-19, and SARS-CoV-2 infection does not result in obvious azotemia and AKI.

Based on the clinical, pathologic study, and laboratory features of SARS-CoV infection in SARS patients in 2003, the data showed that AKI was uncommon, but carried a formidably high mortality (91.7%, 33 of 36 cases) [21]. In this study, all of the patients without CKD showed no obvious abnormality of renal function during the hospitalization of COVID-19, and none of the patients showed by AKI. Because 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.

In this study, we also observed that the patients with CKD who were undergone regular CRRT were infected with SARS-CoV-2 and confirmed as COVID-19. Except regular CRRT, the monitoring of renal function indicators showed stable state, without exacerbation of CKD in the course of treatment of COVID-19. The reexamination of CT showed that pulmonary inflammation was gradually absorbed. Unlike a formidably high mortality in SARS complicated with renal impairment, none of the patients died from the aggravation of CKD or from COVID-19 itself caused by infection with SARS-CoV-2. It was also suggested that CRRT plays an important role in the treatment of COVID-19 complicated with CKD. Nevertheless, the renal function of patients with COVID-19 needs to be monitored regularly, especially in patients with elevated plasma creatinine. In the event of signs of AKI, potential interventions, including CRRT, should be used to protect renal function as early as possible. A STROBE checklist about this paper is available as online supplementary material (appendix; see www.karger.com/doi/10.1159/000507471).

Statement of Ethics

Oral consent was obtained from all patients. This study was approved by the Institutional Ethics Committee of Renmin Hospital of Wuhan University (IRB number is WDRY2020-K115).

Disclosure Statement

We declare no competing interests.

Author Contributions

Z.G. and Y.L. made substantial contributions to the study concept and design. L.W. was in charge of the manuscript draft. X.L., H.C., S.Y., and D.L. took responsibility for obtaining written consent from patients, obtaining ethical approval, collecting samples, and confirming data accuracy. L.W. and Z.G. participated in drafting the manuscript and revising it on the basis of reviewers’ comments. L.W. made substantial contributions to data acquisition, analysis, and interpretation.
References

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J Med Virol. 2020 Apr;92(4):401–2.
2. Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020 Feb;91:264–6.
3. Wuhan Municipal Health Commission. Report of clustering pneumonia of unknown etiology in Wuhan City. [Published December 31, 2019]. Available from: http://wjw.wuhan.gov.cn/front/web/showDetail/2019123108989.
4. National Health Commission of the People’s Republic of China. Update on novel coronavirus pneumonia epidemic situation as of 24:00 on [March 16, 2020]. Available from: http://www.nhc.gov.cn/xcs/yqtb/202003/28d026a0422844969226913ec3d56d77.shtml.
5. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 56. Data as reported by 16 March 2020. Available from: https://www.who.int/publications-detail/coronavirus-situation-reports/20200316-sitrep-56-covid-19.pdf?sfvrsn=9fda7db2_6.
6. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al.; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Feb;382(8):727–33.
7. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb;395(10223):507–13.
8. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020 Feb;395(10223):514–23.
9. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb;395(10223):497–506.
10. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020, Epub ahead of print.
11. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance V 1.2. March 13, 2020. Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.
12. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179–84.
13. Thongprayoon C, Cheungpasitporn W, Kittanamongkolchai W, Srivali N, Ungprasert P, Kashani K. Optimum methodology for estimating baseline serum creatinine for the acute kidney injury classification. Nephrology (Carlton). 2015 Dec;20(12):881–6.
14. Thongprayoon C, Cheungpasitporn W, Harrison AM, Kittanamongkolchai W, Ungprasert P, Srivali N, et al. The comparison of the commonly used surrogates for baseline renal function in acute kidney injury diagnosis and staging. BMC Nephrol. 2016 Jan;17(1):6.
15. Kidney Disease: improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.
16. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. 2020 Mar;63(3):457–60.
17. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar;579(7798):270–3.
18. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020, Epub ahead of print.
19. Li Z, Wu M, Guo J, Yao J, Liao X, Song S, et al. Caution on Kidney Dysfunctions of 2019-nCoV Patients. MedRxiv. 2020. Epub ahead of print.
20. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of 2019 novel coronavirus infection in China. MedRxiv. 2020, Epub ahead of print.
21. Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int. 2005 Feb;67(2):698–705.