Journal of Nephrology and Kidney Diseases
Volume 2 | Issue 1

Research Article Open Access

Kidney Injury in Ordinary Adult Cases of Coronavirus Disease 2019

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Citation: Yang H, Yu H, Li H, Pan K, Zhang G, et al. (2021) Kidney Injury in Ordinary Adult Cases of Coronavirus Disease 2019. J Nephrol Kidney Dis 2(1): 101

Received Date: February 04, 2021 **Accepted Date**: February 16, 2021 **Published Date:** February 18, 2021

Summary

Background: Kidney injury has been observed broadly in severe and critical coronavirus disease 2019 (COVID-19) patients, but the impairment of renal function in ordinary cases has rarely reported. We conducted this study to explore whether patients in ordinary condition suffered from kidney injury during the course of COVID-19 and to find out a proper indicator for detecting kidney injury in COVID-19 patients.

Methods: We designed a cross-sectional study and enrolled seventy patients with ordinary form of COVID-19 admitted by the Wuhan support team from Sir Run Run Shaw Hospital. We evaluated the renal function for the patients during hospitalization with serum creatinine (Cr), serum cystatin-C (Cys-C), and estimated glomerular filtration rate (eGFR).

Results: Serum Cr levels of most patients (96.9%) were within the normal range during hospitalization. Elevated serum Cys-C levels were observed in 56.9% of the patients on admission and in 87.7% after 5 days. Cys-C levels increased significantly during the 5 days. Proportions of patients with decreased eGFR estimated with Cr alone and with Cr and Cys-C were 43% and 67.7%, respectively on admission and 50.8% and 87.7%, respectively 5 days later. Significant decrease was observed in eGFR estimated using the combination of Cr and Cys-C during hospitalization. Values of eGFR estimated by the two methods were significantly correlated. Patients with underlying diseases showed worse renal function.

Conclusions: Ordinary cases of COVID-19 showed kidney injury during the course of the disease. Clinicians should pay more attention to renal function monitoring during hospitalization and in subsequent follow-up.

Keywords: COVID-19; Renal injury; Ordinary cases; Cystatin-C; eGFR

Introduction

In December 2019, an outbreak of "pneumonia of unknown cause" occurred in Wuhan, China. The cause of the disease was soon confirmed as a novel type of coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], and the disease was named coronavirus disease 2019 (COVID-19) [2]. Since the disease could spread quickly by person-to-person transmission, the number of cases rapidly increased around the world [3]. Worldwide, the number of deaths is increasing daily, as some patients develop acute respiratory distress syndrome and multiple-organ failure [4]. The disease has become a public health emergency and has raised broad concerns globally.

Handling patients with severe or critical status properly and in a timely manner is a hard task for physicians. Meanwhile, the integrated management of ordinary cases should not be ignored. Although most of the patients have mild manifestations and favorable prognosis after antiviral treatments and supportive treatment, follow-up is still an essential process for these patients, as the long-term effects of SARS-Cov-2 infection are not clear. Acute kidney injury has already been observed as a common complication in critical cases and the proportion of patients that require renal replacement therapy ranged from 25% to 56.6% [5,6]. However, for ordinary cases, serum creatinine (Cr) is not sensitive enough for detecting kidney injury. When the clinical manifestations of kidney injury are not obvious, the incidence rate of kidney injury may be underestimated. It is essential for physicians to assess the renal function in these patients using more sensitive indicators such as estimated glomerular filtration rate (eGFR) and cystatin-C (Cys-C).

In the present study, we collected the data of patients admitted by the Wuhan support team of Sir Run Run Shaw Hospital and analyzed some of the indicators of renal function to explore weather kidney injury is general in ordinary COVID-19 cases.

Materials and Methods

Patients and study design

The present cross-sectional study was approved by the institutional research ethics committee of Sir Run Run Shaw hospital (NO. 20200407-33).The overall procedures are illustrated in a flow chart (Figure 1).

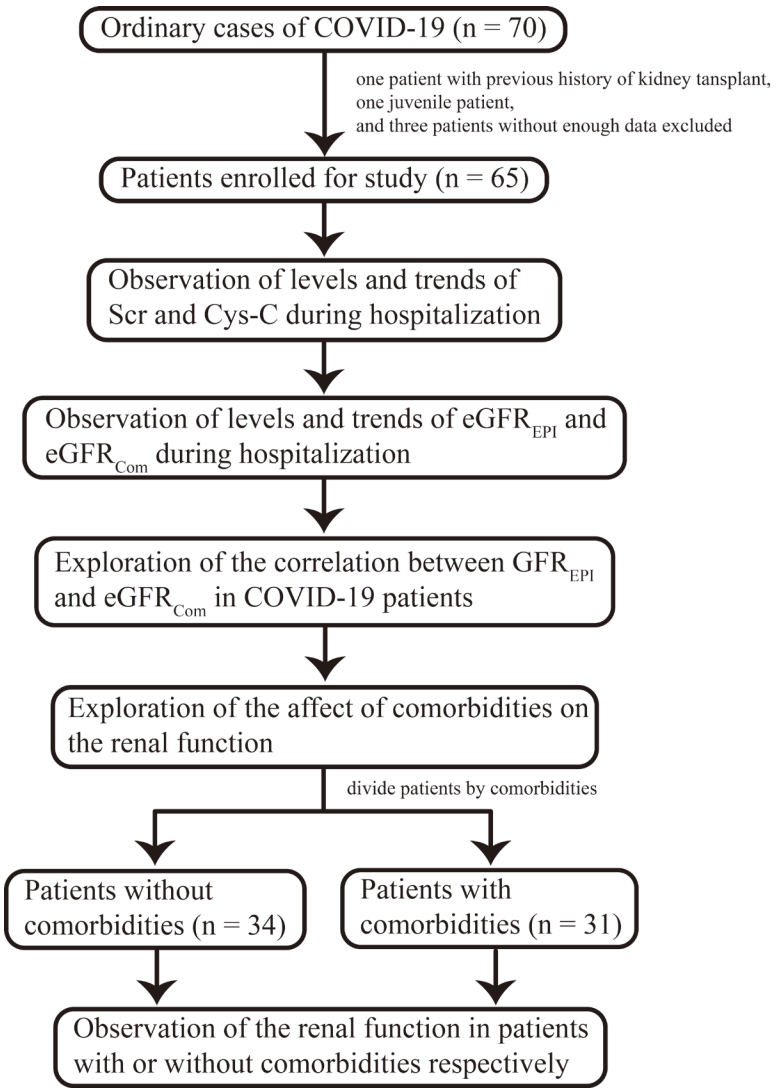

Figure 1: Flow chart of the overall procedures of our research

Data collection

We enrolled 70 COVID-19 patients with ordinary condition according to the guidelines of the national health commission of China (version 6, http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2.shtml) admitted by the Wuhan support team of Sir Run Run Shaw Hospital. The diagnostic criteria for ordinary cases were patients have a positive result in nucleic acid test of COVID-19, have fever or respiratory symptoms, and have CT findings of pneumonia, pulse oxygen saturation (SpO2) higher than 93%, arterial partial pressure of oxygen (PaO2): oxygen concentration (FiO2) ≤ 300 mmHg, and development of pulmonary lesions less than 50% in 24 to 48 hours. Patients were admitted from February 15, 2020 to February 29, 2020. All patients were Chinese. The inclusion criteria were patients meeting the diagnostic criteria for COVID-19, ordinary cases, patients aged 18 years or older, patients with no previous history of chronic kidney diseases (CKD), patients with one or more repeat blood examinations excluding the first one performed on admission. According to the inclusion criteria, 5 patients were excluded (Figure 1). We carried out physical examinations, complete blood counts, serum biochemical tests, tests for inflammatory biomarkers, urine analyses, and other necessary routine examinations at admission. Patients were mainly treated with antiviral drug Arbidol hydrochloride. Meanwhile, supportive treatments such as antipyretic drugs, anti-cough drugs, and oxygen inhalation were administered on demand. The laboratory examinations were repeated 5 days later.

Data for our study was collected from the electronic medical system. The data were recorded by one researcher and checked by another. Details collected for the study including demographic information, examinations, and comorbidities are listed in Supplementary text 1.

Assessment of kidney injury and the normal ranges of the markers

We used serum Cr, serum Cys-C, and eGFR as criteria for evaluating kidney injury. We estimated eGFR twice (with Cr alone and with the combination of Cr and Cys-C). We adopted the Epidemiology (EPI) equation propose by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which is the most frequently used equation in clinic to estimate GFR with Cr alone [7]. GFR estimated with EPI equation was abbreviated as $eGFR_{EPI}$.

We simultaneously estimated GFR using a newly proposed equation with the combination of Cr and Cys-C [8]. CKD-EPI also participated in the development of the new equation, but the authors did not name the equation. Hence, we provisionally name it as $eGFR_{Com}$ in our study, as it involved the combination of Cr and Cys-C. Both equations are presented in Supplementary text 2.

According to the criterion of our hospital, the normal value of Cr ranges from 44 to 106 μmol/L. The normal range of Cys-C is lower than 1.0 mg/L. The normal range of eGFR is higher than 90 mL/min/1.73 m^2.

Statistical Analysis

Quantitative data were expressed as mean ± standard deviation and enumeration data were expressed as percentage. Statistical differences of the renal function in different time points were compared by paired t-test. Statistical differences between groups were assessed using analysis of variance (ANOVA). Correlation was tested using Pearson's correlation analysis. Criteria of statistical significance were set as *P*-value < 0.01 for correlation and *P*-value < 0.05 for difference. All statistical analyses were performed under R Environment (version 3.6.1, R foundation for Statistical Computing, Vienna, Austria).

Results

Baseline information of patients

The baseline information of 65 patients is presented in Table 1. All COVID-19 patients included in the study showed ordinary disease manifestation.

Characteristics	Value
Age, year	55.2 (41.3-69.1)
Sex	
Male	32 (49.2%)
Female	33 (50.8%)
Comorbidity	31 (47.7%)
Hypertension	18 (27.7%)
Diabetes	**5 (7.7%)**
Hyperlipidaemia	12 (18.5%)
Coronary heart disease	4 (6.2%)
Hyperuricemia (gout included)	6 (9.2%)

Table 1: Patient Characteristics

Levels and trends of serum Cr and Cys-C during hospitalization

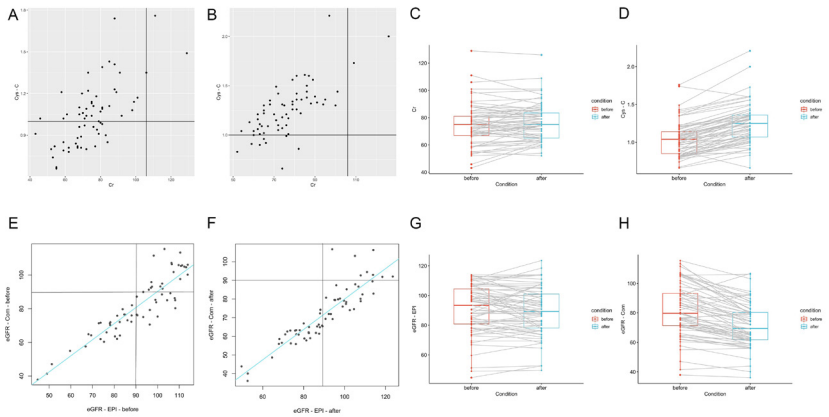

Figure 2: Levels and trend of the renal function of all COVID-19 patients during hospitalization **(A)** Levels of Cr and Cys-C on admission; **(B)** Levels of Cr and Cys-C 5 days after admission; **(C)** Trend of Cr from admission to 5 days after admission; **(D)** Trend of Cys-C from admission to 5 days after admission; **(E)** Levels of $eGFR_{EPI}$ and $eGFR_{Com}$ and correlation of $eGFR_{EPI}$ and $eGFR_{Com}$ on admission (correlation coefficient (cor) = 0.898, $P < 0.001$); **(F)** Levels of $eGFR_{EPI}$ and $eGFR_{Com}$ and correlation of $eGFR_{EPI}$ and $eGFR_{Com}$ 5 days after admission (cor = 0.889, $P < 0.001$); **(G)** Trend of $eGFR_{EPI}$ from admission to 5 days after admission; **(H)** Trend of $eGFR_{Com}$ from admission to 5 days after admission

	On admission (mean ± SD)	5 days after admission (mean ± SD)	P value
Cr (μmoI/L)	75.014 ± 15.258	76.237 ± 9.359	0.08
Cys-C (mg/L)	1.046 ± 0.288	1.252 ± 0.261	< 0.001
$eGFR_{EPI}$ (ml/min/1.73m²)	91.003 ± 16.504	89.879 ± 16.242	0.2
$eGFR_{Com}$ (ml/min/1.73m²)	81.668 ± 17.554	71.729 ± 14.877	< 0.001

Table 2: Renal function of all patients

None of the 65 patients had a known history of CKD and none of the patients showed symptoms of kidney injury such as oliguria and edema during hospitalization.

Most of the patients (63, 96.6%) showed Cr within the normal range on admission and 5 days after admission. We compared the level of Cr at different time points using paired t-test and Cr did not show significant elevation from the day of admission to 5 days after the admission (Figures 2A, B and C, and Table 2).

Thirty-seven (56.9%) patients were admitted with already elevated Cys-C level and number of patients with elevated Cys-C increased to 57 (87.7%) at 5 days after admission. Cys-C level increased significantly during the 5 days of hospitalization (Figure 2A, B and D, and Table 2).

These results indicate that the majority of the patients had elevated Cys-C level and the Cys-C level significantly elevated along with the course of COVID-19, while almost none of them showed elevated Cr levels.

Levels and trends of $eGFR_{EPI}$ and $eGFR_{Com}$ during hospitalization

Twenty-eight (43%) patients showed signs of decreased renal function according to $eGFR_{EPI}$ and the number increased to 33 (50.8%) at 5 days after admission. No significant difference was found between the two values of $eGFR_{EPI}$ at different time points (Figures 2E, F, and G, and Table 2).

When eGFR was estimated with the $eGFR_{Com}$ formula, 44 (67.7%) patients showed decreased renal function and the number of patients with decreased renal function increased to 57 (87.7%) at 5 days after admission. $eGFR_{Com}$ was significantly decreased at 5 days after admission (Figures 2E, F, and H, and Table 2).

Correlation between $eGFR_{EPI}$ and $eGFR_{Com}$

The results of the correlation analysis indicated that $eGFR_{EPI}$ and $eGFR_{Com}$ were significantly correlated at both time points (Figure 2E and F).

Influence of comorbidities on renal function

Results of ANOVA between patients with and without comorbidities indicated that Cys-C, $eGFR_{EPI}$, and $eGFR_{Com}$ were statistically different between patients with and without comorbidities (Table 3).

Patients without comorbidities			
	On admission (mean±SD)	5 days after admission (mean±SD)	P value
Cr (μmoI/L)	74.588 ± 11.34	75.147 ± 11.904	0.3
Cys-C (mg/L)	0.985 ± 0.195	1.185 ± 0.225	< 0.001
$eGFR_{EPI}$ (ml/min/1.73m²)	95.913 ± 12.224	95.814 ± 14.331	0.5
$eGFR_{Com}$ (ml/min/1.73m²)	86.842 ± 15.041	77.147 ± 14.141	< 0.001
Patients with comorbidities			
	On admission (mean±SD)	5 days after admission (mean±SD)	P value
Cr (μmoI/L)	75.481 ± 18.619	77.432 ± 15.04	0.1
Cys-C (mg/L)	1.112 ± 0.242	1.325 ± 0.278	< 0.001
$eGFR_{EPI}$ (ml/min/1.73m²)	85.618 ± 18.756	83.370 ± 16.433	0.1
$eGFR_{Com}$ (ml/min/1.73m²)	75.993 ± 18.342	65.786 ± 13.313	< 0.001

Table 3: The renal function of patients with or without comorbidities

Repeat analyses in patients with or without comorbidities

The aforementioned results suggested that the renal function at 5 days after admission was worse in patients with comorbidities. Various diseases such as diabetes mellitus and hypertension have already been proven to influence the renal function. Thus, we repeated the analyses to explore if kidney injury was general in COVID-19 patients without any comorbidity and to clarify whether the renal function in patients with comorbidities were influenced by COVID-19 or the comorbidities.

For patients without comorbidities, none of them had elevated Cr from admission to 5 days later. Fifteen out of 34 (44.1%) patients had elevated Cys-C on admission and the number of patients increased to 28 (82.4%) 5 days later. $eGFR_{Com}$ was decreased significantly. Significant correlation was observed between $eGFR_{EPI}$ and $eGFR_{Com}$. All results are presented in Figure 3 and Table 3.

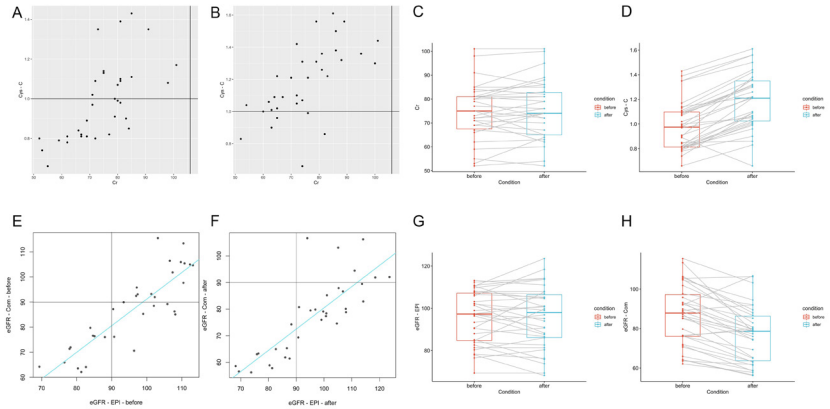

Figure 3: Levels and trends of the renal function of patients without comorbidities **(A)** Levels of Cr and Cys-C on admission; **(B)** Levels of Cr and Cys-C 5 days after admission; **(C)** Trend of Cr from admission to 5 days after admission; **(D)** Trend of Cys-C from admission to 5 days after admission; **(E)** Levels of $eGFR_{EPI}$ and $eGFR_{Com}$ and correlation of $eGFR_{EPI}$ and $eGFR_{Com}$ on admission (cor = 0.861, $P < 0.001$); **(F)** Levels of $eGFR_{EPI}$ and $eGFR_{Com}$ 5 days after admission and correlation of $eGFR_{EPI}$ and $eGFR_{Com}$ 5 days after admission (cor = 0.810, $P < 0.001$); **(G)** Trend of $eGFR_{EPI}$ from admission to 5 days after admission; **(H)** Trend of $eGFR_{Com}$ from admission to 5 days after admission

For patients with comorbidities, 2 (6.4%) of them had elevated Cr from admission to 5 days later. Twenty-two out of 34 (71.0%) patients had elevated Cys-C on admission and the number of patients increased to 29 (93.5%) 5 days later. $eGFR_{Com}$ also decreased significantly. Significant correlation was observed between $eGFR_{EPI}$ and $eGFR_{Com}$. All results are presented in Figure 4 and Table 3.

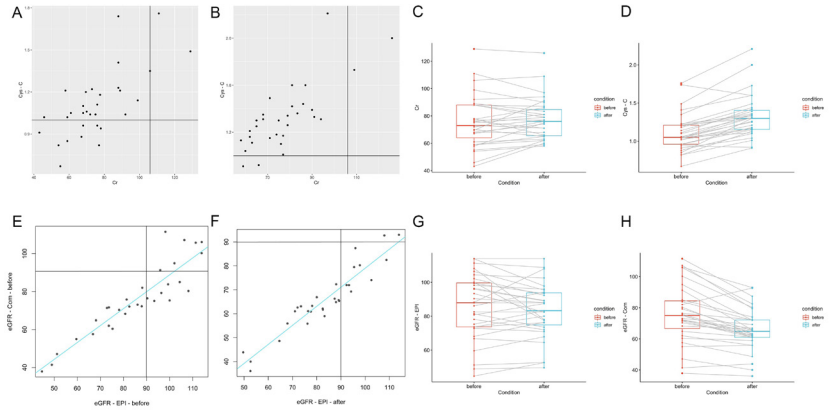

Figure 4: Levels and trend of the renal function of patients with comorbidities **(A)** Levels of Cr and Cys-C on admission; **(B)** Levels of Cr and Cys-C 5 days after admission; **(C)** Trend of Cr from admission to 5 days after admission; **(D)** Trend of Cys-C from admission to 5 days after admission; **(E)** Levels of $eGFR_{EPI}$ and $eGFR_{Com}$ and correlation of $eGFR_{EPI}$ and $eGFR_{Com}$ on admission (cor = 0.861, $P < 0.001$); **(F)** Levels of $eGFR_{EPI}$ and $eGFR_{Com}$ and correlation of $eGFR_{EPI}$ and $eGFR_{Com}$ 5 days after admission (cor = 0.810, $P < 0.001$); **(G)** Trend of $eGFR_{EPI}$ from admission to 5 days after admission; **(H)** Trend of $eGFR_{Com}$ from admission to 5 days after admission

Thus, the results obtained from patients without or without comorbidities were consistent with the results from all patients.

Subsequent observations of Cr and Cys-C

We examined the renal function for the third time (8 to 28 days after admission) in 22 patients with longer duration of hospitalization. As the sample size was not big enough for statistical analysis, we have listed only the numerical observations. Cr of all patients was within the normal range. All patients showed elevated Cys-C in the second test. Cys-C levels of 16 patients were decreased in the third examination, but the levels reverted to normal in only eight patients. Cys-C levels were further increased in 6 patients in the third examination.

Discussion

In the present study, we collected the clinical information of 65 hospitalized adult COVID-19 patients in ordinary condition. Interestingly, we found that Cr levels of almost all the patients were normal during the disease course. However, Cys-C, which is another indicator for kidney injury, showed abnormal levels. Cys-C levels of the majority of the patients (56.9%) were already elevated beyond normal range on admission and kept increasing during hospitalization. Almost all (87.7%) patients had aberrant Cys-C levels at 5 days after admission. Along with elevation of Cys-C levels, eGFR (especially $eGFR_{Com}$) showed evident decrease. According to the $eGFR_{EPI}$ values, approximately 50% of the patients had impaired renal function on admission and the proportion did not change significantly 5 days later. According to $eGFR_{Com}$, the majority (67.7%) of the patients had kidney injury on admission and the proportion increased to 87.7% at 5 days after admission. Significant correlation was observed between $eGFR_{EPI}$ and $eGFR_{Com}$. Although ANOVA showed that the renal function was significantly worse in patients with comorbidities, identical conclusions could be drawn in patients with or without underlying diseases. Thus, kidney injury was consistently present in COVID-19 patients irrespective of the comorbidities. More efforts are needed for observing whether the kidney injury is reversible.

Serum Cys-C is known to be a more sensitive indicator than Cr for detecting early kidney injury. Reports have revealed that Cys-C could detect kidney injury 1–3 days earlier than Cr in cases such as surgeries, trauma, and acute or chronic diseases [9-12]. Importantly, studies have found that Cys-C could predict the risk of developing CKD and act as an independent prognostic predictor for long-term survival in various chronic diseases [13-15]. Although Cr did not change during the COVID-19 disease course in our patients, elevation of Cys-C level was observed.

Cys-C is a 13 kD basic protein, belonging to the cystatin superfamily of cysteine protease inhibitors. Cys-C is produced in all kinds of nucleated cells in a stable rate, which would not be influence by inflammation, age, diet, gender, muscle mass, tumor, and other factors. Cys-C could be filtered freely by glomerular, so that the serum concentration of Cys-C is mainly decided by GFR of individuals [16]. Thus, Cys-C has come into the views of researchers as a new indicator for renal function assessment.

Growing evidence suggests that GFR estimation based on Cr is relatively imprecise. Cys-C is considered a novel alternative for estimating GFR, which is potentially superior to Cr alone. A study including 5352 participants proposed a new equation for GFR estimation based on both Cr and Cys-C and the authors proved that eGFR estimated by the novel equation showed better approximation to GFR values directly measured by the gold standard than equations based on Cr or Cys-C alone [8]. The new equation is broadly adopted and subsequent studies have found that it has superior precision in diagnosing kidney injury and better prognostic value in prediction of long-term outcome in various diseases [17-19]. In the present study, impairment of eGFR was detected by both the methods, but the proportion of patients detected with kidney injury varied greatly between the two methods (Cr alone and the combination of Cr and Cys-C). Our results were consistent with the fact that Cys-C is a more sensitive predictor of kidney injury. Hence, we could infer that kidney injury was generally present in COVID-19 patients, but its extent was not serious enough to be detected by Cr alone. Additionally, the increase in Cys-C and the decrease in eGFR were particularly evident in patients with underlying diseases.

In addition, the level of serum Cys-C in some patients increased continuously and did not revert to normal until discharge. Hence, the potential risk of chronic kidney diseases should not be ignored. Thus, physicians should pay more attention to kidney injury during the management of COVID-19 patients.

Although the mechanism of kidney injury in COVID-19 patients is not clear, researchers have already drawn similar conclusions in other infectious diseases caused by coronaviruses. The incidence rate of acute kidney injury (AKI) in severe acute respiratory syndrome (SARS) was about 6% and the mortality of patients with AKI was up to 90% [20,21]. The ribonucleic acid (RNA) of SARS-Cov was detected in the distal convoluted renal tubule in autopsy tissues [22-24]. Nevertheless, it was not clarified whether planting of the virus was the immediate cause of AKI. Middle East respiratory syndrome coronavirus (MERS-CoV) is another deadly coronavirus. AKI is the most common extrapulmonary organ dysfunction in MERS-Cov infection and its high incidence is a unique clinical characteristic not found in other human coronavirus infections. Among patients with MERS-CoV infection, 75% of the critical patients developed AKI and 48% of the patients needed renal replacement therapy [25,26]. MERS-CoV was found to localize in the renal proximal tubular epithelial cells [27]. Further study has revealed that MERS-CoV may cause direct damage to the infected tubular epithelial cells through induction of apoptosis [28]. Currently, researchers have successfully detected SARS-CoV-2 viral nucleic acid in urine samples [29]. It is not clear whether the virus could plant itself in the renal tissues and whether the kidney injury observed in the present study was due to direct damage caused by the virus. Tissue autopsy experiments are needed to answer these queries.

SARS-CoV-2 enters host cells through an entry receptor known as angiotensin-converting enzyme 2 (ACE2). It is expressed broadly in various types of cells, especially the respiratory epithelial cells [30]. Single cell RNA sequencing has verified the expression of ACE2 in the proximal tubules of kidney [31,32]. Thus, SARS-CoV-2 is likely to invade kidney tissues directly.

Even so, it is certain that the reasons for the kidney injury were not iatrogenic. Elevated Cys-C was observed in 56.9% of the patients on admission and most of these patients had not received any treatment before admission. Moreover, there is no evidence indicating that the medicines used for treatment (such as arbidol hydrochloride, moxifloxacin, and methoxyphenamine) have any side effects of kidney injury.

Regrettably, our study has some limitations. We did not evaluate the renal function using the gold standard (^{99m}Technetium-diethylenetriamine pentacetic acid plasma clearance rate). The sample size was relative small and further verification of our results is needed. Our research lacks a long-term follow-up, which would be completed with telephone subsequently.

Conclusion

The present study confirmed the evident elevation of serum Cys-C and the decrease in eGFR in COVID-19 patients. We also observed a dynamic elevation of Cys-C and a decrease in eGFR during hospitalization. Our work reveals presence of kidney injury in ordinary COVID-19 cases and the incidence rate was not as low as suspected previously. Physicians should monitor the renal function of COVID-19 patients with Cys-C and $eGFR_{Com}$ during hospitalization and pay more attention to the potential long-term kidney injury in discharged patients.

Authors' contributions

Lu M, Yang H and Yu H conceived, designed and conducted the study, as well as wrote the manuscript. Li H, Pan K, and Zhang G collected and analyzed the data. All authors reviewed the manuscript and participated in the language modification.

Support

Financial Disclosure

Not applicable

Other Disclosures

Not applicable

Acknowledgements

Not applicable

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