

# Renal dysfunction and prognosis of COVID-19 patients: a hospital-based retrospective cohort study

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## Research article

**Keywords:** Severe acute respiratory syndrome coronavirus-2, Coronavirus disease 2019, Renal dysfunction, Prognosis

**DOI:** <https://doi.org/10.21203/rs.3.rs-132297/v1>

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# Abstract

**Introduction:** Increasing evidence indicate that coronavirus disease 2019 (COVID-19) is accompanied by renal dysfunction. However, the association of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)-induced renal dysfunction with prognosis remains unclear.

**Materials and methods:** This prospective case-cohort study analyzed 154 COVID-19 patients from the Second People's Hospital of Fuyang City in Anhui Province. Clinical and demographic information were collected. Renal function was evaluated and its prognosis was followed up.

**Results:** Of 154 hospitalized patients with COVID-19, 125 were common and 29 were severe patients. On admission, 16 (10.4%) patients were with renal dysfunction. Serum creatinine and cystatin C were increased, eGFR was decreased in severe patients compared with those in common patients. Renal dysfunction was more common in severe patients. By multivariate logistic regression, male, higher age and hypertension were three importantly independent risk factors of renal dysfunction in COVID-19 patients. Follow-up study found that at least one renal function marker of 3.33% patients remained abnormal in two weeks after discharge.

**Conclusion:** Male elderly COVID-19 patients with hypertension elevates the risk of renal dysfunction. SARS-CoV-2-induced renal dysfunction are not fully recovered in two weeks after discharge.

## Background

At the winter of 2019, Coronavirus Disease 2019 (COVID-19), a newly recognized infectious disease with unclear etiology broke out in Wuhan City, Hubei Province, China [1]. Later, this unknown virus was clarified and named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [2, 3]. Now, it has been pandemic in the world. Up to May 20th, there were 4 927 861 accumulated confirmed patients of SARS-CoV-2 infections in approximate 150 countries, of them 320 921 cases have died [4]. The entire earth is suffering great public health threat from SARS-CoV-2 [5]. Therefore, all medical staff, scientific research personnel and all sectors of the entire society must cooperate to slow-down COVID-19 spread and search useful cures.

Previous studies have found that COVID-19 patients mainly accompanied with fever, diarrhea, dry cough, lymphocyte reduction and radiographic evidence of pneumonia [6]. Now, more and more studies have confirmed that SARS-CoV-2 not only evoked severe acute respiratory syndrome, but also induced multiple organ injuries, such as immune system damage, myocardial injury and even liver dysfunction [7–10]. Nevertheless, the clinical characteristics of renal dysfunction caused by SARS-CoV-2 are rarely described. In addition, the clinical significance of SARS-CoV-2-induced renal dysfunction and its recovery situation are still unclear.

The aim of this study was to investigate SARS-CoV-2-induced renal dysfunction, its risk factors and prognosis after discharge. Our results suggest that male elderly COVID-19 patient with hypertension are

more prone to renal dysfunction. Our research firstly reveals that SARS-CoV-2-evoked renal dysfunction are not fully recovered in two weeks after discharge.

## Materials And Methods

### Study design and participants

In the present study, 154 patients with COVID-19 were enrolled in the Second People's Hospital of Fuyang City of Anhui Province from January 1 to February 30, 2020. The Second People's Hospital of Fuyang City was the designated infectious hospital and assigned responsibility for the treatment of COVID-19 patients in the Fuyang City. All patients were confirmed with SARS-CoV-2 infection using RT-PCR on pharyngeal swab specimens. Diagnosis of COVID-19 was based on the New Coronavirus Pneumonia Prevention and Control Program (5th edition) published by the National Health Commission of China. There was no death case with COVID-19 in the Fuyang City. All patients were discharged. At last, 150 cured COVID-19 patients were performed follow-up research in two weeks after discharge. Renal function was assessed and blood routine was measured in 150 patients with COVID-19. This project was approved by the institutional ethics board of the Second People's Hospital of Fuyang City (No. 2020-5). Oral consent was gained from patients or patients' next of kin.

### Data collection

The medical record of COVID-19 patients was collected. Demographic data, clinical characteristics and comorbidities were counted. Patients' signs and symptoms were evaluated. The date of onset and outcomes of COVID-19 patients were recorded. Uric acid, urea nitrogen, creatinine, cystatin C and eGFR were measured on admission. All laboratory tests were measured by the clinical laboratory in the Second People's Hospital of Fuyang City.

### Statistical analysis

All statistical analysis was performed using SPSS19.0 software. Categorical variables were expressed with frequencies and percentages. Continuous variables were shown using median values. All categorical variables were compared for the study outcome by using Fisher exact test or  $\chi^2$  test, and continuous variables were compared via *t* test or the Mann-Whitney U test, as appropriate. Moreover, the main risk factors of renal dysfunction were examined using multivariable logistic regression models adjusted for potential confounders. Significant differences were reported with *P* values less than 0.05.

## Results

### Demographic and clinical characteristics

All 154 COVID-19 patients' clinical characteristics were analyzed in the Second People's Hospital of Fuyang City of Anhui Province. As shown in Table 1, mild patient, defined as oxygenation index higher than 300, was 125 (81.2%). For severe patient, whose oxygenation index was lower than 300, accounted for 18.8% (Table 1). Besides, the demographic data were then collected. As shown in Table 2, 92 (59.7%)

were male and 62 (40.3%) were female. There were 69 patients younger than 39 years old, 68 patients aged between 40 and 59, and 17 patients older than 60 years old. Among 154 COVID-19 patients, 22 (14.3%) cases had hypertension, 8 (5.19%) cases had diabetes and 12 (7.79%) cases had other chronic diseases.

Table 1. The association between the severity of COVID-19 patients and renal functional indexes.

Parameters	Mild	Severe
Cases, N	125	29
Uric acid ( $\mu\text{mol/L}$ )	239.0 (180.0, 306.8)	218.0 (186.0, 247.5)
Urea nitrogen (mmol/L)	3.7 (3.1, 4.7)	4.0 (2.8, 5.4)
Creatinine ( $\mu\text{mol/L}$ )	65.0 (52.0, 77.0)	70.0 (54.5, 83.5) *
Cystatin C (mg/L)	0.81 (0.70, 0.92)	0.89 (0.71, 0.93) *
eGFR (mL/min)	126.4 (103.4, 150.6)	118.6 (99.3, 142.7) *
Renal dysfunction, N (%)	5 (4.0%)	11 (37.9%)

Renal dysfunction was defined as any of renal functional indexes beyond normal range.

\* $P < 0.05$ , \*\* $P < 0.01$ .

Table 2

The effects of demographic characteristics and complications on renal function indexes.

	Cases	Uric acid ( $\mu\text{mol/L}$ )	Urea nitrogen ( $\text{mmol/L}$ )	Creatinine ( $\mu\text{mol/L}$ )	Cystatin C ( $\text{mg/L}$ )	eGFR ( $\text{mL/min}$ )
<b>Gender</b>						
Male	92	274.0 (218.0, 336.0)	4.3 (3.6, 5.2)	75.0 (66.0, 82.0)	0.84 (0.75, 0.94)	110.3 (97.0, 133.1)
Female	62	201.0 (157.5, 245.0) **	3.2 (2.7, 3.6) *	51.5 (44.0, 57.0) **	0.72 (0.64, 0.81) *	142.2 (124.3, 175.3) **
<b>Age</b>						
<39	69	253.0 (191.5, 306.5)	3.6 (3.2, 4.3)	65.0 (49.5, 78.5)	0.76 (0.66, 0.87)	133.5 (108.5, 181.6)
40–59	68	243.0 (186.0, 329.0)	3.6 (3.0, 4.8)	63.5 (53.0, 76.3)	0.80 (0.71, 0.94)	122.9 (103.4, 142.9) *
>60	17	288.0 (229.5, 347.0) ***	5.3 (3.6, 6.9) *#	72.0 (60.5, 87.0) *#	0.90 (0.81, 1.39) ***	105.4 (84.5, 121.1) ##
<b>Hypertension</b>						
Yes	22	225.0 (195.0, 354.5)	5.1 (3.1, 6.7)	65.0 (52.0, 78.0)	0.89 (0.75, 1.07)	110.0 (94.3, 144.1)
No	132	235.5 (178.3, 295.5)	3.7 (3.1, 4.6) **	66.0 (52.0, 77.0)	0.80 (0.69, 0.89) *	126.4 (103.2, 148.7)
<b>Diabetes</b>						
Yes	8	327.0 (235.0, 372.0)	6.3 (5.5, 10.6)	72.0 (57.0, 108.0)	0.99 (0.87, 1.54)	106.2 (63.9, 133.0)
No	146	234.0 (182.0, 298.0) **	3.7 (3.1, 4.6) **	65.0 (52.0, 77.0) *	0.80 (0.70, 0.90) **	126.0 (103.3, 150.1) *
<b>Other diseases</b>						
Yes	12	227.0 (190.5, 344.5)	4.5 (2.5, 6.0)	69.0 (59.5, 76.8)	0.90 (0.81, 0.94)	109.8 (96.0, 129.8)
No	142	236.0 (181.0, 298.0)	3.7 (3.1, 4.7)	65.0 (52.0, 77.8)	0.79 (0.70, 0.91)	126.5 (103.3, 150.1) *
Note: Cases in Gender, compared with "Male", * $P < 0.05$ , ** $P < 0.01$ .						
Cases in Age, compared with "<39", * $P < 0.05$ , ** $P < 0.01$ ; Compared with "40–59", # $P < 0.05$ , ## $P < 0.01$ .						
Cases in Hypertension, Diabetes and Other diseases, compared with "Yes", * $P < 0.05$ , ** $P < 0.01$ .						

## Correlation of renal dysfunction with the severity of COVID-19 patients

The correlation between renal dysfunction and the severity of COVID-19 was analyzed in patients. Serum renal function indexes, including uric acid, urea nitrogen, creatinine, cystatin C and eGFR, were measured. As shown in Table 1, the level of serum creatinine and cystatin C were higher, the level of serum eGFR was lower in severe patients than those of mild patients. There was no difference of uric acid, urea nitrogen and cystatin C between mild patients and severe patients. Renal dysfunction was defined as any of renal functional indexes beyond normal range. Our results indicated that 5 (4.0%) COVID-19 patients were with renal dysfunction in mild patients and 11 (37.9%) patients were with renal dysfunction in severe patients on admission. Besides, the correlations between renal function indexes and inflammatory cytokines were analyzed. As shown in Fig. 1, no significant correlations were observed between inflammatory cytokines with uric acid and creatinine. Besides, there was a weakly positive correlation between urea nitrogen with CRP and IL-6 ( $r = 0.208, P = 0.012$ ;  $r = 0.421, P < 0.012$ ). Further analysis indicated that cystatin C was negatively correlated with IL-6 ( $r = -0.472, P = 0.001$ ) and eGFR was negatively correlated with CRP ( $r = -0.210, P = 0.012$ ).

## Male elderly COVID-19 patients with hypertension are more prone to renal dysfunction

The influences of demographic characteristics and complications on renal dysfunction were researched. As shown in Table 2, the level of uric acid, urea nitrogen, creatinine and cystatin C were higher and eGFR were lower in males than those in females. The effect of age on renal function was analyzed. The results revealed that the level of eGFR was lower in patients between 40 to 59 years old than those of younger than 39 years old. Moreover, our results also revealed that the levels of uric acid, urea nitrogen, creatinine and cystatin C were higher in patients older than 60 years than those younger patients. The level of eGFR was lowest in the patients older than 60 years old. In addition, the effects of comorbidities on renal dysfunction markers were then analyzed. As shown in Table 2, the level of urea nitrogen was increased and the level of cystatin C was reduced in COVID-19 patients with hypertension. In addition, the levels of uric acid, urea nitrogen, creatinine and cystatin C were increased and the level of eGFR was decreased in COVID-19 patients with diabetes. Meanwhile, we found that the level of eGFR was slightly lower in COVID-19 patients with other chronic diseases than those without chronic disease. In addition, the risk factors of renal dysfunction were analyzed using multivariable logistic regression among COVID-19 patients. As shown in Table 3, the *OR* of male gender was 1.465 (95% *CI*: 1.124, 4.001), the *OR* of age was 1.945 (95% *CI*: 1.024, 3.128) and the *OR* of hypertension was 2.345 (95% *CI*: 1.135, 3.458) for renal dysfunction, respectively. Diabetes and other diseases had no obvious effect on renal dysfunction among COVID-19 patients (Table 3).

Table 3.

Multivariable logistic regression analysis between demographics characteristics and complications with renal dysfunction among COVID-19 patients.

	b	Wald	P value	OR (95% CI)
Male	0.584	4.123	0.008	1.465 (1.124, 4.001)
Age	0.784	6.512	0.021	1.945 (1.024, 3.128)
Hypertension	0.457	2.354	0.031	2.345 (1.135, 3.458)
Diabetes	0.468	2.324	0.564	0.865 (0.654, 1.231)
Other diseases	0.384	1.128	0.387	0.721 (0.324, 1.178)

### Renal function indexes were abnormal in two weeks after discharge

The recovery situation of renal dysfunction was investigated in COVID-19 patients. Renal function indexes were evaluated between on admission and in two weeks after discharge in the Second People's Hospital of Fuyang City. As shown in Table 4, there was no significant difference in the levels of urea nitrogen, creatinine, cystatin C and eGFR between on admission and after discharge. However, uric acid was increased in two weeks after discharge than on admission. At early stage, the levels of uric acid in 4 (2.6%) patients, the levels of urea nitrogen in 4 (2.6%) patients, the levels of creatinine in 1 (0.6%) patient and the levels of cystatin C in 6 (3.9%) patients were above the normal range. The levels of eGFR in 6 (3.9%) patients were below the normal range. There were total 16 (10.4%) patients with renal dysfunction. The prognosis of COVID-19 patients with renal dysfunction was tracked until two weeks after discharge. The levels of uric acid and urea nitrogen were fully recovered in two weeks after discharge. Additionally, the levels of creatinine in 1 (0.7%) patients and the levels of cystatin C in 2 (1.4%) patients were above the normal range, the levels of eGFR in 2 (1.4%) patients were below the normal range (Table 4). Further analysis found that 5 (3.33%) COVID-19 patients persisted with renal dysfunction in two weeks after discharge (Table 4).

Table 4  
Renal functional indexes on admission and after discharge among COVID-19 patients.

Renal indexes	On admission (N = 154)			Discharge (N = 150)		
	Median	Below the range, N (%)	Above the range, N (%)	Median	Below the range, N (%)	Above the range, N (%)
Uric acid (μmol/L)	235.0 (183.0, 299.5)	52 (33.8)	4 (2.6)	283.0 (237.0, 351.0) *	43 (28.6)	0 <sup>#</sup>
Urea nitrogen (mmol/L)	3.7 (3.1, 4.7)	35 (22.7)	4 (2.6)	3.9 (3.4, 4.8)	17 (11.5)	0 <sup>#</sup>
Creatinine (μmol/L)	65.5 (52.0, 77.0)	3 (1.9)	1 (0.6)	59.0 (48.0, 71.0)	5 (3.4)	1 (0.7)
Cystatin C (mg/L)	0.8 (0.7, 0.9)	15 (9.7)	6 (3.9)	0.76 (0.69, 0.87)	14 (9.5)	2 (1.4)
eGFR (mL/min)	125.8 (103.0, 148.6)	6 (3.9)	86 (55.8)	134.1 (118.7, 156.5)	2 (1.4)	72 (48.6)
Renal dysfunction, N (%)		16 (10.4%)			5 (3.33%) <sup>†</sup>	
Compared with "Median values" among COVID-19 patients on admission, ** $P < 0.01$ ;						
Compared with "Above the range" among COVID-19 patients on admission, # $P < 0.05$ , ## $P < 0.01$ ;						
Compared with "On admission", <sup>†</sup> $P < 0.05$ .						

## Discussion

This research mainly analyzed SARS-CoV-2-induced renal dysfunction, its risk factors and prognosis in two weeks after discharge. Our results indicate that male elderly COVID-19 patients with hypertension were more prone to renal dysfunction. In addition, SARS-CoV-2-evoked renal dysfunction were not fully recovered in two weeks after discharge.

Increasing data have confirmed that SARS-CoV-2 induced multiple organ injuries, mainly including liver dysfunction, myocardial injury, lymphocyte reduction and even respiratory failure [7–10]. In this research, the levels of serum uric acid, urea nitrogen, creatinine, cystatin C and eGFR were detected and renal function was evaluated among COVID-19 patients on admission and discharge. Our results indicated that creatinine and cystatin C were increased, eGFR was decreased in severe COVID-19 patients. There was no difference of uric acid, urea nitrogen and cystatin C between mild and severe COVID-19 patients. Furthermore, the number of COVID-19 patients with renal dysfunction was more in severe patients than

those in mild patients. Renal dysfunction was more pervasive in severe patients with COVID-19. Our data indicate that renal dysfunction on admission is positively correlated with the severity of COVID-19 patients.

Earlier studies have confirmed that older age elevated the risk of death in COVID-19 patients [11, 12]. Several comorbidities aggravated the severity of COVID-19 patients [13, 14]. In this research, the influences of demographic characteristics on renal dysfunction were evaluated. No difference was observed in urea nitrogen between female and male patients. Uric acid and cystatin C were decreased, eGFR was increased in females. Additionally, we found that the levels of uric acid, urea nitrogen, creatinine and cystatin C were higher and the level of eGFR was lower in the older patients than those in younger patients. Of 154 COVID-19 patients, there were 22 (14.3%) patients with hypertension, 8 (5.19%) patients with diabetes and 12 (7.79%) patients with other chronic diseases. Furthermore, the influences of basic complications on renal dysfunction were analyzed. Our results indicated that the levels of urea nitrogen and cystatin C were increased in COVID-19 patients with hypertension. Further analysis found that uric acid, urea nitrogen, creatinine and cystatin C were increased and eGFR was decreased in COVID-19 patients with diabetes. Furthermore, we also found that eGFR was decreased in COVID-19 patients with other chronic diseases. These results indicate that male, older age and basic comorbidities with hypertension and diabetes may aggravate the risk of renal dysfunction in COVID-19 patients. For the sake of analyzing the risk factors of renal dysfunction among COVID-19 patients, the multivariate logistic regression was performed. These results suggested that male, older age and hypertension were three independent risk factors of renal dysfunction among COVID-19 patients. Generally speaking, male elderly COVID-19 patients with hypertension are more prone to renal dysfunction.

The prognosis of renal dysfunction in COVID-19 patients remained obscure. This is an urgent problem which is worthy of researching whether renal dysfunction recovers during a short-term after discharge. In the present project, 150 cases with COVID-19 were followed up and renal function were measured via blood routine tests. Every renal marker and the rate of renal dysfunction were compared between on admission and in two weeks after discharge among COVID-19 patients. Although, no significant difference of urea nitrogen, creatinine, cystatin C and eGFR were observed before and after discharge. However, the levels of uric acid were slightly increased in two weeks after discharge compared with COVID-19 patients on admission. Moreover, the abnormal number of patients with creatinine, cystatin C and eGFR were similar between on admission and in two weeks after discharge. Interestingly, a few patients with serum creatinine, cystatin C and eGFR were still out of the normal range in two weeks after discharge. These data suggest that renal function indexes of 3.33% cases with COVID-19 were not fully recovered in two weeks after discharge. Hence, whether SARS-CoV-2 evokes a long-time renal dysfunction is needed to be researched in the next therapeutic methods.

The mechanism of which SARS-CoV-2 evokes renal dysfunction is still unknown. More and more reports have revealed that SARS-CoV-2 plays a pathogenetic role in COVID-19 patients through the receptor of angiotension converting enzyme (ACE)2 [15, 16]. At present, several researches demonstrated that ACE2 is also expressed in renal tubular epithelium [17]. Therefore, we speculate that SARS-CoV-2 may directly

damage kidney tissue through binding to the ACE2 receptor. Besides, earlier studies found that inflammatory cytokines were dramatically elevated in patients with COVID-19 [18–20]. It is generally known that cytokine storm was associated with the severity and the levels of IL-6 and CRP can predict the severity and prognosis of COVID-19 patients [21, 22]. IL-6 is a multifunctional cytokine that transmits cell signaling and regulates immune cells [23]. CRP is an acute-phase proinflammatory cytokine and a sensitive biomarker of infection and tissue damage [24]. High levels of CRP or IL-6 always induces cytokine storm and impairs multiple organs function. In the present study, we found that IL-6 and CRP were positively associated with renal dysfunction. Therefore, these results indicated that SARS-CoV-2-induced cytokine storm may be one of the mechanisms of renal dysfunction.

There are several weaknesses in this study. Firstly, this was only a single center research, all patients were from the Fuyang City in Anhui Province which caused selection bias. All patients with COVID-19 were timely found and treated in the Fuyang City, so COVID-19 patients only were mild and severe cases in the Fuyang City, the prevalence was very low and severity of renal dysfunction was modest. Secondly, renal dysfunction was evaluated only through the linear determination of biomarkers and not in an accepted and comparable way (AKIN, KADIG, etc), more assessment methods are needed to evaluate the renal dysfunction in the next project. Thirdly, because of minor specimen, a larger sample size is needed to perform. Fourthly, this current study was only a hospital-based prospective cohort study, the mechanism by which SARS-CoV-2 induced renal dysfunction in COVID-19 patients was unclear, more animal studies and in vivo experiment are needed in the future research.

## Conclusion

In summary, this study mainly described SARS-CoV-2-evoked renal dysfunction in patients with COVID-19 in the Second People's Hospital of Fuyang City of Anhui Province. These data reveal that SARS-CoV-2-induced renal dysfunction is more common in severe patients with COVID-19. Moreover, male elderly COVID-19 patients with hypertension are more prone to renal dysfunction. Our study firstly finds that SARS-CoV-2-induced renal dysfunction is not fully recovered in two weeks after discharge. So, it is needed to further explore whether SARS-CoV-2 evokes a long-period renal dysfunction in COVID-19 patients.

## Abbreviations

COVID-19: coronavirus disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; IL-6: Interleukin-6; CRP: C-reactive protein; ACE: angiotension converting enzyme; eGFR: estimated glomerular filtration rate.

## Declarations

### Ethics approval and consent to participate

This project was approved by the institutional ethics board of the Second People's Hospital of Fuyang City (No. 2020-5). Individual signed informed consent was gained from patients. In unconscious patients or those with mechanical ventilation, consent was obtained from the guardians of these participants.

### **Consent for publication**

Not applicable.

**Availability of data and materials** The data generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests.

### **Funding**

This study was supported by National Natural Science Foundation Incubation Program of the Second Affiliated Hospital of Anhui Medical University (grant number: 2019GQFY06).

### **Author contribution**

L.F. and H.Z. designed research; H.X.X., J.F., S.J.H., and X.Y.L. conducted research; H.X.X. analyzed data; L.F. and H.X.X. wrote the paper; L.F. and H.Z. had primary responsibility for final content. All authors read and approved the final manuscript.

### **Acknowledgements**

We greatly appreciate all doctors and nurses of respiratory and critical care medicine in the Second People's Hospital of Fuyang City for recruiting participants. Moreover, we also thank all patients and their families participated in this research.

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