Clinical characteristics of hospitalized patients with 2019 novel coronavirus disease indicate potential proximal tubular dysfunction

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In December 2019, highly infectious 2019 novel coronavirus disease (COVID-19) broke out in Wuhan, China. The pathogen was identified as 2019 novel coronavirus (2019-nCoV).[1] The 2019-nCoV had the capacity to cause systematic injury including renal injuries besides pneumonia.[2] Angiotensin-converting enzyme 2 (ACE2) acts as a cell entry receptor for 2019-nCoV.[1] ACE2 expression was dominant in proximal tubules within the kidney. In this study, the clinical data from hospitalized patients were retrospectively analyzed at their admission to identify if there is any evidence of proximal tubule injury.

This was a single-center, retrospective study performed in the Sino-French branch of Tongji Hospital in Wuhan, China. Data of patients admitted to the hospital from January 28, 2020 to February 10, 2020 were collected. The patients were diagnosed and classified according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 4)."[3] Patients with a history of chronic kidney disease (CKD) and with any abnormal urinalysis result in the past 3 months before admission were excluded.[4] This study was conducted in accordance with the *Declaration of Helsinki* and approved by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. TJ-C20200132). Written informed consent was waived in light of the rapid emergence of this infectious disease.

The clinical electronic medical records, nursing records, and laboratory findings for all patients were reviewed. Data on age, sex, history of chronic diseases, days from symptoms onset to hospital admission, and laboratory values at admission were collected. The estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Hematuria and proteinuria were defined as more than 1+ hemoglobin or protein in urine dipstick tests. CKD was defined and diagnosed according to the Kidney Disease: Improving Global Outcomes criteria.

Statistical analyses were performed using SPSS 21.0 (SPSS for Windows; IBM Corp., Chicago, IL, USA). Categorical variables were presented as counts and percentages, and continuous variables were expressed as median and interquartile range (IQR) or mean ± standard deviation according to the distribution of normality. The Student's *t* test or the Wilcoxon rank-sum test was used for analysis of continuous variables. The Chi-squared test or the Fisher exact test was used for categorical variables as appropriate. A two-sided $P < 0.05$ was considered statistically significant.

A total of 93 COVID-19 patients were enrolled in this study, including 22 (23.7%) common and 71 (76.3%) severe cases. The median age was 60 years (IQR, 46–68 years; range, 20–88 years). Further, 45 (48.4%) patients were older than 60 years. The median duration from the first symptom onset to hospital admission was 9.0 days (IQR, 6.0–11.0 days). Of the 93 patients, 46 (49.5%) had one or more coexisting medical conditions. Hypertension (34 [36.6%]), diabetes (13 [14.0%]), cardiovascular disease (4 [4.3%]), chronic respiratory disease (2 [2.2%]), and malignancy (1 [1.1%]) were the most common coexisting conditions. Three (3.2%) patients and five (5.4%) patients presented with vomiting and diarrhea, respectively.

The patients' clinical data were analyzed according to sex [Supplementary Table 1, http://links.lww.com/CM9/A252]. Compared with female patients (n = 52), male patients (n = 41) exhibited a significantly lower serum sodium level (136.8 ± 3.7 mmol/L *vs.* 139.0 ± 2.9 mmol/L; $t = 3.191$, $P = 0.002$) and eGFR (86.7 ± 20.6 mL·min^{-1}·1.73 m^{-2} *vs.*

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96.8 ± 19.7 mL·min^{-1}·1.73 m^{-2}, $t = 2.384$, $P = 0.019$), and higher serum potassium (4.3 ± 0.5 mmol/L *vs.* 4.1 ± 0.4 mmol/L, $t = -2.044$, $P = 0.044$) and high-sensitivity C-reactive protein (hs-CRP) level (46.0 [23.8, 140.0] mg/L *vs.* 34.9 [8.5, 60.0] mg/L; $Z = -2.364$, $P = 0.018$). Also, 24 (25.8%) patients exhibited hyponatremia at admission, and men (16 [39.0%]) were more likely to have hyponatremia as compared with women (8 [15.4%]) ($\chi^2 = 6.691$, $P = 0.010$). Thirty-two (34.4%) patients had hypochloridemia, and a sex-related difference (male *vs.* female: 53.7% *vs.* 19.2%, $\chi^2 = 12.039$, $P = 0.001$) was found. Nineteen (20.4%) patients with hypouricemia did not show any sex-related difference (male *vs.* female: 26.8% *vs.* 15.4%, $\chi^2 = 1.847$, $P = 0.174$).

At admission, a total of 79 patients had urinalysis results. The urinalysis data showed that 27 (34.2%) patients had proteinuria, and 16 (20.3%) patients had hematuria [Supplementary Table 2, http://links.lww.com/CM9/A252]. Only mild proteinuria (+ to ++) was found in all these 27 patients. Twenty-five patients with proteinuria were severe cases, whereas two patients were common cases, and the proportion of severe cases in patients with proteinuria was significantly higher than in patients without proteinuria (92.6% *vs.* 3.8%, $\chi^2 = 6.958$, $P = 0.008$). We observed a significantly decreased serum sodium level in patients with proteinuria (136.8 ± 3.7 mmol/L *vs.* 139.0 ± 3.0 mmol/L, $t = 2.793$, $P = 0.007$). Patients with proteinuria demonstrated a higher incidence of hematuria (37.0% *vs.* 11.5%, $\chi^2 = 7.154$, $P = 0.007$). Increased serum urea (5.1 [3.5, 6.6] mmol/L *vs.* 3.5 [2.9, 4.4] mmol/L; $Z = 3.046$, $P = 0.002$) and uric acid levels (266.1 ± 109.8 μmol/L *vs.* 216.9 ± 88.0 μmol/L; $t = -2.056$, $P = 0.046$) and decreased eGFR (87.9 ± 22.7 mL·min^{-1}·1.73 m^{-2} *vs.* 97.4 ± 17.7 mL·min^{-1}·1.73 m^{-2}; $t = 2.057$, $P = 0.043$) were seen in patients with proteinuria [Supplementary Table 2, http://links.lww.com/CM9/A252].

Moreover, 11 patients (13.9%) had glucosuria [Supplementary Table 3, http://links.lww.com/CM9/A252]. Among these patients, the median age was 64 years (range: 50–84 years). Three patients had diabetes and none had a history of CKD. None had a genetic tubular disorder or had a history of taking medication that could cause glucosuria (eg, sodium-glucose cotransporter-2 inhibitors). At admission, random blood glucose levels were above the normal range (4.11–6.05 mmol/L) in five patients, including three diabetic patients. On the following day, fasting blood glucose (FBG) levels were found to be abnormal in three patients with diabetes, while the other two patients were back to the normal range (4.86 and 4.57 mmol/L, respectively). These data revealed that eight patients (10.1%) presented with renal glucosuria. Five of them had both proteinuria and hematuria, and one of them only had proteinuria.

Renal involvement was evident in coronavirus infection-related diseases, including severe acute respiratory syndrome, Middle East respiratory syndrome, and COVID-19. Abnormal urinalysis results and renal function impairment are common findings in COVID-19.[4] The abundance of ACE2 in the kidney might account for the renal vulnerability in coronavirus infection.

This study found significantly lower eGFR and serum sodium levels and higher hs-CRP levels in male patients than in female patients. These findings were consistent with other reports showing that male patients carried the pre-disposition toward COVID-19 and had poor prognosis as compared with female patients.[2] Whether male patients have poor renal prognosis needs further investigation.

This study reported the incidence of hyponatremia was 25.8%. Hyponatremia was also reported in patients with severe acute respiratory syndrome with an incidence of 29% to 60%. However, the underlying mechanism has not been elucidated. One interpretation is that vomiting and diarrhea, which can induce hypovolemic hyponatremia, are symptoms found in patients with COVID-19. However, these symptoms only accounted for 3.2% and 5.4% of patients in this study respectively and 3.8% to 5.0% of patients in previous studies.[2] Hyponatremia has been reported in pneumonia in which systemic inflammation plays a central role.[5] Another factor responsible for hyponatremia is proximal tubule injury. However, whether 2019-nCoV affects the transportation of sodium and other electrolytes by disrupting the function of transportation channels remains unknown.

Notably, glycosuria was found in eight of non-diabetic patients. All these patients had FBG within the normal range, and two patients had a slightly increased random blood glucose level but less than renal threshold for glucose which is generally accepted as 10 mmol/L. As the FBG level does not exceed renal threshold for glucose in any of the patients, it is reasonable to speculate that proximal tubule injury accounts for renal glucosuria in non-diabetic patients.

The proximal tubule injuries can manifest as tubular proteinuria, renal glycosuria, renal hypouricemia, and characteristic electrolyte and acid-base balance disorders. This study found that 10.1% of the patients presented with renal glucosuria, 34.2% with mild proteinuria, 25.8% with hyponatremia, and 20.4% with hypouricemia. No patient presented with nephrotic range proteinuria, but 27 had mild proteinuria (+ to ++). Patients with proteinuria were more severe than those without proteinuria which indicated that proteinuria is a marker for disease severity. However, urine protein electrophoresis and urine protein quantification were not performed in these patients to confirm the existence of tubular proteinuria. And the levels of urinary markers for tubular injuries, such as neutrophil gelatinase-associated lipocalin, were not measured as well. Additionally, the possibility of transient proteinuria resulting from a fever and systemic inflammation in the milieu of infection could not be ruled out. Taken together, these characteristics indicated potential proximal tubule dysfunction in patients with COVID-19.

This study had several limitations. First, it was a retrospective study, and therefore important examinations were not performed to obtain more solid evidence for renal tubular injury. Clinicians should pay more attention to the workups for tubular injury especially when COVID-19 is pandemic now. Second, because of the local authority's

admission policy, the majority of the patients enrolled in this study were severe cases according to the diagnostic criteria; however, most of the patients with COVID-19 were non-severe cases.[2] Therefore, the study had a selection bias. Whether sex-related differences exist in the general patient population needs to be confirmed through studies with a larger sample size.

In conclusion, this study reported that male patients with COVID-19 had lower eGFR and higher incidence of hyponatremia as compared with female patients. The presence of renal glucosuria, mild proteinuria, and hyponatremia in patients with COVID-19 indicated the possibility of proximal tubular injury, highlighting the necessity for further investigation.

Conflicts of interest

None.

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