PERSPECTIVE

NEPHROLOGY

Focus on kidney disease among the coronavirus disease 2019 patients: A comparative perspective between China, Italy and the United States

Coronavirus disease 2019 (COVID-19) has rapidly spread to more than 200 countries and areas. As of May 11, 2020, more than four million cases have been confirmed globally and more than 280 000 deaths have been recorded. In China, Italy and the United States, the mortality was 5.5% (4644/84451), 14.0% (30739/219814) and 6.1% (78652/1298287), respectively.[1]

COVID-19 is caused by a novel coronavirus, tentatively named 2019-nCoV or Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Angiotensin-converting enzyme 2 (ACE2) is the receptor for 2019-nCoV. Kidneys had the highest *ACE2* expression levels among the 31 Genotype-Tissue Expression human tissue and the Human Protein Atlas database showed that ACE2 protein had relatively high expression levels in the kidneys.[2] Furthermore, isometric vacuolisation was shown in virally infected tubular cells on light microscopy and intracellular viral arrays were identified in proximal tubular epithelial cells by electron microscopy. These findings provide confirmatory evidence of direct kidney infection by SARS-CoV-2 in a patient.[3]

The available data from China, Italy as well as the United States indicate that COVID-19 is relatively mild condition in most affected individuals, but in others, it can be severe and deadly. Previous data showed that older individuals, particularly those with underlying chronic diseases were both more susceptible to COVID-19 and more prone to critical conditions and death, especially in severe or critical cases. More and more studies have begun to focus on the effect of renal function on COVID-19, but there are still unknown mechanisms of the SARS-CoV-2's effect on kidney disease among COVID-19 patients.

1 | DIFFERENCE OF RENAL DISEASE AMONG COVID-19 PATIENTS BETWEEN THREE COUNTRIES

The case-fatality rate was elevated among those with preexisting comorbid conditions as compared with the overall patients with COVID-19, and the proportion of deceased patients with no comorbidities was 32.8%, 3.9% and 6.0% in China, Italy and the United States (all among patients aged ≥19 years).[4-6] Patients with pre-existing disease, including kidney disease, require extra attention. Regarding combined underlying chronic kidney disease, laboratory tests of creatinine and blood urea, as well as complications of acute kidney disease, reported studies in China, Italy and the United States have common and different points.

1.1 | Coexisting disease of chronic kidney disease

The proportion of COVID-19 patients with chronic kidney disease in China was relatively low, about 0.7% (8/1099), 0.5% (5/926) and 1.7% (3/173) in total, mild/moderate and severe/critical patients, respectively.[7] However, it was 3.0% (213/7162), 2.3% (157/6705) and 12.3% (56/457) in the United States[6] Arentz et al reported that 47.6% (10/21) of critically ill patients had underlying chronic kidney disease and 9.5% (2/21) were with end-stage kidney disease.[8] Another study from Richardson et al, including 5700 COVID-19 patients in the New York City Area, reported that 5% and 3.5% were patients with chronic kidney disease and end-stage kidney disease, respectively.[9] In Italy, deceased patients with underlying chronic kidney disease was 20.3% (533/2621), and male patients was higher than female patients (21.4% (379/1771) versus 18.1% (154/850)).[5] The proportion of chronic kidney disease in the critically ill and deceased patients in the United States and Italy is much higher than that in China, which might be related to the large number of chronic kidney disease population in the United States and the ageing population in Italy.

1.2 | Laboratory examination of creatinine and blood urea

As the disease progresses and clinical status deteriorates, the levels of creatinine and blood urea progressively increases before death. The median level of creatinine in COVID-19 patients is mostly in the normal range and the proportion of patients with creatinine higher than normal value is 1.6% (12/752), 1.0% (6/614) and 4.3% (6/138) in total, mild/moderate and severe/critical patients, and the proportion is relatively low in China.[7] While in the United States, the median level of creatinine in critically ill patients is 1.45 mg/dL (128.2 μmol/L), which is higher than the reports from China.[8] The larger chronic kidney disease population in the United States could be a reason for this difference. There was no available data about creatinine in Italy patients. In previous reports in China, the median level of blood urea in COVID-19

patients was mostly in the normal range, even in severe/critical and dead patients. But there are little reports about blood urea abroad.

1.3 | Complication of acute kidney injury

Attention should be paid to acute kidney injury. The proportion of acute kidney injury with COVID-19 patients is 0.5% (6/1099), 0.1% (1/926) and 2.9% (5/173) in total, mild/moderate and severe/critical patients in China.[7] While in the United States critical ill patients, the proportion could rise to 19.1% (4/21).[8] Richardson et al reported the proportion of acute kidney injury with COVID-19 patients was 22.2% (523/2351) and in deceased patients it could be up to 72.1% (347/481).[9] In Italy, 22.6% of acute conditions in dead patients were acute kidney disease, the second most common acute condition after acute respiratory distress syndrome.[5] The number of COVID-19 patients who suffer from acute kidney injury in Italy and the United States are higher than it in China, especially in critical ill or dead patients. Acute kidney disease could be induced by infections and use of antiviral or corticoids, particularly in patients with underlying chronic kidney disease, which in turn aggravated cardiac function and infections, causing a poor prognosis. Although the proportion of acute kidney disease in these three countries is relatively low, still some patients have experienced varying degrees of acute kidney injury during illness. Thus, much more available studies need to be reported.

2 | POTENTIAL CAUSES OF THESE DIFFERENCES

The majority of the infected population of COVID-19 patients are the elderly. The median age of COVID-19 patients in China was 47 years old, while in Italy and the United States, it was 62 years old and 63 years old, respectively.[5,7,9] This difference is even more pronounced for deaths: the median age of deaths in Italy is 81 years old, which may be related to its population structure.[5] The demographic characteristics of the Italian population differ from the other two countries. With the increase of age, renal function is gradually declining. Elderly patients may already have a decline in renal function and the renal function of patients with severe infection will be further impaired. The deteriorated renal function will in turn affect cardiac function and infection, which have effect on poor prognosis. In addition, elderly patients often have coexisting with chronic diseases such as hypertension and diabetes, which both have influence on renal function. Using ACE-inhibitor or angiotensin receptor blockers to treat the underlying diseases can also upregulate the expression of AEC2 receptors in several organs, including the kidney, affecting the prognosis.[2]

The chronic kidney disease prevalence among the total adult population in China, Italy and the United States was 10.8%, 7.1% and 13.1%.[10] Chronic kidney disease by stages G3-4 (%) (Reduced glomerular filtration rate 15 to 60 mL/min/1.73 m^2) was 2.9%, 1.7% and 8.1%, respectively, in these countries.[10] The age-standardised prevalence rate per 100 000 for chronic kidney disease in China, Italy and

the United States was 7180 (6658 to 7747), 5156 (4792 to 5602) and 8144 (7615 to 8783), respectively.[11] The age- standardised death rate of chronic kidney disease was 10.0 (9.2 to 10.4), 7.3 (6.8 to 7.9) and 14.6 (14.3 to 14.9) in China, Italy and the United States, respectively.[11] The United States has the highest basic chronic kidney disease population among these three countries. *ACE2* expression levels in kidneys have no significant differences between males and females, between young and old persons, indicating that SARS-CoV-2 may infect persons with different genders, ages.[2] However, the difference of *ACE2* expression levels in kidneys between races was not shown. In the future, attention could be paid to the correlations between *ACE2* expression and immune signatures in racial differences; since such differences may partially explain the varying characteristics of kidney disease among COVID-19 patients in these three countries.

3 | CONCLUSIONS

COVID-19 has now constituted a global pandemic and the number of confirmed cases is still growing. The prognosis of severe and critically ill patients with kidney disease is worse and the mortality rate is higher. Compared with Chinese data, Italy's population has a higher median age; the United States population has a higher proportion of chronic kidney disease and most of them are in the G3-G4 period. Among patients with underlying renal conditions, COVID-19 could aggravate the underlying diseases, which may worsen the initial cardiovascular disease and have a poor prognosis. These differences may also be related to genetic makeup of different races. Extra attention needs to be paid to COVID-19 patients with renal disease. Research on the prognosis, evaluation, and the management of kidney diseases and their complications in COVID-19 patients is essential.

DISCLOSURE

None of the authors had any conflict of interest relevant to this study.

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