Research Article

Acute Kidney Injury Is Associated With In-hospital Mortality in Older Patients With COVID-19

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Abstract

Background: The epidemic of COVID-19 presents a special threat to older adults. However, information on kidney damage in older patients with COVID-19 is limited. Acute kidney injury (AKI) is common in hospitalized adults and associated with poor prognosis. We sought to explore the association between AKI and mortality in older patients with COVID-19.

Method: We conducted a retrospective, observational cohort study in a large tertiary care university hospital in Wuhan, China. All consecutive inpatients older than 65 years with COVID-19 were enrolled in this cohort. Demographic data, laboratory values, comorbidities, treatments, and clinical outcomes were all collected. Data were compared between patients with AKI and without AKI. The association between AKI and mortality was analyzed.

Results: Of 1764 in-hospital patients, 882 older adult cases were included in this cohort. The median age was 71 years (interquartile range: 68–77), 440 (49.9%) were men. The most presented comorbidity was cardiovascular diseases (58.2%), followed by diabetes (31.4%). Of 882 older patients, 115 (13%) developed AKI and 128 (14.5%) died. Patients with AKI had higher mortality than those without AKI (68 [59.1%] vs 60 [7.8%]; p < .001). Multivariable Cox regression analysis showed that increasing odds of in-hospital mortality are associated with higher interleukin-6 on admission, myocardial injury, and AKI.

Conclusions: Acute kidney injury is not an uncommon complication in older patients with COVID-19 but is associated with a high risk of death. Physicians should be aware of the risk of AKI in older patients with COVID-19.

Keywords: Acute kidney injury, Aging kidney, Coronavirus, COVID-19, SARS-CoV-2

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is becoming a pandemic and has spread rapidly worldwide. As of April 14, 2020, more than 200 countries have reported to have confirmed cases, and globally infected patients have reached 1,773,084, with 111,652 (6.30%) deaths (1).

The epidemic of COVID-19 carries a high risk to older adults, and older patients are more likely to be severe cases, a cascade of complications, and death (2,3). In fact, a larger amount of studies well demonstrated that older age is an independent risk factor for death in patients with COVID-19 (4–8). Recently, Chen et al. (9) reported that male, interval from disease onset to hospitalization, abnormal kidney function, and elevated serum procalcitonin might be associated with a higher risk of death in older patients with COVID-19, but with limited sample size (36 survivors and 19 nonsurvived patients). Studies with large numbers of patients are...
needed to explore the risk factors for mortality in older patients with COVID-19.

Kidney disease has been shown to be associated with death in patients with COVID-19 (4), and the reported prevalence of acute kidney injury (AKI) varied from 0.5% to 36.6% in these patients (4,10–12). Aging kidneys with declined function are associated with increased susceptibility to acute injury (13–15). Cheng et al. (4) reported that elevated baseline serum creatinine levels were more often observed in older adults (median age 73 years), whereas normal kidney function was observed in relatively younger adults (median age 61 years). Previous studies showed that deceased patients were older adults and with a higher proportion of AKI (6,8,16), suggesting that an aging kidney might contribute to the poor outcome in older patients with COVID-19. A recent study indicated that elevated baseline serum creatinine level was associated with mortality in older patients with COVID-19; however, it was not indicated whether the renal dysfunction was caused by AKI or preexisting chronic renal diseases (9). To the best of our knowledge, no study has explored the causality between AKI and death rate in older COVID-19 patients. Herein, we retrospectively studied the incidence of AKI and its association with mortality in older patients with COVID-19.

Material and Methods

Study Design and Participants

In this retrospective study, patients were recruited from Tongji Hospital, one of the main tertiary teaching hospitals in Wuhan. Since late January 2020, the 2 branches of Tongji Hospital, Optical Valley Branch and Sino-French New City Branch, were urgently redesigned as designated hospitals for severe COVID-19 patients transferred from other hospitals in Wuhan. All adult patients were confirmed with COVID-19 according to WHO interim guidance (17).

Consecutive adult patients older than 65 years hospitalized between January 27, 2020 and February 17, 2020 were included in the study. Severe acute respiratory syndrome coronavirus 2 infection was confirmed in Tongji hospital with real-time polymerase chain reaction on pharyngeal swab specimens standardized to the local health institutions, as described elsewhere (16). Exclusion criteria were younger than 65 years, having history of renal replacement therapy, kidney transplantation within 3 months before admission, being discharged or died within 24 hours after admission, or missing important data. The clinical outcomes (ie, death, discharged, or remaining in hospital) were followed up until March 18, 2020. Due to the emergency of this infectious disease, the sample size was determined by the number of cases admitted into our hospital.

The study was approved by the Ethics Committee of Tongji Hospital (TJ-IRB20200328). Written informed consent was waived by the Ethics Commission of the designated hospital because of the nature of emerging infectious diseases.

Data Collection

Medical records, nursing records, and laboratory finding reports for each patient were reviewed and the following data were collected: time of symptoms onset, hospitalization and discharge or death; age, gender, comorbidities (cardiovascular disease, chronic respiratory disease, chronic kidney disease, cerebrovascular disease, diabetes, and malignancy), and vital signs; and laboratory parameters on the first day of admission (leukocytes, lymphocytes, platelet count, high-sensitivity C-reactive protein, procalcitonin, lactate dehydrogenase, alanine transaminase, aspartate transaminase, p-dimer, estimated glomerular filtration rate, cardiac troponin I, and interleukin-6). Additionally, complications (sepsis, septic shock, acute respiratory distress syndrome [ARDS], myocardial injury, liver injury, and AKI) and treatments during hospitalization (mechanical ventilation, renal replacement therapy, vasoactive therapy, corticosteroid, diuretics, renin-angiotensin–aldosterone system [RAAS] inhibitors, and nonsteroidal antiinflammatory drugs [NSAIDs]) were also collected.

Definitions

AKI was diagnosed according to KDIGO (Kidney Disease: Improving Global Outcomes) criteria, as an increase in the serum creatinine level up to 1.5 times the baseline level or increase at least 0.3 mg/dL within the past 48 hours (18). Baseline serum creatinine was defined as serum creatinine level within 3 months prior to the hospitalization; when previous creatinine concentration was unavailable, the minimum of either serum creatinine at the first day of admission, or a calculated creatinine concentration using the Modification of Diet in Renal Disease formula as recommended by the Acute Dialysis Quality Initiative in patients without chronic kidney disease, was used to define baseline creatinine (19). Sepsis and septic shock were defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock (20). Acute respiratory distress syndrome was defined according to the ARDS Berlin definition (21). Myocardial injury was diagnosed when the levels of cardiac troponin I in serum were above the upper limit of the reference range (>34.2 pg/mL).

Statistical Analysis

All continuous variables were presented as mean ± SD or median (interquartile range [IQR]); categorical variables were presented as frequency or percentages (%). Descriptive statistics for all variables were calculated by Student’s t test, Mann–Whitney U test, χ2 test, or Fisher’s Exact Test, as appropriate. Survival curves were plotted by the Kaplan–Meier method in AKI patients and non-AKI patients using the log-rank test. Multivariable Cox regression analysis was performed to explore the association between AKI and in-hospital death. Covariables included in the multivariable Cox regression model were age, sex, and comorbidities (cardiovascular disease, chronic respiratory disease, chronic kidney disease, cerebrovascular disease, diabetes, and malignancy), lymphopenia, p-dimer, lactate dehydrogenase, interleukin-6, myocardia injury, and liver injury, which were previously reported to be the risk factors of COVID-19 or associated with adverse clinical outcomes in adults with SARS and Middle East Respiratory Syndrome Coronavirus (MERS) (8,22,23). Variables that were established as causes of death (ARDS, sepsis, or septic shock) thus had multicollinearity among all variables were excluded. The odds for in-hospital mortality were expressed as the hazard ratio (HR) and its 95% confidence interval (CI); p < .05 was considered statistically significant. Standard SPSS 26.0 statistical package (IBM) or Prism 8.4 (GraphPad) was used for all analyses.

Results

Patients Characteristics

A total of 1764 patients with confirmed COVID-19 were admitted to the hospital as of February 17, 2020. Of them, 915 patients were older than 65 years. Ten patients receiving long-term dialysis were excluded; 18 were excluded due to death or discharged within 24 hours after admission; and 5 were excluded as they had missed important data. Eight hundred and eighty-two
patients were ineligible and enrolled in this study (Figure 1). The median duration of follow-up after admission was 27 days (IQR 19–36) and none of the participants were lost to follow-up during the study.

Clinical characteristics of the 882 older patients are given in Table 1. The median age of these patients was 71 years (IQR 68–77), ranging from 65 years to 95 years; 440 (49.9%) were male. Median systolic blood pressure and diastolic blood pressure were 134 mmHg (IQR 120–147) and 71 mmHg (IQR 68–77), respectively. Cardiovascular disease was the most common comorbidity (515/882, 58.2%), followed by diabetes (277/882, 31.4%). Eighty-six (9.8%) had chronic respiratory disease, 38 (4.3%) had cerebrovascular disease, and 41 (4.7%) had a history of malignancy. Duration from the onset of symptoms to hospitalization was 12 days (IQR 7–16).

Of 882 older patients with COVID-19, 115 developed AKI (13%). Compared with non-AKI patients, AKI patients were older by a difference of 5 years. Moreover, the prevalence of cardiovascular diseases, chronic respiratory disease, and diabetes was higher among AKI patients than that among non-AKI patients (Table 1).

**Treatments**

Of all older patients, 39.6% received corticosteroid therapy, 34.6% received nonsteroidal antiinflammatory drugs, 26.0% received diuretics, and 10.8% received renin–angiotensin–aldosterone system inhibitors. Vasoactive therapy was given to 178 (20.2%) patients and mechanical ventilation was given to 172 (19.5%) patients. Renal replacement therapy was required in 17 patients (1.9%; Table 1).

Compared with non-AKI patients, AKI patients had a higher proportion of mechanical ventilation (65.2% vs 12.6%, p < .001), renal replacement therapy (14.8% vs 0.0%, p < .001), vasoactive therapy (64.3% vs 13.6%, p < .001), corticosteroid (69.6% vs 35.1%, p < .001), and diuretics treatment (66.1% vs 19.9%, p < .001; Table 1). In contrast, usage of renin–angiotensin–aldosterone system inhibitors (8.7% vs 11.1%, p = .271) and nonsteroidal antiinflammatory drugs (39.1% vs 33.9%, p = .441) was comparable between patients with and without AKI.

**Laboratory Findings**

Among 882 patients, median levels of high-sensitivity C-reactive protein (34.6, IQR 7.1–85.9), procalcitonin (0.07, IQR: 0.05–0.14), lactate dehydrogenase (293, IQR 236–393), d-dimer (1.18, IQR 0.58–2.47), and interleukin-6 (10.36, IQR 3.77–35.91) were

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**Table 1.** Clinical Characteristics and Treatments of Older Patients With COVID-19

| Characteristic                        | All Patients, N = 882 | Non-AKI Patients, N = 767 | AKI Patients, N = 115 | p Value |
|--------------------------------------|-----------------------|---------------------------|-----------------------|---------|
| Age, median (IQR)                    | 71 (68–77)            | 70 (68–76)                | 75 (69–81)            | <.001   |
| Male sex, n (%)                      | 440/882 (49.9)        | 354/767 (46.2)            | 86/115 (74.8)         | <.001   |
| Systolic blood pressure, mmHg—median (IQR) | 134 (120–147)        | 135 (120–147)            | 133 (120–146.5)       | .928    |
| Diastolic blood pressure, mmHg—median (IQR) | 71 (68–77)           | 80 (72–87)               | 80 (72.5–88)          | .729    |
| Duration from the onset of symptoms to hospitalization, days—median (IQR) | 12 (7–16)            | 12 (8–16)                | 10 (6–15)             | <.001   |
| Chronic medical illness, n (%)       | 515/882 (58.2)        | 436/767 (56.8)            | 79/115 (68.7)         | .016    |
| Cardiovascular diseases              | 86/882 (9.8)          | 69/767 (9.0)              | 17/115 (14.8)         | .069    |
| Chronic respiratory disease          | 83/882 (9.4)          | 46/767 (6.0)              | 37/115 (32.2)         | <.001   |
| Chronic kidney disease               | 38/882 (4.3)          | 31/767 (4.0)              | 7/115 (6.1)           | .314    |
| Cerebrovascular disease              | 277/882 (31.4)        | 231/767 (30.1)            | 46/115 (40.0)         | .033    |
| Diabetes                             | 41/881 (4.7)          | 34/766 (4.4)              | 7/115 (6.1)           | .434    |
| Malignancy                           | 172/882 (19.5)        | 97/767 (12.6)             | 75/115 (65.2)         | <.001   |
| Mechanical ventilation               | 17/882 (1.9)          | 0/767 (0.0)               | 17/115 (14.8)         | <.001   |
| Renal replacement therapy            | 178/882 (20.2)        | 104/767 (13.6)            | 74/115 (64.3)         | <.001   |
| Vasoactive therapy                   | 349/882 (39.6)        | 269/767 (35.1)            | 80/115 (69.6)         | <.001   |
| Corticosteroid                       | 229/882 (26.0)        | 153/767 (19.9)            | 76/115 (66.1)         | <.001   |
| Diuretics                            | 95/882 (10.8)         | 85/767 (11.1)             | 10/115 (8.7)          | .441    |
| RAAS inhibitors                      | 305/882 (34.6)        | 260/767 (33.9)            | 45/115 (39.1)         | .271    |

Notes: AKI = acute kidney injury; COVID-19 = coronavirus disease 2019; IQR = interquartile range; NSAIDs = nonsteroidal antiinflammatory drugs; RAAS = renin–angiotensin–aldosterone system. p values were calculated by Student’s t test, Mann–Whitney U test, χ² test, or Fisher’s Exact Test, as appropriate.
Complications and Outcomes

Overall, sepsis and septic shock occurred in 262 (29.7%) and 178 (20.2%) patients, respectively. Acute respiratory distress syndrome developed in 202 (22.9%), myocardial injury developed in 106 (12.8%), and liver injury developed in 280 (31.8%) patients. In addition, these complications were more commonly seen among patients with AKI than those without AKI (Table 2).

As to the outcomes of 882 older patients, 105 (11.9%) were admitted to the intensive care unit, 128 (14.5%) died, 428 (48.5%) discharged from hospital, and the remaining 326 (40.0%) survived and were still in the hospital. Compared with those without AKI, patients with AKI had higher intensive care unit admission rate (50.4% vs 6.1%) and higher in-hospital mortality (59.1% vs 7.8%; Table 3).

AKI and Mortality

The Kaplan–Meier survival curves showed that mortality was higher in patients with AKI than that without AKI (50.4% vs 6.1%; Figure 2). In multivariable Cox regression analysis, after adjusting for age, sex, comorbidities (cardiovascular disease, chronic respiratory disease, chronic kidney disease, cerebrovascular disease, ARDS), and estimated glomerular filtration rate were significantly decreased in AKI patients compared with non-AKI patients (Table 2).
diabetes, and malignancy), lymphocytes count less than 0.8×10^9/L, d-dimer more than 0.5 μg/mL, lactate dehydrogenase more than 225 U/L, interleukin-6 more than 6 pg/mL, myocardial injury, and liver injury, HR of in-hospital death was higher in patients with AKI diagnosed at symptom onset (HR 4.78, 95% CI: 2.97–7.70, p < .001) or during the time from admission to the final date of follow-up (HR 5.20, 95% CI: 3.24–8.35, p < .001; Table 4). Besides, lymphocytes, interleukin-6, and myocardial injury were also associated with a higher risk of death in older patients with COVID-19 (Table 4).

**Discussion**

In this retrospective study, we demonstrated the association between AKI and in-hospital mortality in older patients with COVID-19. Acute kidney injury developed in 13% (115 of 882) of older patients with COVID-19 and was associated with an unexpected high risk of in-hospital mortality among this population.

It is well established that the incidence of AKI increases with age. Indeed, aging is tightly associated with a declining function of the kidney. The structural remodeling includes vascular sclerosis, decreased kidney mass, and increased portion of sclerosing glomeruli. The functional changes include declining glomerular filtration rate and decreased functional reserve. All these age-related changes lead to an increased risk of AKI. Moreover, with the increasing number of preexisting comorbidities in the older population, the incidence rate of AKI may also increase (13–15). In SARS-CoV-2 and MERS-CoV infected patients, the incidence of AKI was considerable and carried a high rate of death. In 536 patients infected with SARS-CoV-2 in Hong Kong, acute renal impairment occurred in 36 (6.7%) patients with a median age of 53.5 years (IQR 34–77), older than patients with normal renal function (median age 38 years, IQR:18–96) (24). Of 12 critically ill patients with MERS in Saudi Arabia, 7 (58%) patients developed AKI and required renal replacement therapy, also with advanced age (median 59 years, IQR [36–83]) (25). These

![Figure 2. Kaplan–Meier survival curves for mortality during the time from symptom onset (A) and time from admission (B). AKI = acute kidney injury.](image)

**Table 4. Multivariable Cox Regression Analysis on the Risk Factors Associated With Death in Older Patients With COVID-19**

| Factor                        | From Symptom Onset | From Admission |
|-------------------------------|--------------------|----------------|
| Age, years*                   | 1.01 (0.98–1.05)   | 1.01 (0.98–1.04) |
| Male sex (vs female)          | 1.36 (0.83–2.24)   | 1.45 (0.88–2.38) |
| Cardiovascular diseases       | 1.51 (0.91–2.51)   | 1.45 (0.89–2.38) |
| Chronic respiratory disease   | 1.60 (0.89–2.88)   | 1.65 (0.93–2.91) |
| Chronic kidney disease        | 1.09 (0.60–1.97)   | 0.97 (0.94–1.75) |
| Cerebrovascular disease       | 0.70 (0.28–1.80)   | 0.60 (0.23–1.53) |
| Diabetes                      | 1.17 (0.73–1.86)   | 1.12 (0.71–1.77) |
| Malignancy                    | 1.45 (0.62–3.39)   | 1.42 (0.61–3.30) |
| Lymphocytes <0.8 × 10^9/L     | 1.57 (1.01–2.44)   | 1.63 (1.06–2.51) |
| D-dimer >0.5 μg/MI            | 0.96 (0.33–2.75)   | 1.17 (0.41–3.34) |
| Lactate dehydrogenase >225 U/L | 2.31 (0.87–6.03) | 2.28 (0.87–5.93) |
| Interleukin-6 >6 pg/mL        | 24.83 (3.39–181.70)| 25.53 (3.50–186.04)|
| Cardiac injury                | 3.05 (1.91–4.85)   | 3.63 (2.31–5.72) |
| Liver injury                  | 1.28 (0.80–2.05)   | 1.21 (0.76–1.91) |
| AKI                           | 4.78 (2.97–7.70)   | 5.20 (3.24–8.35) |

**Notes:** AKI = acute kidney injury; CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio. p values were calculated by multivariable Cox regression analysis.

*Per 1-year increase.
findings indicate that older age may have higher incidence rate of AKI and death rate in patients infected with lethal coronavirus. The incidence of AKI in older patients with COVID-19 was 13% (115 of 882) in this study, which is higher than that reported in the general population with COVID-19 (4). In addition, older COVID-19 patients with AKI had higher in-hospital mortality than patients without AKI. Given the evidence that the advanced age patients infected with coronavirus are more likely to develop AKI, it is conceived that the aging kidney is more vulnerable to acute stress upon viral infection.

So far, limited studies described the incidence of AKI in patients with COVID-19. Cheng et al. (4) conducted a study focusing on kidney disease in patients with COVID-19. In 701 cases with a median age of 63 years (IQR 50–71) , the incidence of AKI was 5.1%. Furthermore, AKI was associated with a higher death risk in these patients. In another retrospective study, 27% (23 of 85) of patients developed AKI in a single medical center in Wuhan, China (11). However, in a nationwide retrospective study including 1099 COVID-19 patients in China, the incidence of AKI was only 0.5% (10). It should be noted that patients with adverse outcomes (admission to intensive care unit, mechanical ventilation, and death) had a higher rate of AKI (40.3% vs 1%) and were older (63 years, IQR: 53–71; vs 46 years, IQR: 35–57) than that of patients without adverse outcomes, suggesting that aging kidney damage may prone to be developed in patients with advanced age or severe cases. Thus, the different incidence of AKI in COVID-19 patients might be due to a different proportion of older patients or severe cases included in these studies. Indeed, the incidence of AKI is substantially higher in critically ill patients with COVID-19. In an earlier study included 52 critically ill patients, the incidence of AKI was 29% (15 of 52). Compared with survivors, nonsurvivors were older (median age 64.6 vs 31.9 years) and with a higher rate of AKI (37.5% vs 15%). In another study, 50% (27 of 54) of the deceased COVID-19 cases developed AKI, with a median age of 69 years (IQR 63–76) (8).

The exact mechanism of kidney involvement in SARS-CoV-2 infection is still unclear. It was reported that angiotensin-converting enzyme 2, the functional receptor for SARS-CoV-2, was detected in the kidney (26). In addition, SARS-CoV-2 RNA had been detected in urine sediments in patients with COVID-19 (10,26,27). A recent study found that SARS-CoV-2 nucleocapsid protein antigen could be detected in human kidney autopsy samples in 6 non-survived severe COVID-19 patients with kidney function impairment (11). Another study on 26 nonsurvived critically ill patients with COVID-19 provided direct evidence to show viral infection in parenchymal tubular epithelium and podocyte (28). It is worth mention that acute proximal tubule injury was more commonly presented in patients with advanced age, again suggesting that an aging kidney may accelerate kidney damage after SARS-CoV-2 infection. However, the direct viral invasion of kidney in nonsevere patients with COVID-19 is still unclear and more studies are required to investigate the underlying mechanisms of AKI in COVID-19 patients.

The higher incidence of AKI in older patients with COVID-19 may also be attributed to an increased number of comorbidities and polypharmacy-induced renal toxicity, which are common in older patients (29). Besides, age-related proinflammatory responses upon SARS-CoV-2 infection might also play a role in the increased rate of AKI, as shown in this study. Inflammatory markers such as high-sensitivity C-reactive protein, procalcitonin, and interleukin-6 were all elevated and higher in older patients with AKI than those without AKI. It should be noted that emerging data proved that interleukin-6 was associated with adverse clinical outcomes in patients with COVID-19 (8,29,30), and interleukin-6 receptor antagonists (ie, tocilizumab) have been used in COVID-19 patients with elevated interleukin-6 (ie, NCT04315298 registered with ClinicalTrials.gov and ChiCTR2000029765 registered with chictr.org.cn). These ongoing clinical trials might shed some light on the efficacy of immunosuppressing treatment on cytokine storm in COVID-19.

A large amount of evidence has demonstrated that older age was an independent risk factor for poor outcome in patients with COVID-19 (4,7,8,16,25). Male, interval from disease onset to hospitalization, abnormal kidney function, and procalcitonin might be associated with death in older patients with COVID-19 (9). In this cohort, we found that interleukin-6, myocardial injury, and AKI were associated with in-hospital mortality in older patients with COVID-19. Age-related immunological changes such as stronger host innate and prolonged proinflammation responses to viral infection (31) and the more comorbid conditions such as respiratory or cardiovascular diseases may render the older patients with COVID-19 of higher interleukin-6 level and development of ARDS, myocardial injury, or AKI in these patients. In this study, we found that patients with AKI had a higher frequency of ARDS, myocardial injury, and liver injury, indicating multiple organ dysfunction in COVID-19 patients with AKI. Therefore, AKI might be recognized as a clinical indicator of multiple organ impairment and disease severity among COVID-19 patients, particularly in those older individuals.

Limitations
So far to the best of our knowledge, this is the first study focusing on AKI in older patients with COVID-19. Nevertheless, it has several limitations. First, data of this study were collected from a single center and generalizability of the cohort queue characteristics could not be determined. Second, although we have adjusted for several covariates which were proved to be risk factors for death in COVID-19 patients for potential confounders, there may be other unmeasured confounders that possibly represent confusion biases. In addition, the baseline serum creatinine was estimated by either admission creatinine or calculated by the Modification of Diet in Renal Disease equation for these patients who do not have the previous value of serum creatinine, which might lead to an elevated incidence of AKI. Finally, urine output data of most patients were missing in the medical record and not been collected for defining AKI. Thus, the incidence of AKI may be underestimated.

Conclusions
AKI is common among hospitalized older COVID-19 patients and is associated with a higher risk of in-hospital mortality. Early detection and treatment of AKI may lead to a better outcome in older patients with COVID-19.

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Author Contributions
Research idea and study design: Q.Y., C.T.Z., and H.Y.G.; data acquisition: Q.Y., P.Y.Z., L.C., Y.Y.L., K.X.S., Y.C., D., and Y.Y.; data analysis/interpretation: Q.Y., L.Z., W.W.Y., Y.S.L., M.X., C.T.Z., and H.Y.G.; statistical analysis: Q.Y.; supervision or mentorship: C.T.Z. and H.Y.G. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author’s own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Conflict of Interest
None declared.

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