The Involvement of Chronic Kidney Disease and Acute Kidney Injury in Disease Severity and Mortality in Patients with COVID-19: A Meta-Analysis

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Keywords
COVID-19 · Chronic kidney disease · Acute kidney injury · Disease severity · Mortality · Meta-analysis

Abstract
Background: A meta-analysis was performed to evaluate the association of chronic kidney disease (CKD) and acute kidney injury (AKI) with the clinical prognosis of patients with coronavirus disease 2019 (COVID-19). Methods: The PubMed, EMBASE, Cochrane Library, medRxiv, Social Science Research Network, and Research Square databases (from December 1, 2019 to May 15, 2020) were searched to identify studies that reported the associations of CKD/AKI and disease severity/mortality. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated and meta-regression was performed. Results: In total, 42 studies enrolling 8,932 participants were included in this meta-analysis. The quality of most included studies was moderate to high. Compared with patients without previously diagnosed CKD, those with CKD had a significantly increased risk of progressing to a severe condition (OR 2.31, 95% CI 1.64–3.24) or death (OR 5.11, 95% CI 3.36–7.77). Similarly, compared with patients without AKI, those with AKI had a significantly increased risk of progressing to a severe condition (OR 11.88, 95% CI 9.29–15.19) or death (OR 30.46, 95% CI 18.33–50.59). Compared with patients with previously diagnosed CKD, those with AKI were more likely to progress to a severe condition ($p_{\text{group}} < 0.001$, $I^2 = 98.3\%$) and even to death ($p_{\text{group}} < 0.001$, $I^2 = 96.5\%$). Age had a significant impact on the association between CKD and disease severity ($p = 0.001$) but had no impact on the associations between AKI and disease severity ($p = 0.80$), between CKD and mortality ($p = 0.51$), or between AKI and mortality ($p = 0.86$). Four important complications (cardiac injury, shock, acute respiratory distress syndrome, and liver injury) did not significantly affect the associations between CKD/AKI and disease severity/mortality, indicating that CKD/AKI may be independent clinical prognostic indicators for patients with COVID-19. Conclusions: In COVID-19 patients, CKD/AKI was associated with worse outcomes compared with those without CKD/AKI. AKI was associated with higher risks of severity and mortality than CKD.

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Introduction

Since December 2019, a severe pneumonia outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly around the world [1]. On February 11, 2020 the World Health Organization declared the name of the pandemic condition to be coronavirus disease 2019 (COVID-19).

In patients with severe COVID-19, the infection may rapidly progress to hypoxemia, septic shock, acute respiratory distress syndrome (ARDS), need for intensive care unit (ICU) care, and even death. Recently, several reports have revealed that comorbidities or other conditions can affect the clinical progression of patients with COVID-19 [2, 3]. Several meta-analyses have demonstrated the impact of diabetes [4], cardiac injury [5, 6], and chronic obstructive pulmonary disease and smoking [7] on the clinical progression of patients with COVID-19.

A meta-analysis reported that the incidence of acute kidney injury (AKI) was estimated to be 3% in hospitalized patients with COVID-19, while this incidence was increased to 19% in patients admitted to an ICU [8]. Serum creatinine levels ≥133 μmol/L were reported to be associated with disease severity in a meta-analysis (three studies enrolling 979 patients) [9]. Another meta-analysis (three studies enrolling 944 patients) reported that AKI was associated with a higher risk of mortality [10]. However, the number of studies included in these published meta-analyses was relatively small. During the past half year, numerous new studies evaluating the association of chronic kidney disease (CKD)/AKI and disease severity/mortality have been published. Therefore, a systematic review of the accumulated evidence with the aim of providing an up-to-date assessment of the association between kidney impairment (CKD/AKI) and clinical prognosis (disease severity/mortality) in patients with COVID-19 is important.

Methods

Literature Search

This meta-analysis was performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) method [11]. The MOOSE checklist is provided in online supplemental Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000512211). The databases (MEDLINE, Embase, and Cochrane Library) were systematically searched for eligible published studies, with the medRxiv, Social Science Research Network, and Research Square websites searched for eligible unpublished studies from December 1, 2019 to May 15, 2020. The key words “COVID-19,” “2019 novel coronavirus infection,” “corona-virus disease 2019,” “coronavirus,” “SARS-CoV-2,” “2019-nCoV,” “mortality,” “severe,” “survival,” “outcomes,” “prognosis,” “chronic kidney disease,” “acute renal failure,” “acute kidney injury,” and “renal replacement therapy” were used in various combinations.

Study Eligibility Criteria

After candidate articles had been collected, further selection was conducted according to the following inclusion criteria: (1) Adult patients. (2) The numbers of patients who were diagnosed with CKD or AKI were reported or could be calculated. In the absence of explicit definitions of CKD or AKI in the included studies, patients with high serum creatinine before or on admission were considered to be diagnosed with CKD (meeting the diagnostic criteria of the Kidney Disease: Improving Global Outcomes [KDIGO] guidelines) [12], while patients who had an increase in serum creatinine (meeting the diagnostic criteria of the KDIGO guidelines [12]) after SARS-CoV-2 infection were considered to have AKI. The definition of AKI was the same as that in the KDIGO guidelines. Patients with both preexisting CKD before infection and an increase in serum creatinine after infection were still considered to be diagnosed with CKD, but not AKI, during data extraction and synthesis. (3) The primary outcomes were disease severity and mortality. Diagnosis of the severe cases was defined by the authors in each individual study. Most of the included studies defined severe cases as ICU admission, mechanical ventilation, or both. In the absence of an explicit definition of severe cases, guidelines for the diagnosis and treatment of SARS-CoV-2 issued by the National Health Commission of China (sixth edition) were used [13]. In detail, severe cases were defined as patients with dyspnea, respiratory rate ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, lung infiltrates >50% within 24–48 h, or needing ICU care. (4) The patients were to be consecutively confirmed and enrolled. The studies were in the following cases: (1) reviews, editorials, conference abstracts, systematic reviews, and meta-analyses; (2) children <18 years old; (3) insufficient data provided to explore the associations between kidney impairment and the clinical outcomes; (4) repeated or updated reports containing or overlapping with the same group of participants.

Data Extraction and Quality Assessment

The extracted data included publication status, study type, regions/countries, enrollment hospitals and departments, enrollment periods, numbers of patients, age, sex, complications (cardiac injury, ARDS, shock, and liver injury), and treatment strategies. Quality assessment of the studies was conducted using the Newcastle-Ottawa Scale (NOS) for all included studies [14]. Eight different domains, including selection bias (adequate case definition, representativeness of the cases, selection of controls, and definition of controls), comparability (comparability of cases and controls on the basis of the design or analysis), and exposure (ascertainment of exposure, same method of ascertainment for cases and controls, and reports of nonresponse rate) were assessed. The total scores for each included study ranged from 0 to 10 points. These scores were chosen a priori to simplify description for the present review.

Data Synthesis and Statistical Analysis

Dichotomous variables were expressed as odds ratio (OR) and 95% confidence interval (CI). Heterogeneity was assessed using
the Q test and quantified using the $I^2$ statistic [15]. The threshold $p$ value of heterogeneity was 0.10. $I^2$ statistics $< 25\%$, $25\%-49\%$, $50\%-75\%$, and $> 75\%$ were interpreted to indicate low, medium, high, and very high levels of heterogeneity, respectively. If the $I^2$ value was $< 50\%$, the fixed-effect model was used. Otherwise, the random-effects model was used. For subgroup difference analysis, the $I^2$ value indicated the percentage of the variability in effect estimates from the different subgroups that is due to genuine subgroup differences rather than sampling error. Publication bias was explored using a funnel plot if more than 10 studies were included. Subgroup analyses were performed to evaluate whether the results differed according to the location of the studies (Wuhan city or non-Wuhan regions) and the publication status (published or unpublished). Meta-regression was performed to investigate the effects of age and complications such as cardiac injury, ARDS, shock, and liver injury on the relationship between kidney impairment and clinical prognosis. The Review Manager (version 5.3, The Cochrane Collaboration) software was used for data synthesis and publication bias. The STATA 14.0 (StataCorp, College Station, TX, USA) software was used for meta-regression. The searching and selection of the studies, data extraction and quality assessment, data synthesis, and statistical analysis were performed independently by two of the researchers (B. Wang and Q. Luo), and any discrepancies were resolved by consulting a third investigator (Y. Chen).

### Results

#### Literature Search Results

A total of 1,724 papers were screened, and finally 42 studies with 8,932 participants were included in this meta-analysis. Eighteen of the 42 studies were published [16–33], and the remaining 24 studies were rapidly posted on the medRxiv, Social Science Research Network, and Research Square websites without peer review [34–57]. A flow diagram outlining the literature search process is provided in Figure 1. The characteristics of the included studies are presented in Table 1. The median number of participants was 147 (range 16–1,000). Twelve studies

![Fig. 1. Flow diagram of search strategy and study selection. SSRN, Social Science Research Network.](image-url)
| Study first author | Publication status | Study type | Study region | Enrollment hospitals and department | Enrollment period | Patients, n | Age, years | Male sex | Complications | Treatments |
|-------------------|-------------------|------------|--------------|-------------------------------------|------------------|-------------|------------|----------|---------------|------------|
| Aggarwal [16]    | Diagnosis         | retrospective, single-center | Iowa, USA | UnityPoint Clinic | until April 4, 2020 | 16 | 67 (range 38–95) | 75% | cardiac injury (25%), ARDS (31%), shock (50%), liver injury (38%) | HCQ (69%), vitamin C (50%), antithrombin (43%), glucocorticoids (59%) |
| Argenziano [38]  | medRxiv           | retrospective, multicenter | New York, USA | New York Presbyterian/ Columbia University Irving Medical Center | March 1 to April 5, 2020 | 1,000 | 63 (range 50–75) | 59.6% | cardiac injury (16.5%), ARDS (18.1%), shock (13.9%), liver injury (7.9%) | antibiotic therapy (64.9%), HCQ (63.9%) |
| Bai [52]         | SSRN              | retrospective | Wuhan, China | Wuhan Jinyintan Hospital, tuberculosis and respiratory department | December 26 to January 31, 2020 | 127 | 55 (range 44–67) | 63% | cardiac injury (16.5%), ARDS (31%), shock (19%), liver injury (62%) | – |
| Bi [62]          | medRxiv           | prospective, single-center | Shenzhen, China | Shenzhen Third People’s Hospital | January 11 to March 10, 2020 | 420 | 45.0 (IQR 340–660) | 47.6% | cardiac injury (5%), ARDS (9.3%), liver injury (33.3%) | antiviral: lopinavir/ritonavir (76.8%), frowarvir (10.1%), antibacterial therapy (12.4%) |
| Cao [17]         | Clinical Infectious Diseases | retrospective, single-center | Wuhan, China | Wuhan University Zhongnan Hospital, department of cardiology | January 3 to February 1, 2020 | 102 | 54 (range 37–67) | 52% | cardiac injury (14.7%), ARDS (19.6%), shock (9.8%), liver injury (33.3%) | oxygen inhalation (74.5%), ventilation (18.6%), CRRT (5.9%) |
| Cao [39]         | medRxiv           | retrospective, single-center | Shanghai, China | Shanghai Public Health Clinical Centre | January 20 to February 15, 2020 | 198 | 50.1±16.3 (SD) | 51% | cardiac injury (11.3%), liver injury (17.4%) | – |
| Chen [18]        | Infection         | retrospective, single-center | Taizhou, Zhejiang Province, China | Taizhou Public Health Medical Center | January 1 to March 1, 2020 | 145 | 47.5±14.6 (SD) | 54.3% | – | oral antiviral therapy (97.2%), at omace inhalation of interferon therapy (96.6%), TCM treatment (90.3%) |
| Chen [19]        | British Medical Journal | retrospective, single-center | Wuhan, China | Wuhan Tongji Hospital, department of infectious diseases | January 13 to February 12, 2020 | 274 | 62.0 (IQR 440–700) | 62.4% | cardiac injury (44%), ARDS (72%), shock (17%), liver injury (5%) | antiviral (86%), glucocorticoids (77%), antibiotics (98%), IVIG (30%), mechanical ventilation (43%) |
| Colaneri [20]    | Euro Surveillance  | retrospective, single-center | Pavia, Northern Italy | Fondazione IRCCS Policlinico | February 21 to February 28, 2020 | 44 | 67.5 (range 10–94) | 36.4% | – | antiviral therapy (70.5%), antibiotics (72.6%) |
| Feng [47]        | medRxiv           | prospective, single-center | Wuhan, China | Wuhan Union Hospital | January 23 to February 22, 2020 | 114 | 640±13.4 (SD) | 62.3% | cardiac injury (24.6%), ARDS (19%), shock (7%), liver injury (60.5%) | antibiotic (100%), anti-coronavirus (99.1%), glucocorticoids (42.2%), etc. |
| Hu [37]          | medRxiv           | retrospective, single-center | Wuhan, China | Wuhan Tianyous Hospital | January 8 to February 20, 2020 | 323 | 61 (range 23–91) | 51.4% | cardiac injury (7.4%), ARDS (4%), shock (13.3%) | oseltamivir (69.7%), ganciclovir (21.2%), Arbidol (64.4%) |
| Huang [211]      | Lancet           | prospective, single-center | Wuhan, China | Wuhan Jinyintan Hospital, department of surgery | until December 31, 2019 | 41 | 49.0 (IQR 410–580) | 73% | cardiac injury (12%), ARDS (29%), shock (7%) | antiviral therapy (99%), antibiotic (100%), use of corticosteroid (22%), CRRT (7%), etc. |
| Jiang [48]       | medRxiv           | retrospective, single-center | Wuxi, Jiangsu Province, China | Wuxi Fifth People’s Hospital | until April 6, 2020 | 55 | 450 (IQR 270–660) | 49.1% | cardiac injury (1.8%), ARDS (7.3%), shock (1.8%), liver injury (29.1%) | antiviral therapy (100%), antibiotic (52.7%), corticosteroid (10.5%), IVIG (9.5%) |
| Study (first author) | Publication status | Study type | Study region | Enrollment hospitals and departments | Enrollment period | Patients, n | Age, years | Male sex | Complications | Treatments |
|---------------------|--------------------|------------|--------------|--------------------------------------|------------------|------------|------------|---------|---------------|------------|
| Li [44]             | medRxiv            | retrospective, multicenter | Wuhan, Hubei, and Chongqing, China | Two hospitals in Wuhan, one hospital in Hubei, and one hospital in Chongqing | January 6 to February 21, 2020 | 193 | 57.0 (IQR 46.0–67.0) | 49.0% | cardiac injury (12%), ARDS (28%), shock (18%) | antiviral (98%), oxygen therapy (94%), glucocorticoid (92%), CRRT (4%), mechanical ventilation (4%) |
| Luo [51]            | medRxiv            | retrospective, single-center | Wuhan, China | Jianghan Fangliang Hospital | February 5 to March 9, 2020 | 148 | 56.0 (IQR 46.0–62.0) | 49.0% | – | antibiotics, antiviral therapy, and TCM (38.1%), antibiotics and antiviral therapy (11.9%) |
| Liu [54]            | SSRN               | retrospective, multicenter, cohort | Jiangsu Province, China | 24 hospitals in Jiangsu Province, China | January 10 to February 18, 2020 | 620 | 44.8 (IQR 36.0–60.0) | 52.6% | shock (0.3%) | Chinese medicine (15.8%), IVIG (25.2%), glucocorticoid (22.9%), antibiotics (33.5%) |
| Liu [50]            | medRxiv            | retrospective, single-center | Wuhan, China | Central Hospital of Wuhan | January 2 to February 1, 2020 | 109 | 55.0 (IQR 43.0–66.0) | 54.1% | – | antibiotics (96.3%), antiviral therapy (96.3%), glucocorticoid (39.4%), IVIG (29.4%) |
| Luo [55]            | SSRN               | retrospective, single-center | Wuhan, China | Eastern Campus of Renmin Hospital, Wuhan University | until February 23, 2020 | 403 | 56 (range 39–68) | 47.9% | cardiac injury (20.6%), ARDS (35.5%), shock (21.4%) | antiviral agents (97.8%), antibiotics (86.6%), glucocorticoids (41.2%), IVIG (40.1%) |
| Ma [36]             | medRxiv            | retrospective, single-center | Yongzhou, Chongqing, China | Yongzhou Yongzhou Hospital | until March 2, 2020 | 84 | 48.0 (IQR 42.3–62.5) | 57.1% | cardiac injury (42.9%), liver injury (33.7%) | – |
| Mei [41]            | Research Square    | retrospective, multicenter | Wuhan, China | four Wuhan hospitals | until March 8, 2020 | 223 | 72.0 (IQR 68.0–77.5) | 50.2% | ARDS (62.8%), liver injury (48.8%) | HRT (96%), antiviral therapy (96%), glucocorticoid (71.8%), IVIG (40%) |
| Qin [22]            | Clinical Infectious Diseases | retrospective, single-center | Wuhan, China | Wuhan Tongji Hospital, department of neurology | January 10 to February 12, 2020 | 432 | 58.0 (IQR 47–67, range 22–95) | 52.0% | – | – |
| Regina [36]         | SSRN               | observational, retrospective | Switzerland | Lausanne University Hospital | March 1 to March 25, 2020 | 200 | 70.00 (IQR 55–81) | 60% | cardiac injury (1%), ARDS (22%), shock (6%), liver injury (5.5%) | any SARS-CoV-2 treatment (59%), protease inhibitor (51.5%), HCQ (41.5%), antibiotic (33%) |
| Shubamishu [40]     | medRxiv            | retrospective, single-center | Mecca, Saudi Arabia | Noor Specialist Hospital | March 12 to March 31, 2020 | 150 | 46.1±15.3 (SD) | 60.0% | – | antiviral therapy (9.3%), antimalarial therapy (26.7%), antibiotics (38.7%) |
| Shi [28]            | Critical Care      | retrospective, single-center | Zhejiang Province, China | First Affiliated Hospital of Zhejiang University | until February 17, 2020 | 487 | 46.0±19.0 (SD) | 53.2% | – | – |
| Sun [24]            | Journal of Medical Virology | retrospective, single-center | Beijing, China | Fifth Medical Center of PLA General Hospital | until February 15, 2020 | 55 | 44.0 (IQR 34.0–56.0) | 56.4% | – | interferon alpha inhalation (93.7%), antiviral therapy (87.3%), antibiotics (52.7%), etc. |
| Wan [25]            | Journal of Medical Virology | retrospective, single-center | Chongqing, China | Chongqing University Three Gorges Hospital | January 23 to February 8, 2020 | 135 | 47.0 (IQR 36.0–55.0) | 53.3% | cardiac injury (7.4%), ARDS (13.8%), shock (20.7%) | antiviral therapy (100%), use of corticosteroid (26.7%), TCM (91.8%) |
| Wang [26]           | Journal of the American Medical Association | retrospective, single-center | Wuhan, China | Wuhan University Zhongnan Hospital, department of critical care medicine | January 1 to January 28, 2020 | 138 | 56.0 (IQR 42.0–68.0) | 54.3% | cardiac injury (7.2%), ARDS (19.6%), shock (8.7%) | antiviral therapy (88.9%), glucocorticoid (44.9%), oxygen inhalation (76.8%), etc. |
| Wang [27]           | Critical Care      | retrospective, single-center | Wuhan, China | Wuhan University Zhongnan Hospital, department of critical care medicine | until February 10, 2020 | 107 | 51.0 (IQR 36.0–63.0) | 53.3% | cardiac injury (11.2%), ARDS (26.2%), shock (20.6%) | antiviral therapy (98.6%), antibiotic (79.4%), glucocorticoid (57.9%), etc. |
| Wang [46]           | Research Square    | retrospective, multicenter | Hubei Province, China | four hospitals in Hubei | until March 1, 2020 | 446 | 55.0 (IQR 42–66) | 47.8% | liver injury (27%) | – |
| Study (first author) | Publication status | Study type | Study region | Enrollment hospitals and departments | Enrollment period | Patients, n | Age, years | Male sex | Complications | Treatments |
|---------------------|--------------------|------------|--------------|--------------------------------------|-------------------|-------------|------------|----------|----------------|------------|
| Yan [57]            | SSRN               | multicenter, retrospective, observational | Hunan Province, China | Shaoyang Central Hospital, Loudi Central Hospital, and Xiangtan Central Hospital in Hunan Province | January 10 to February 24, 2020 | 193         | 64.0 (IQR 49.0–73.0) | 39.1%   | – | glucocorticoid treatment (70.3%), mechanical ventilation (50.7%) |
| Yan [58]            | BMJ Open Diabetes Research and Care | retrospective, single-center | Wuhan, China | Wuhan Tongji Hospital, department of endocrinology | January 10 to February 24, 2020 | 193         | 64.0 (IQR 49.0–73.0) | 39.1%   | – | glucocorticoid treatment (70.3%), mechanical ventilation (50.7%) |
| Yin [49]            | Research Square retrospective, single-center | Wuhan, China | Hubei Provincial Hospital of Integrated Chinese and Western Medicine | January 10 to February 24, 2020 | 193         | 64.0 (IQR 49.0–73.0) | 39.1%   | – | glucocorticoid treatment (70.3%), mechanical ventilation (50.7%) |
| Zhang [34]          | medRxiv retrospective, single-center | Wuhan, China | Wuhan No. 1 Hospital | December 25, 2019 to February 15, 2020 | 193         | 64.0 (IQR 49.0–73.0) | 39.1%   | – | glucocorticoid treatment (70.3%), mechanical ventilation (50.7%) |
| Zhang [29]          | Journal of Clinical Virology single-center | Wuhan, China | Wuhan University Zhongnan Hospital, department of respiratory and critical care medicine | January 10 to February 10, 2020 | 193         | 64.0 (IQR 49.0–73.0) | 39.1%   | – | glucocorticoid treatment (70.3%), mechanical ventilation (50.7%) |
| Zhang [33]          | medRxiv retrospective, single-center | Wuhan, China | First People’s Hospital of Jiangxia District | February 1 to March 5, 2020 | 193         | 64.0 (IQR 49.0–73.0) | 39.1%   | – | glucocorticoid treatment (70.3%), mechanical ventilation (50.7%) |
| Zhang [30]          | Allergy retrospective, single-center | Wuhan, China | The Seventh Hospital of Wuhan, department of infectious diseases | January 16 to February 3, 2020 | 193         | 64.0 (IQR 49.0–73.0) | 39.1%   | – | glucocorticoid treatment (70.3%), mechanical ventilation (50.7%) |
| Zhao [41]           | medRxiv retrospective, single-center | Beijing, China | Beijing YouAn Hospital | January 21 to February 10, 2020 | 193         | 64.0 (IQR 49.0–73.0) | 39.1%   | – | glucocorticoid treatment (70.3%), mechanical ventilation (50.7%) |
| Zhao [31]           | BMC Infectious Diseases retrospective, single-center | non-Wuhan area of Hubei Province, China | Jingshou Central Hospital | January 10 to February 10, 2020 | 193         | 64.0 (IQR 49.0–73.0) | 39.1%   | – | glucocorticoid treatment (70.3%), mechanical ventilation (50.7%) |
| Zheng [32]          | British Medical Journal retrospective, single-center | Zhejiang Province, China | First Affiliated Hospital of Zhejiang University | January 19 to March 20, 2020 | 193         | 64.0 (IQR 49.0–73.0) | 39.1%   | – | glucocorticoid treatment (70.3%), mechanical ventilation (50.7%) |
| Zhou [30]           | Lancet retrospective, multicenter | Wuhan, China | Wuhan Jinyintan Hospital and Wuhan Pulmonary Hospital | December 29, 2019 to January 31, 2020 | 193         | 64.0 (IQR 49.0–73.0) | 39.1%   | – | glucocorticoid treatment (70.3%), mechanical ventilation (50.7%) |

ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy; HCQ, hydroxychloroquine; IQR, interquartile range; IVIG, intravenous immunoglobulin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SSRN, Social Science Research Network; TCM, traditional Chinese medicine.
used mortality as the primary outcome, 29 studies used disease severity as the primary outcome, and 1 study used both disease severity and mortality as the primary outcomes. Five studies were performed outside China (2 in the United States [16, 38], 1 in Italy [20], 1 in Switzerland [56], and 1 in Saudi Arabia [40]). The remaining 37 studies were conducted in China (22 in Wuhan City and 15 in non-Wuhan regions). In the studies conducted in China and Saudi Arabia, severe disease was defined by the National Health Commission of China criteria [13]. In the Italian study, severe disease was defined as a requirement for high-flow oxygen support. In the study conducted in Switzerland, severe disease was defined as the requirement for mechanical ventilation. For the studies conducted in the United States, severe disease was defined as the need for mechanical ventilation or ICU admission. Twenty-two of the included studies were performed in Wuhan city. Among them, 2 studies were conducted in two different departments with different enrollment periods (surgery department until December 31 [21] and respiratory department from December 26 to January 31 [52]) in the same hospital (Wuhan Jinyintan Hospital). Two studies were conducted in two different departments with overlapping enrollment periods (respiratory department from January 1 to February 15 [53] and infectious disease department from January 16 to February 3 [30]) in the same hospital (Seventh Hospital of Wuhan City). Three studies were conducted in three different departments with similar enrollment periods (infectious disease department from January 13 to February 12 [19], neurology

Fig. 2. Association between CKD/AKI and disease severity in patients with COVID-19. A Forest plot analyzing the association of CKD/AKI with disease severity in patients with COVID-19. B Funnel plot analyzing the publication bias in the association of CKD/AKI with disease severity. C Funnel plot analyzing the publication bias in the association of AKI with disease severity. AKI, acute kidney injury; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019.
department from January 10 to February 12 [22], and endocrinology department from January 10 to February 24 [28]) in the same hospital (Wuhan Tongji Hospital). Four studies were conducted in three different departments with similar enrolment periods (ICU department from January 1 to January 28 [26], ICU department until February 10 [27], cardiology department from January 3 to February 1 [17], and respiratory department from January 2 to February 10 [29]) in the same hospital (Wuhan University Zhongnan Hospital). The remaining 11 studies were conducted in different hospitals.

**Quality Assessment Results**

Twenty-eight studies had NOS points ranging from 6 to 7 (13 studies scored 6 points and 15 studies scored 7 points), 14 studies had NOS points >7 (8 studies scored 8 points and 6 studies scored 9 points), and no included study had <6 points (online suppl. Table S2).

**The Association of Previously Diagnosed CKD or AKI with Disease Severity**

A total of 27 studies with 5,155 patients reported an association between previously diagnosed CKD and disease severity (Fig. 2A). The overall prevalence of CKD was 3.03% (155/5,115) in all included studies. Compared with COVID-19 patients without previously diagnosed CKD, those with previously diagnosed CKD had a significantly increased risk of progressing to a severe condition (OR = 2.31, 95% CI 1.64–3.24, p < 0.001, $I^2 = 13\%$, $p_{\text{het}} = 0.27$). Eighteen studies with 3,850 patients reported an association between AKI and disease severity (Fig. 2A). The overall incidence of AKI was 14.68% (565/3,850) in all included studies. Compared with COVID-19 patients without AKI, those with AKI had a significantly increased risk of progressing to a severe condition (OR = 2.23, 95% CI 1.41–3.51, $p_{\text{het}} = 0.83$, $I^2 = 0\%$; AKI: OR = 11.67, 95% CI 6.90–19.73 vs. OR = 11.95, 95% CI 9.06–15.77, $p_{\text{het}} = 0.94$, $I^2 = 0\%$) (online suppl. Fig. S2A, S2B). Neither the publication status nor the geographic region had an influence on the associations of CKD/AKI with disease severity.

**The Association of Published versus Unpublished Studies**

Eleven studies with 2,140 participants reported an association between previously diagnosed CKD and disease mortality (Fig. 3A). The overall prevalence of CKD was 6.73% (144/2,120) in all included studies. Compared with COVID-19 patients without previously diagnosed CKD, those with previously diagnosed CKD had a significantly increased risk of death (OR = 5.11, 95% CI 3.36–7.77, $p < 0.001$, $I^2 = 0\%$, $p_{\text{het}} = 0.68$). Six studies with 1,220 patients reported an association between AKI and disease mortality. The incidence of AKI was 13.28% (162/1,220) in all included studies. Compared with COVID-19 patients without AKI, those with AKI had a significantly increased risk of death, with medium heterogeneity (OR = 30.46, 95% CI 18.33–50.59, $p < 0.001$, $I^2 = 42\%$, $p_{\text{het}} = 0.12$) (Fig. 3A). Subgroup analysis indicated that patients with AKI were more likely to die than patients with previously diagnosed CKD, which was demonstrated by the significant difference between the AKI and CKD groups (AKI vs. CKD: OR = 11.88, 95% CI 9.29–15.19, $p < 0.001$, $I^2 = 0\%$, $p_{\text{het}} = 0.55$). Subgroup analysis indicated that patients with AKI were more likely to progress to a severe condition compared with patients with previously diagnosed CKD, which was demonstrated by the significant difference between the AKI and CKD groups (AKI vs. CKD: OR = 2.23, 95% CI 1.41–3.51, $p_{\text{het}} < 0.001$, $I^2 = 98.3\%$) (Fig. 2A). The funnel plots indicated no publication bias for the associations of CKD/AKI with disease severity (Fig. 2B, C).

Subgroup analyses indicated that the publication status did not significantly affect the associations between CKD/AKI and disease severity (CKD: published vs. unpublished studies: OR = 2.41, 95% CI 1.36–4.30 vs. OR = 2.25, 95% CI 1.47–3.43, $p_{\text{het}} = 0.84$, $I^2 = 0\%$; AKI: published vs. unpublished studies: OR = 6.53, 95% CI 3.02–14.11 vs. OR = 12.74, 95% CI 9.82–16.52, $p_{\text{het}} = 0.11$, $I^2 = 61.5\%$) (online suppl. Fig. S1A, S1B). Similarly, subgroup analyses revealed that the geographic region did not significantly affect the associations of CKD/AKI with disease severity (CKD: Wuhan City vs. non-Wuhan regions: OR = 2.40, 95% CI 1.43–4.01 vs. OR = 2.23, 95% CI 1.41–3.51, $p_{\text{het}} = 0.83$, $I^2 = 0\%$; AKI: OR = 11.67, 95% CI 6.90–19.73 vs. OR = 11.95, 95% CI 9.06–15.77, $p_{\text{het}} = 0.94$, $I^2 = 0\%$) (online suppl. Fig. S2A, S2B). Neither the publication status nor the geographic region had an influence on the associations of CKD/AKI with disease severity.
The subgroup analyses to explore the impact of geographic region on the association of CKD/AKI with disease mortality were not performed because all the included studies were conducted in Wuhan City.

The Impact of Age and Complications on the Association between Kidney Impairment and Clinical Prognosis

The meta-regression analysis indicated that age had a significant impact on the association between CKD and disease severity ($p = 0.001$) (Fig. 4A). However, meta-regression analyses indicated that age did not significantly affect the associations between AKI and disease severity ($p = 0.80$) (Fig. 4B), between CKD and mortality ($p = 0.51$) (Fig. 4C), or between AKI and mortality ($p = 0.86$) (Fig. 4D). Meta-regression analyses indicated that four important complications (cardiac injury, shock, ARDS, and liver injury) did not significantly affect the associations between CKD/AKI and disease severity/mortality (Table 2).

### Table 2. Meta-regression analyzing the impact of complications on the association between kidney injury and clinical prognosis

| Association | Disease severity | Disease mortality |
|-------------|------------------|-------------------|
|              | cardiac injury   | ARDS              | shock | liver injury | cardiac injury | ARDS | shock | liver injury |
| CKD          | $p = 0.84$       | $p = 0.51$        | $p = 0.31$ | $p = 0.43$ | $p = 0.86$ | $p = 0.55$ | $p = 0.66$ | $p = 0.33$ |
| AKI          | $p = 0.93$       | $p = 0.22$        | $p = 0.07$ | $p = 0.85$ | $p = 0.82$ | $p = 0.83$ | $p = 0.14$ | $p = 0.70$ |

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CKD, chronic kidney disease.

### Discussion

We provide an up-to-date analysis of the evidence regarding the associations of CKD/AKI with clinical prognosis in patients with COVID-19 (42 studies with 8,932 patients). We demonstrated that COVID-19 patients with previously diagnosed CKD or AKI had significantly
Fig. 4. Meta-regression investigating the impact of age on the association between CKD/AKI and clinical prognosis. 

A Impact of age on the association between CKD and disease severity. 

Impact of age on the association between AKI and disease severity. 

Impact of age on the association between CKD and mortality. 

Impact of age on the association between AKI and mortality. AKI, acute kidney injury; CKD, chronic kidney disease.
increased risks of progression to a severe condition and even death. Compared with patients with previously diagnosed CKD before SARS-CoV-2 infection, patients with AKI after SARS-CoV-2 infection were more likely to progress to a severe condition or death.

Since the outbreak of the COVID-19 epidemic, several meta-analyses concerning kidney impairment and clinical prognosis have been published. Ng et al. [8] reported that the overall risk of AKI in hospitalized patients was 3% and that this risk increased to 19% when patients were admitted to an ICU. Zheng et al. [9] found that serum creatinine could impact the risk of progression of COVID-19. Ali et al. [10] revealed that severe AKI was associated with a higher risk of mortality (relative risk = 3.08, 95% CI 1.54–6.19). Potere et al. [58] reported that the incidence of AKI was 6% in hospitalized patients. Lim et al. [59] demonstrated that AKI was associated with increased mortality, severe condition, and the need for ICU care. In our study, we demonstrated that not only previously diagnosed CKD but also AKI significantly affected the disease severity and mortality of COVID-19. We also found that AKI was associated with a more severe condition and a higher risk of mortality than CKD. Four major complications (cardiac injury, ARDS, shock, and liver injury) did not participate substantially in the associations between CKD/AKI and clinical prognoses, indicating that kidney impairment may be an independent clinical prognostic indicator for these patients.

The reason why COVID-19 patients with CKD comorbidity exhibited an increased risk of progression to a severe condition or death has not been fully elucidated to date. Plausible explanations are as follows: (1) Patients with CKD have a proinflammatory milieu and functional defects in innate and adaptive immune cell populations [60]. In a community-based cohort of nearly 10,000 adult individuals, reduced glomerular filtration rate and elevated albumin-creatinine ratios were associated with a higher risk of hospitalization, with infection and subsequent mortality [61]. (2) Patients with CKD have a high risk of upper respiratory tract infection and pneumonia [62, 63], which may become important concurrent infections with SARS-CoV-2. (3) CKD frequently coexists with comorbidities, especially diabetes and cardiovascular disease, which are also known to be associated with worse outcomes in patients with COVID-19 [9]. (4) CKD prevalence rises with age, and the burden of COVID-19 morbidity and mortality is heavily concentrated in older age groups. An important limitation of the present study is that we were unable to determine the extent to which age and comorbidities independently contribute to poor outcomes in patients with CKD.

AKI is a syndrome of abrupt loss of kidney function that is strongly associated with increased mortality and morbidity in several conditions [64]. There is a high incidence of AKI in patients with COVID-19, especially in the cohort with severe disease [46, 49, 65]. The following reasons have been postulated to explain why an increased incidence of AKI occurs after SARS-CoV-2 infection: (1) The severity of the disease may be associated with an increase in the initial renal viral load or severe systemic inflammation, or both. SARS-CoV-2 can penetrate cells via two receptors – angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2) [66] –, and ACE2 is highly expressed in proximal tubular epithelial cells and in podocytes. Nine of 26 autopsied Chinese patients with AKI after SARS-CoV-2 infection had diffuse proximal tubular injury, with some frank necrosis and no glomerular injury [67]. (2) The fever, vomiting, diarrhea, and shock often observed with SARS-CoV-2 infection can cause kidney hypoperfusion. These reasons may cooperatively contribute to an increased risk of AKI. Additionally, COVID-19 patients with severe conditions also have complications involving various organ dysfunctions, which may in turn lead to AKI.

This meta-analysis has several limitations: (1) Twenty-two of the included studies were from Wuhan, China, and although it is unlikely that the same patients were included in multiple studies, the low heterogeneity in the outcome of our study may be attributable to the fact that these patients from the same region with similar genetic background were infected by the same strain of SARS-CoV-2 virus in similar periods. This may limit generalizability, although subgroup analysis showed that the association with CKD/AKI and disease severity was consistent between studies from China and outside China. (2) Half of the included studies were posted on academic websites and were not peer-reviewed, and subgroup analysis demonstrated that the impact of AKI on the mortality in published studies was significantly higher than that in unpublished studies. This significant subgroup difference indicated the existence of publication bias. (3) The comparability of the baseline characteristics between the two groups (severe/nonsevere, survivors/deaths) was not well matched in a majority of studies, indicating that residual confounding is likely.

In conclusion, not only previously diagnosed CKD before SARS-CoV-2 infection, but also AKI after SARS-CoV-2 infection were associated with disease severity and mortality. AKI had a higher risk of disease progression and death compared with CKD.
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Statement of Ethics

Our study adhered to the MOOSE guidelines [11]. Institutional approval and patient consent were not necessary.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

B. Wang, Q. Luo, Y. Chen, and Xiangmei Chen designed the study, with input into the study protocol from all authors. B. Wang, Q. Luo, and Y. Chen searched the literature and extracted the data. W. Zhang and S. Yu performed the statistical analyses. Xiaowei Cheng and L. Wang contributed to the discussion section. B. Wang and Q. Luo drafted the manuscript. Y. Chen and Xiangmei Chen supervised the study and provided critical revision to the intellectual content. All authors contributed to the interpretation of the data and approved the final version.
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