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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 ($p_{group} < 0.001$, $I^2 = 98.3\%$) and even to death ($p_{group} < 0.001$, $I^2 = 96.5\%$). 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 supplementary 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," "coronavirus 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, the 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

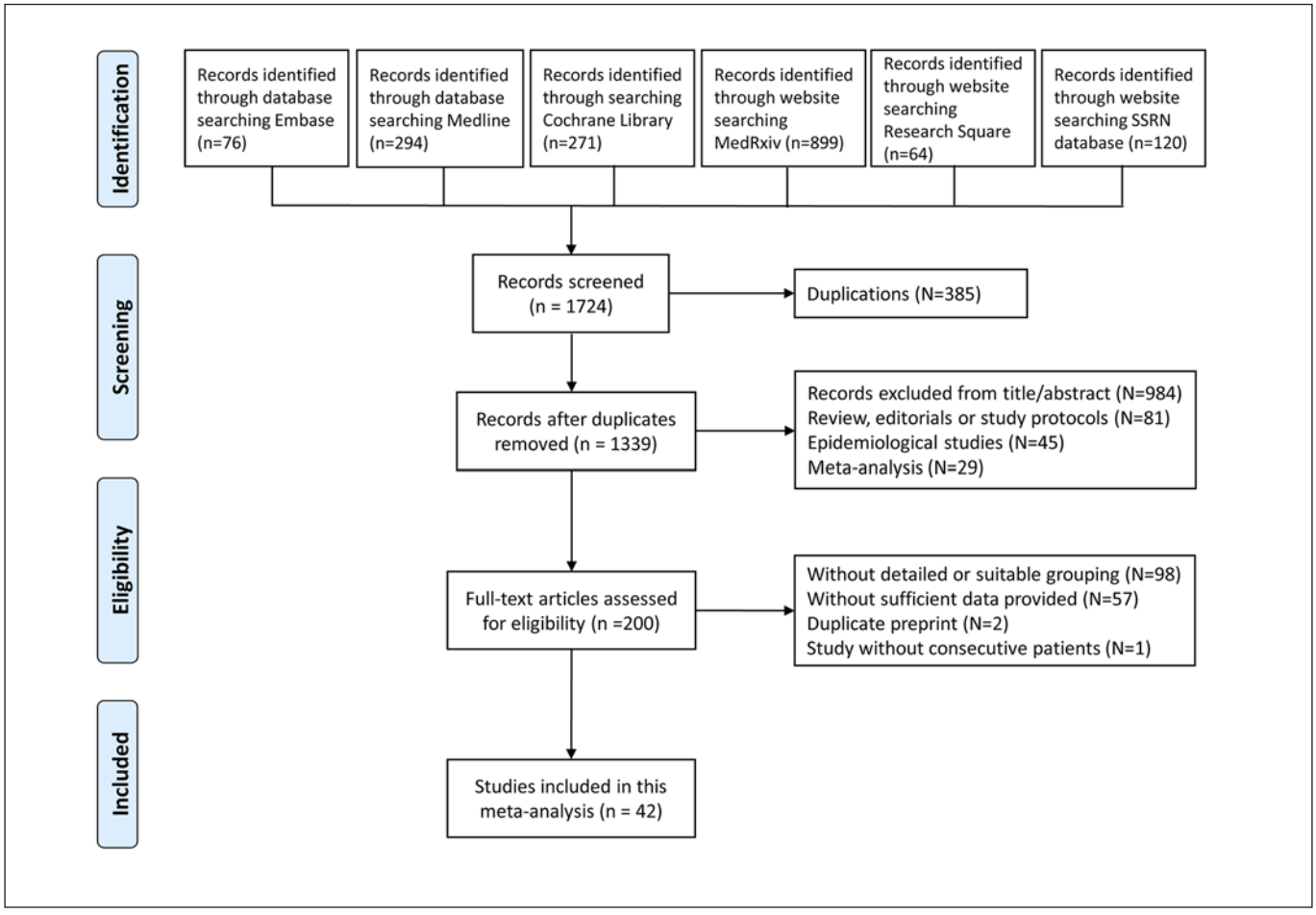

Fig. 1. Flow diagram of search strategy and study selection. SSRN, Social Science Research Network.

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

Table 1. Characteristics of the studies included in this meta-analysis

Study (first author)	Publication status	Study type	Study region	Enrollment hospitals and departments	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%), azithromycin (43%), glucocorticoids (19%)
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%	ARDS (35.2%)	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 (18.1%), shock (3.9%), liver injury (7.9%)	–
Bi [42]	medRxiv	prospective, single-center	Shenzhen, China	Shenzhen Third People's Hospital	January 11 to March 10, 2020	420	45.0 (IQR 34.0–60.0)	47.6%	cardiac injury (1%), ARDS (9.3%), liver injury (67%)	–
Cai [43]	medRxiv	retrospective, single-center	Shenzhen, China	Shenzhen Third People's Hospital	January 11 to February 6, 2020	298	47 (range 33–61)	50%	cardiac injury (6.7%), liver injury (14.8%)	antiviral: lopinavir/ritonavir (76.8%), favipiravir (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 [53]	SSRN	retrospective	Wuhan, China	Seventh Hospital of Wuhan City, respiratory department	January 1 to February 15, 2020	123	57.8 (mean)	49.6%	cardiac injury (27.6%), ARDS (34.1%), shock (11.4%), liver injury (15.4%)	antiviral therapy (oseltamivir 69%, ribavirin 40.7%, umifenovir 25.2%), antibiotics (87%), glucocorticoid (55.3%), respiratory support (34.1%)
Chen [18]	Infection	retrospective, single-center	Taizhou, Zhejiang Province, China	Taizhou Public Health Medical Center	January 1 to March 11, 2020	145	47.5±14.6 (SD)	54.5%	–	oral antiviral therapy (97.2%), atomized 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 44.0–70.0)	62.4%	cardiac injury (44%), ARDS (72%), shock (17%), liver injury (5%)	antiviral (86%), glucocorticoid (77%), antibiotics (91%), IVIG (20%), oxygen treatment (92%), 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 (72.7%)
Feng [47]	medRxiv	prospective, single center	Wuhan, China	Wuhan Union Hospital	January 23 to February 22, 2020	114	64.0±13.4 (SD)	62.3%	cardiac injury (24.6%), ARDS (36%), shock (7%), liver injury (60.5%)	antibiotic (100%), anti-coronavirus (99.1%), glucocorticoids (41.2%), etc.
Hu [37]	medRxiv	retrospective, single-center	Wuhan, China	Wuhan Tianyou 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 (71.2%), Arbidol (64.4%)
Huang [21]	Lancet	prospective, single-center	Wuhan, China	Wuhan Jinyintan Hospital, department of surgery	until December 31, 2019	41	49.0 (IQR 41.0–58.0)	73%	cardiac injury (12%), ARDS (29%), shock (7%)	antiviral therapy (93%), 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	45.0 (IQR 27.0–60.0)	49.1%	cardiac injury (1.8%), ARDS (7.3%), shock (1.8%), liver injury (29.1%)	antiviral therapy (100%), antibiotic (52.7%), corticosteroid (10.9%), IVIG (9.5%)

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Table 1 (continued)

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, Huangshi, and Chongqing, China	Two hospitals in Wuhan, one hospital in Huangshi, 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 (62%), CRRT (4%), mechanical ventilation (43%)
Liao [51]	medRxiv	retrospective, single-center	Wuhan, China	Jianghan Fangfang Shelter Hospital	February 5 to March 9, 2020	148	56.0 (IQR 48.0–62.0)	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	44.48±17.16 (SD)	52.6%	shock (0.3%)	Chinese medicine (15.8%), IVIG (25.2%), glucocorticoid (22.9%), antibiotics (53.5%)
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 25, 2020	403	56 (range 39–68)	47.9%	cardiac injury (20.6%), ARDS (35.5%), shock (21.6%)	antiviral agents (97.8%), antibiotics (86.6%), glucocorticoids (41.2%), IVIG (49.1%)
Ma [36]	medRxiv	retrospective, single-center	Yongchuan, Chongqing, China	Chongqing Yongchuan Hospital	until March 2, 2020	84	48.0 (IQR 42.3–62.5)	57.1%	cardiac injury (42.9%), liver injury (35.7%)	–
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 (49.8%)	antibiotics (86.1%), antiviral therapy (96%), glucocorticoid (71.3%), IVIG (48%)
Qin [22]	Clinical Infectious Diseases	retrospective, single-center	Wuhan, China	Wuhan Tongji Hospital, department of neurology	January 10 to February 12, 2020	452	58.0 (IQR 47–67, range 22–95)	52.0%	–	–
Regina [56]	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 (35%)
Shabrawishi [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 [23]	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 (92.7%), 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 (15.6%), shock (0.7%)	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 (89.9%), 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 36.0–65.0)	53.3%	cardiac injury (11.2%), ARDS (26.2%), shock (20.6%)	antiviral (98.1%), 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%)	–

Table 1 (continued)

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 21 to March 11, 2020	218	42.9 (IQR 32.0, 52.3)	56%	cardiac injury (43%), shock (6%), liver injury (2%)	oxygen treatment (72%), lopinavir/ritonavir (88%), antibiotics (53%), Chinese medicine (90%), corticosteroid (22%), gamma globulin (15%)
Yan [28]	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)	59.1%	–	glucocorticoid treatment (70.5%), mechanical ventilation (50.7%)
Yin [49]	Research Square	retrospective, single-center	Wuhan, China	Hubei Provincial Hospital of Integrated Chinese and Western Medicine	January 1 to February 29, 2020	292	61.2±13.1 (SD)	50.7%	–	antiviral, antibacterial, nutrition, TCM, etc.
Zhang [34]	medRxiv	retrospective, single-center	Wuhan, China	Wuhan No. 1 Hospital	December 25, 2019 to February 15, 2020	48	64.0±16.5 (SD)	54.5%	–	antiviral (98%), antibiotic (95.8%), corticosteroids (45.8%), IVIG (12.5%)
Zhang [29]	Journal of Clinical Virology	retrospective, single-center	Wuhan, China	Wuhan University Zhongnan Hospital, department of respiratory and critical care medicine	January 2 to February 10, 2020	221	55.0 (IQR 39.0–66.5)	48.9%	cardiac injury (7.7%), ARDS (21.7%), shock (6.8%)	antiviral therapy (88.7%), glucocorticoid therapy (52%), CRRT (2.3%), etc.
Zhang [35]	medRxiv	retrospective, single-center	Wuhan, China	First People's Hospital of Jiangxia District	February 1 to March 15, 2020	135	56.0 (IQR 42.0–68.0)	49.6%	–	antibiotic, corticosteroid, respiration-assisted ventilation
Zhang [30]	Allergy	retrospective, single-center	Wuhan, China	The Seventh Hospital of Wuhan, department of infectious diseases	January 16 to February 3, 2020	140	57.0 (range 25–87)	50.7%	–	–
Zhao [45]	medRxiv	retrospective, single-center	Beijing, China	Beijing YouAn Hospital	January 21 to February 8, 2020	77	52±20 (SD)	44.2%	ARDS (3.9%), shock (1.3%), liver injury (32.5%)	–
Zhao [31]	BMC Infectious Diseases	retrospective, single-center	non-Wuhan area of Hubei Province, China	Jingzhou Central Hospital	January 16 to February 10, 2020	91	46.0	53.8%	cardiac injury (15.4%), liver injury (19.8%)	glucocorticoid (86.8%), antiviral therapy (89%), antibacterial therapy (98.9%), immunoglobulin (38.5%), oxygen therapy (31.9%)
Zheng [32]	British Medical Journal	retrospective, single-center	Zhejiang Province, China	First Affiliated Hospital of Zhejiang University	January 19 to March 20, 2020	96	55.0 (IQR 44.3–64.8)	60.0%	–	gamma globulin (55%), glucocorticoids (81%), antibiotics (34%), antivirals (100%)
Zhou [33]	Lancet	retrospective, multicenter	Wuhan, China	Wuhan Jinyintan Hospital and Wuhan Pulmonary Hospital	December 29, 2019 to January 31, 2020	191	56.0 (IQR 46.0–67.0)	62%	cardiac injury (17%), ARDS (31%), shock (20%)	antibiotics (95%), antiviral treatment (21%), corticosteroids (30%), IVIG (24%), mechanical ventilation (31%)

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.

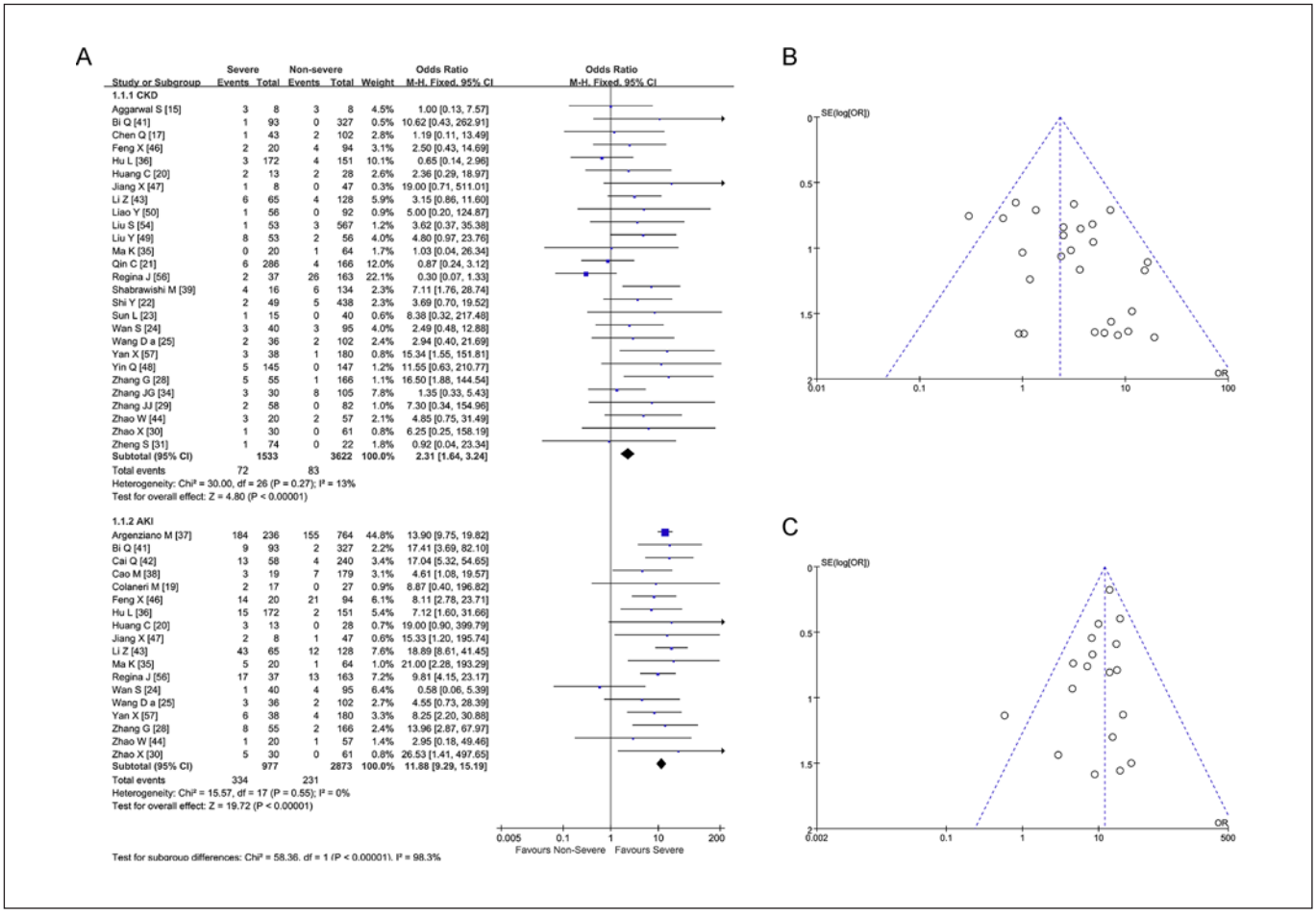


Fig. 2. Association between CKD/AKI and disease severity in patients with COVID-19. **A** Forest plot analyzing the association of CKD/AKI with disease severity in patients with COVID-19. **B** Funnel plot analyzing the publication bias in the association of CKD with disease severity. **C** Funnel plot 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.

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

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 enrollment 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, $p < 0.001$, $I^2 = 13\%$, $p_{heterogeneity} = 0.27$). 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 = 11.88, 95% CI 9.29–15.19, $p < 0.001$, $I^2 = 0\%$, $p_{heterogeneity} = 0.55$). 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 = 11.88, 95% CI 9.29–15.19 vs. OR = 2.31, 95% CI 1.64–3.24; $p_{group} < 0.001$, $I^2 = 98.3\%$) (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, $p_{subgroup} = 0.84$, $I^2 = 0\%$; AKI: published vs. unpublished studies: OR = 6.53, 95% CI 3.02–14.11 vs. OR = 12.74, 95% CI 9.82–16.52, $p_{subgroup} = 0.11$, $I^2 = 61.5\%$) (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, $p_{subgroup} = 0.83$, $I^2 = 0\%$; AKI: OR = 11.67, 95% CI 6.90–19.73 vs. OR = 11.95, 95% CI 9.06–15.77, $p_{subgroup} = 0.94$, $I^2 = 0\%$) (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 Previously Diagnosed CKD or AKI with Disease Mortality

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% (144/2,140) 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, $p < 0.001$, $I^2 = 0\%$, $p_{heterogeneity} = 0.68$). 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, $p < 0.001$, $I^2 = 42\%$, $p_{heterogeneity} = 0.12$) (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 = 30.46, 95% CI 18.33–50.59 vs. OR = 5.11, 95% CI 3.36–7.77, $p_{group} < 0.001$, $I^2 = 96.5\%$) (Fig. 3A). The funnel plot indicated no publication bias for the associations of CKD with disease mortality (Fig. 3B). Publication bias was not explored for the association of AKI and mortality because the number of included studies was <10.

Subgroup analysis indicated that the publication status did not significantly affect the association between CKD and disease mortality (published vs. unpublished studies: OR = 4.77, 95% CI 1.93–11.77 vs. OR = 5.21, 95% CI 3.25–8.36, $p_{subgroup} = 0.87$, $I^2 = 0\%$) (online suppl. Fig. S3A). However, subgroup analysis revealed that the publication status had a significant impact on the association of AKI with disease mortality (published vs. unpublished studies: OR = 86.13, 95% CI 25.26–293.68 vs. OR = 18.61, 95% CI 10.49–33.02, $p_{subgroup} = 0.03$, $I^2 = 79.7\%$) (online suppl.

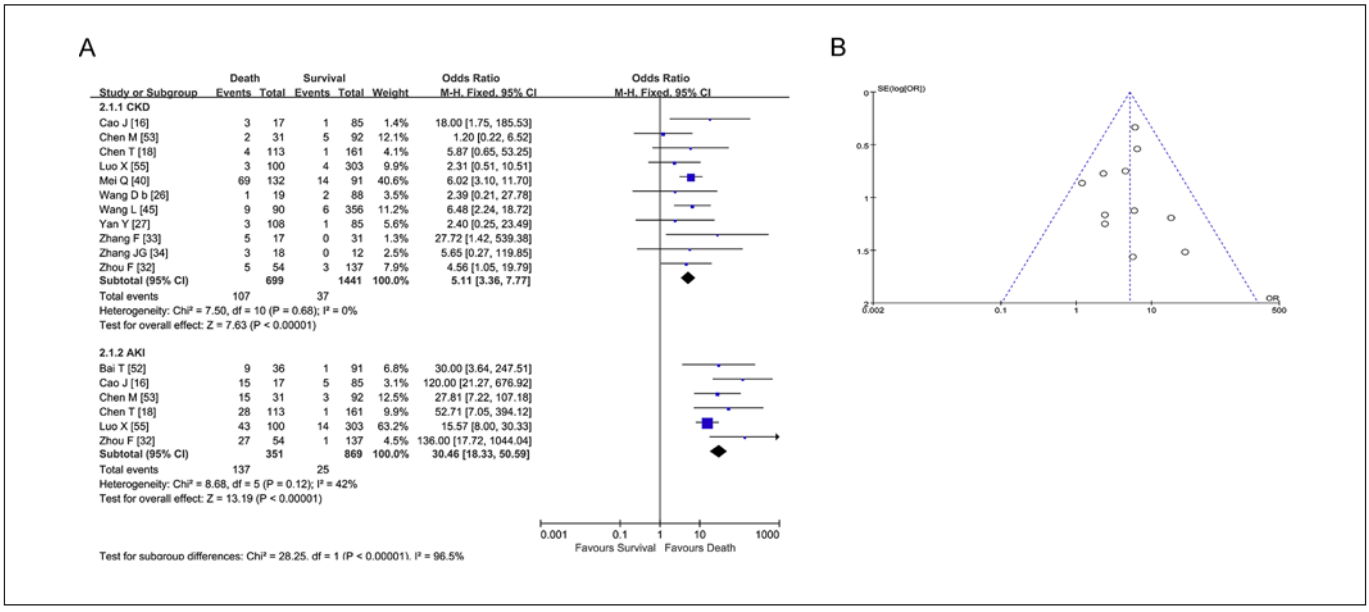


Fig. 3. Association between CKD/AKI and disease mortality in patients with COVID-19. **A** Forest plot analyzing the association of CKD/AKI with disease mortality in patients with COVID-19. **B** Funnel plot analyzing the publication bias in the association of CKD and disease mortality. AKI, acute kidney injury; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019.

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.

Fig. S3B). 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

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).

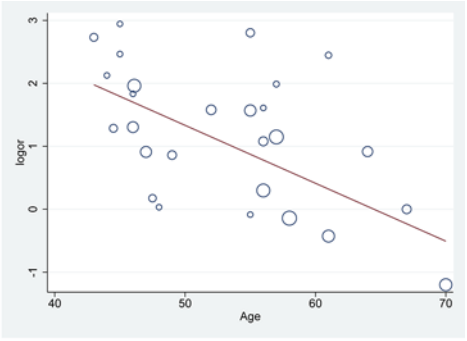
Discussion

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

A CKD and disease severity

Meta-regression — Number of obs = 27
REML estimate of between-study variance — tau2 = 0
% residual variation due to heterogeneity — I-squared_res = 0.00%
Proportion of between-study variance explained — Adj R-squared = 100.00%
With Knapp-Hartung modification

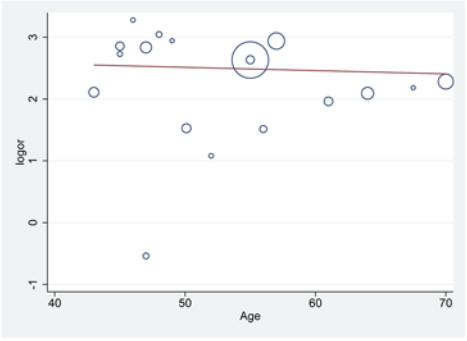
logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
age	.9120811	.0233848	-3.59	0.001	.8651687	.9615373
_cons	377.6982	533.403	4.20	0.000	20.60471	6923.465



B AKI and disease severity

Meta-regression — Number of obs = 18
REML estimate of between-study variance — tau2 = .001753
% residual variation due to heterogeneity — I-squared_res = 0.00%
Proportion of between-study variance explained — Adj R-squared = .%
With Knapp-Hartung modification

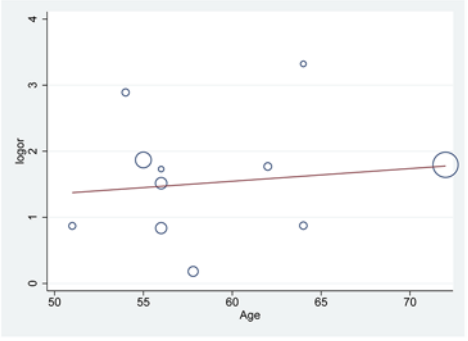
logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
age	.9947018	.0200643	-0.26	0.796	.9530638	1.038159
_cons	16.10508	18.18301	2.46	0.026	1.470661	176.3653



C CKD and disease mortality

Meta-regression — Number of obs = 11
REML estimate of between-study variance — tau2 = 0
% residual variation due to heterogeneity — I-squared_res = 0.00%
Proportion of between-study variance explained — Adj R-squared = .%
With Knapp-Hartung modification

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
age	1.01935	.0282674	0.69	0.507	.957369	1.085344
_cons	1.48674	2.624723	0.22	0.827	.0274037	80.66037



D AKI and disease mortality

Meta-regression — Number of obs = 6
REML estimate of between-study variance — tau2 = .5372
% residual variation due to heterogeneity — I-squared_res = 51.83%
Proportion of between-study variance explained — Adj R-squared = -33.42%
With Knapp-Hartung modification

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
age	.9650731	.1852342	-0.19	0.862	.5663989	1.644364
_cons	287.9122	3134.406	0.52	0.630	2.15e-11	3.86e+15

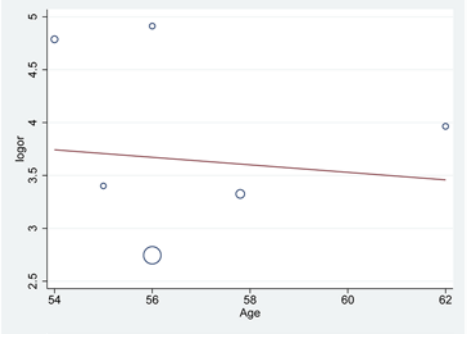


Fig. 4. Meta-regression investigating the impact of age on the association between CKD/AKI and clinical prognosis. **A** Impact of age on the association between CKD and disease severity. **B** Impact of age on the association between AKI and disease severity. **C** Impact of age on the association between CKD and mortality. **D** 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.

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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