Risk factors and prognosis for COVID-19-induced acute kidney injury: a meta-analysis

Lirong Lin,1 Xiang Wang,2 Jiangwen Ren,3 Yan Sun,1 Rongjie Yu,1 Kailong Li,1 Luquan Zheng,1 Jurong Yang 1

ABSTRACT

Objective To analyse the incidence, risk factors and impact of acute kidney injury (AKI) on the prognosis of patients with COVID-19.

Design Meta-analysis.

Data sources PubMed, Embase, CNKI and MedRxiv of Systematic Reviews from 1 January 2020 to 15 May 2020.

Study selection Studies examining the following demographics and outcomes were included: patients’ age; sex; incidence of and risk factors for AKI and their impact on prognosis; COVID-19 disease type and incidence of continuous renal replacement therapy (CRRT) administration during COVID-19 infection.

Results A total of 79 research articles, including 49 692 patients with COVID-19, met the systemic evaluation criteria. The mortality rate and incidence of AKI in patients with COVID-19 in China were significantly lower than those in patients with COVID-19 outside China. A significantly higher proportion of patients with COVID-19 from North America were aged ≥65 years and also developed AKI. European patients with COVID-19 had significantly higher mortality and a higher CRRT rate than patients from other regions. Further analysis of the risk factors for COVID-19 combined with AKI showed that age ≥60 years and severe COVID-19 were independent risk factors for AKI, with an OR of 3.53, 95% CI (2.92–4.25) and an OR of 6.07, 95% CI (2.53–14.58), respectively. The CRRT rate in patients with severe COVID-19 was significantly higher than in patients with non-severe COVID-19, with an OR of 6.60, 95% CI (2.83–15.39). The risk of death in patients with COVID-19 and AKI was significantly increased, with an OR of 11.05, 95% CI (9.13–13.36).

Conclusion AKI was a common and serious complication of COVID-19. Older age and having severe COVID-19 were independent risk factors for AKI. The risk of in-hospital death was significantly increased in patients with COVID-19 complicated by AKI.

INTRODUCTION

An unexplained acute respiratory disease was detected in Wuhan, Hubei Province, China in December of 2019. On 12 February 2020, the International Committee on Taxonomy of Viruses announced that this new coronavirus was officially classified as SARS-CoV-2. The WHO also announced that the disease caused by SARS-CoV-2 had been officially named COVID-19.1 As of 15 May 2020, more than 4.4 million COVID-19 cases have been reported in 215 countries and regions worldwide, with a cumulative death toll of more than 300 000. COVID-19 has become a major infectious disease that seriously endangers human health.

COVID-19 is primarily transmitted through respiratory droplets and direct contact.2–3 Most patients with COVID-19 have dyspnoea as the main clinical manifestation, and some cases may be complicated by heart, kidney, circulatory, liver, nerve and other multisystem injuries.4–6 These patients may eventually die of diffuse alveolar injury and progressive respiratory failure. The cytokine storm syndrome involved in the pathogenesis of acute respiratory distress syndrome and organ failure during SARS-CoV infection seems to be related to a massive inflammatory reaction. Viral replication in targeted organs, including the kidneys, induces systemic viral sepsis and systemic inflammatory responses, as well as subsequent cell damage in multiple organs. In addition, renal failure in patients with COVID-19 may occur due to rhabdomyolysis, hypoxemia, dehydration, presence of...
Widely distributed across humans, other mammals and birds, SARS-CoV and SARS-CoV-2 are enveloped RNA viruses that rely on ACE2 as the receptor to infect normal tissues and cells. One study showed that the affinity of the SARS-CoV-2 S protein to ACE2 was 10–20-fold of that of SARS-CoV to ACE2. In 2003, 6.7% of SARS cases were complicated by acute renal impairment, and 91.7% of patients who died from SARS suffered from acute kidney injury (AKI) as a complication. Studies also have shown that patients infected with SARS-CoV-2 had significantly increased serum creatinine (SCr) and hospital mortality after AKI. However, another study showed that COVID-19 did not cause AKI, and did not aggravate kidney damage in patients with complication of chronic kidney disease. To understand the incidence of COVID-19 in conjunction with AKI and its impact on prognosis, we systematically analysed the relationships between AKI incidence, demographic characteristics, clinical characteristics and prognosis in patients with COVID-19 to provide references for the diagnosis, treatment and prognosis of patients with COVID-19 complicated by AKI in clinical practice.

**METHODS**

**Search strategy**

Articles for this review were identified by comprehensive search in the PubMed, Embase, CNKI and MedRxiv online databases. The search strategy is provided in Table 1. The following Medical Subject Heading terms and free words were used: “COVID 19 virus,” “COVID-19 virus,” “coronavirus disease 2019 virus” OR “SARS-CoV-2” OR “SARS 2” OR “2019-nCoV” OR “2019 novel coronavirus” OR “Wuhan coronavirus” OR “Wuhan seafood market pneumonia virus”.

**Table 1** Search strategy

| Search strategy | Databases | Criteria | Data |
|-----------------|-----------|----------|------|
| **Search strategy** | Pubmed, Embase, CNKI, MedRxiv | Language (in English or Chinese), species (studies on humans) | 1 January 2020 to 15 May 2020 |
| **#1 (MeSH)** | “COVID 19 virus” OR “COVID-19 virus” OR “coronavirus disease 2019 virus” OR “SARS-CoV-2” OR “SARS 2” OR “2019-nCoV” OR “2019 novel coronavirus” OR “Wuhan coronavirus” OR “Wuhan seafood market pneumonia virus” | | |
| **#2 (Entry terms)** | “kidney” OR “renal” | | |
| **Search** | #1 and #2 | | |

MeSH, Medical Subject Headings.

![Flow diagram for selection of studies](http://bmjopen.bmj.com/)

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### Table 2  Demographic and clinical characteristics of patients from 79 COVID-19 studies

| ID  | Country | Study author(s)      | Year | SS (N) | Age in years n (%) | AKI n (%) | CRRT n (%) | Severe disease n (%) | Deaths n (%) |
|-----|---------|----------------------|------|--------|--------------------|-----------|------------|---------------------|--------------|
| 1   | China   | Bicheng Zhang       | 2020 | 82     | <60, 16 (19.5), ≥60, 66 (81.5) | 54/28     | 26 (31.7) | NA                  | NA           |
| 2   | China   | Xiaomin Luo         | 2020 | 403    | <60, 232 (57.6), ≥60, 171 (42.4) | 193/210   | 57 (14.1) | NA                  | 205 (50.9), 100 (24.8) |
| 3   | China   | Wen Zhao            | 2020 | 77     | <65, 55 (71.4), ≥65, 22 (28.6) | 34/43     | 2 (2.6)   | NA                  | 20 (26.0), 5 (6.5) |
| 4   | China   | Hua Fan             | 2020 | 101    | <60, 22 (21.8), ≥60, 89 (78.2) | 64/37     | 8 (7.9)   | 8 (7.9)             | NA           |
| 5   | China   | Qiao Shi            | 2020 | 101    | <60, 26 (25.7), ≥60, 75 (74.3) | 41/60     | 23 (22.8) | 5 (5.0)             | NA           |
| 6   | China   | Jiaqiang Liao       | 2020 | 46     | <60, 46 (100.0) | 24/21     | 3 (6.5)   | NA                  | 1 (2.2)      |
| 7   | China   | Guqin Zhang         | 2020 | 221    | <65, 159 (71.9), ≥65, 62 (29.1) | 108/113   | 10 (4.5)  | 5 (2.3)             | 55 (24.9), NA |
| 8   | China   | Yichun Cheng        | 2020 | 710    | NA      | 374/336   | 22 (3.1)  | NA                  | 252 (35.5), 89 (12.5) |
| 9   | China   | Qingxian Cai        | 2020 | 298    | NA      | 149/149   | 17 (5.7)  | 4 (0.2)             | 58 (19.5), NA |
| 10  | China   | Lin Fu              | 2020 | 200    | <60, 102 (53.8), ≥60, 98 (46.2) | 99/101    | 45 (22.5) | NA                  | NA           |
| 11  | China   | Yi Yang             | 2020 | 36     | NA      | 30/6      | 8 (22.2)  | 22 (61.1)           | NA           |
| 12  | China   | Wang Wenjun         | 2020 | 11     | NA      | 1/10      | 8 (72.7)  | 0 (0.0)             | 11 (100.0), NA |
| 13  | China   | Luwen Wang          | 2020 | 116    | NA      | 67/49     | 12 (10.8) | NA                  | 52 (46.8), 67 (60.4) |
| 14  | China   | Huayan Xu           | 2020 | 53     | NA      | 28/25     | 5 (9.4)   | 4 (7.5)             | NA           |
| 15  | China   | Bo Diao             | 2020 | 85     | <60, 55 (64.7), ≥60, 30 (36.3) | 48/37     | 23 (27.1) | NA                  | NA           |
| 16  | China   | Shijiao Yan         | 2020 | 168    | <65, 135 (80.4), ≥65, 33 (19.6) | 81/87     | 6 (3.6)   | NA                  | 36 (21.4), 6 (3.6) |
| 17  | China   | Di Qi               | 2020 | 267    | <50, 138 (51.7), ≥50, 129 (48.3) | 149/118   | 4 (1.5)   | 0 (0.0)             | 50 (18.7), 4 (1.5) |
| 18  | China   | Chengfeng Qiu       | 2020 | 104    | <60, 90 (86.5), ≥60, 14 (13.5) | 49/55     | 2 (1.9)   | NA                  | 16 (15.4), 1 (1.0) |
| 19  | China   | Yang Tao            | 2020 | 167    | <60, 140 (83.8), ≥60, 27 (16.2) | NA        | 0         | NA                  | 22 (13.2), NA |

Continued
| ID  | Country | Study author(s) | Year | SS (N) | Age in years n (%) | AKI n (%) | CRRT n (%) | Severe disease n (%) | Deaths n (%) |
|-----|---------|----------------|------|--------|-------------------|-----------|------------|---------------------|--------------|
| 20  | China   | Zonghao Zhao   | 2020 | 75     | <60, 62 (82.7) >60, 13 (17.3) | 42/33 15 (20.0) | NA | NA | NA |
| 21  | China   | Yang Xu        | 2020 | 69     | <60, 42 (60.9) >60, 27 (39.1) | 35/34 0 (0) | NA | 25 (36.2) | 1 (1.4) |
| 22  | China   | Guang Chen     | 2020 | 21     | <50, 6 (28.6) >50, 15 (71.4) | 17/4 1 (4.8) | NA | 11 (52.4) | NA |
| 23  | China   | Yonghao Xu     | 2020 | 45     | NA | 29/16 7 (15.6) | 4 (8.9) | 25 (55.6) | NA |
| 24  | China   | Xiaofan Lu     | 2020 | 244    | NA | 128/116 51 (20.9) | NA | 87 (35.7) | NA |
| 25  | China   | Zhen Li        | 2020 | 193    | NA | 95/98 55 (28.5) | 7 (3.6) | 65 (33.7) | 32 (16.6) |
| 26  | China   | Yi Zheng       | 2020 | 34     | NA | 23/11 7 (20.6) | 5 (14.7) | 15 (44.1) | 0 |
| 27  | China   | Ao-Xiang Guo   | 2020 | 159    | <60, 26 (16.4) >60, 133 (83.6) | 99/60 9 (5.3) | NA | NA | 121 (76.1) |
| 28  | China   | Xiufeng Jiang  | 2020 | 55     | NA | 27/28 3 (5.5) | NA | 8 (14.5) | NA |
| 29  | China   | Ling Hu        | 2020 | 323    | <65, 212 (65.6) >65, 111 (34.4) | 166/157 17 (5.3) | 72 (22.3) | 146 (45.2) | 26 (8.0) |
| 30  | China   | Guanhua Xiao   | 2020 | 287    | NA | 160/127 55 (19.2) | NA | 124 (43.2) | 19 (6.6) |
| 31  | China   | Xuelian Liao   | 2020 | 81     | <65, 58 (71.6) >65, 23 (28.4) | 51/30 6 (7.4) | 5 (6.2) | NA | NA |
| 32  | China   | Yan Zhang      | 2020 | 258    | NA | 135/123 7 (2.7) | NA | NA | 15 (5.8) |
| 33  | China   | Xiaobo Yang    | 2020 | 52     | <60, 25 (48.1) >60, 27 (51.9) | 35/17 15 (28.8) | 9 (17.3) | NA | 20 (38.5) |
| 34  | China   | Chaolin Huang  | 2020 | 41     | NA | 30/11 3 (7.3) | 3 (7.3) | NA | 6 (14.6) |
| 35  | China   | Dawei Wang     | 2020 | 138    | NA | 75/63 5 (3.6) | 2 (1.4) | NA | NA |
| 36  | China   | Yingxia Liu    | 2020 | 12     | <60, 5 (41.7) >60, 7 (58.3) | 8/4 2 (16.7) | NA | NA | NA |
| 37  | China   | Xiao Wei Xu    | 2020 | 63     | <65, 60 (96.8) >65, 2 (3.2) | 36/27 3 (4.5) | NA | NA | NA |
| 38  | China   | Nanshan Chen   | 2020 | 99     | <60, 62 (62.6) >60, 37 (37.4) | 67/32 9 (9.1) | 9 (9.1) | NA | 11 (11.0) |
| 39  | China   | Xu S           | 2020 | 355    | NA | 193/162 56 (15.8) | NA | 32 (24.2) | 32 (24.2) |
| 40  | China   | Tie Long Chen  | 2020 | 203    | NA | 108/95 22 (12.3) | NA | NA | 19 (9.4) |
| 41  | China   | Tao Chen       | 2020 | 274    | <60, 121 (44.2) >60, 153 (55.8) | 171/103 29 (10.5) | 3 (1.1) | NA | 113 (41.2) |
| 42  | China   | Yichun Cheng   | 2020 | 701    | NA | 367/334 36 (5.1) | NA | NA | 113 (16.1) |
| 43  | China   | Yan Deng       | 2020 | 225    | NA | 124/101 20 (8.9) | NA | 95 (42.2) | 109 (48.4) |

Table 2 Continued
| ID  | Country | Study author(s) | Year | SS (N) | Age in years n (%) | AKI n (%) | CRRT n (%) | Severe disease n (%) | Deaths n (%) |
|-----|---------|-----------------|------|--------|-------------------|-----------|------------|---------------------|-------------|
| 44  | China   | Shaoqing Lei    | 2020 | 34     | <60, 71 (66.4) ≥60, 36 (33.6) | 14/20     | 2 (5.9)    | 1 (2.9)             | 15 (44.1)   | 7 (20.6) |
| 45  | China   | Xun Li          | 2020 | 25     | NA                 | NA        | NA         | 12 (48.0)           | NA          | 25 (100.0) |
| 46  | China   | Tao Chen        | 2020 | 54     | NA                 | 34/20     | 29 (53.7)  | NA                  | 54 (100)    | NA      |
| 47  | China   | Pei G           | 2020 | 333    | NA                 | 182/151   | 22 (6.6)   | NA                  | 189 (56.8)  | 29 (8.7) |
| 48  | China   | Shaobo Shi      | 2020 | 416    | NA                 | 205/211   | 8 (1.9)    | 2 (0.5)             | NA          | 57 (13.7) |
| 49  | China   | Su H            | 2020 | 26     | NA                 | 7/19      | 9 (34.6)   | 5 (19.2)            | NA          | 26 (100.0) |
| 50  | China   | Wang D          | 2020 | 107    | <60, 20 (18.9) ≥60, 86 (81.1) | 57/50     | 14 (13.1)  | NA                  | NA          | 19 (17.8) |
| 51  | China   | Yang R          | 2020 | 212    | <65, 150 (70.8) ≥65, 62 (29.2) | 107/105   | 28 (13.2)  | NA                  | NA          | 25 (11.8) |
| 52  | China   | Zhang X         | 2020 | 645    | NA                 | 328/317   | 2 (0.3)    | 0 (0.0)             | 64 (9.9)    | NA      |
| 53  | China   | Xiaoobo Feng    | 2020 | 114    | <65, 52 (45.6) ≥65, 62 (54.4) | 71/43     | 35 (30.7)  | 2 (1.8)             | NA          | 9 (7.9)  |
| 54  | China   | Rong Yin        | 2020 | 106    | <65, 20 (18.9) ≥65, 86 (81.1) | 64/42     | 7 (6.6)    | 3 (2.8)             | 59 (55.7)   | 8 (7.5)  |
| 55  | China   | Puyu Shi        | 2020 | 134    | <65, 114 (85.1) ≥65, 20 (14.9) | 65/69     | 3 (2.2)    | 1 (0.7)             | 46 (34.3)   | 1 (0.7)  |
| 56  | China   | Xiaolong Qi     | 2020 | 21     | NA                 | 11/10     | 1 (4.8)    | 2 (9.5)             | NA          | 5 (23.8) |
| 57  | China   | Jie Chen        | 2020 | 1087   | NA                 | 452/635   | 104 (9.5)  | NA                  | NA          | 20 (1.8) |
| 58  | China   | Jianguo Zhang   | 2020 | 135    | NA                 | 67/68     | 11 (8.1)   | NA                  | 30 (22.2)   | 12 (8.9) |
| 59  | China   | Jia Huang       | 2020 | 414    | <55, 268 (64.7) ≥55, 146 (35.3) | 167/247   | 6 (1.4)    | 5 (1.2)             | 92 (22.2)   | 3 (0.7)  |
| 60  | Spain   | Alberto M Borobio| 2020| 2226   | NA                 | 1074/1152 | 173 (7.7)  | NA                  | 75 (3.3)    | 460 (20.7) |
| 61  | USA     | Lili Chan       | 2020 | 3235   | NA                 | 1868/1367 | 1406 (43.5) | 280 (8.7)           | NA          | 638 (19.7) |
| 62  | France  | Sébastien Rubin| 2020 | 71     | NA                 | 55/16     | 57 (80.3)  | 6 (8.5)             | 71 (100.0)  | 4 (5.6)  |
| 63  | Kuwait  | Sulaiman Almazeeed| 2020| 1096   | <65, 1016 (92.7) ≥65, 80 (7.3) | 888/208   | 14 (1.3)   | 5 (0.5)             | 19 (1.7)    | 19 (1.7) |
| 64  | USA     | Sachin J Shah   | 2020 | 26     | NA                 | NA        | 10 (38.5)  | 1 (3.8)             | NA          | 1 (3.8)  |
| 65  | USA     | Ahmad Khan      | 2020 | 6056   | <65, 1617 (26.7) ≥65, 4439 (73.3) | 2383/3671 | 528 (8.7)  | 71 (11.7)           | 598 (9.9)   | 367 (9.9) |
| 66  | Mexico  | Rahul Shekhar   | 2020 | 50     | NA                 | NA        | 13 (26.0)  | 12 (24.0)           | 13 (26.0)   | 10 (20.0) |
| 67  | England | Simon Brill     | 2020 | 450    | <60, 137 (30.4) ≥60, 313 (69.6) | 272/178   | 85 (18.9)  | NA                  | 56 (12.4)   | 173 (38.4) |
| 68  | Germany | Gagiannnis D    | 2020 | 22     | NA                 | 12/10     | 3 (13.6)   | NA                  | 11 (50.0)   | 4 (18.2) |

Continued
alter the results or the heterogeneity for every factor (online supplemental figure S1–5).

Two experienced physician reviewers performed independent and blinded data abstraction on outcome measures using a standardised approach. The reviewers conducted quality ratings based on the Cochrane risk-of-bias criteria for each study. Figure 1 shows the flow chart for the selection of studies. The selected articles and summaries of their findings were submitted to a professionally trained researcher, En Liu, for review.

Data extraction and data analyses
Retrospective analyses, cross-sectional studies and case reports related to confirmed COVID-19 cases were included, and patients’ demographic data, clinical characteristics, comorbidities and epidemiological findings were collected. We excluded articles lacking full text, a clear diagnosis or incidence of AKI, as well as articles that did not meet the requirements (ie, reviews, meta-analyses, guideline recommendations, comments and basic research). The summary data, including authors’ names, year of publication, and the age, sex, clinical characteristics and epidemiological findings of included patients, are recorded in the form of tables and figures.

MATLAB_R2016 software was used for meta-analysis. The effects from count data were presented as ORs and their 95% CIs. The Q test was used (the default test level was set at \( \alpha=0.1 \)) to determine the size of heterogeneity. If Q test results were \( p>0.1 \), there was no heterogeneity between studies and a fixed-effects model was used for meta-analysis. If Q test results were \( p<0.1 \), there was heterogeneity between studies, and a random-effects model was used for meta-analysis. The test level of the combined effect of meta-analysis was \( \alpha=0.05 \).

Definition and interpretation
The disease type, or stage of COVID-19 disease severity, was determined according to the Guidelines for Diagnosis and Treatment of COVID-19 published by NHC China on 18 February 2020 (6th edition). A severe case was defined as having either: (1) a respiratory rate >30/min, (2) an oxygen saturation \( \leq 93\% \) or (3) an arterial oxygen pressure/fractional inspired oxygen ratio \( \leq 300 \) mm Hg. Lung imaging showed that the lesions progressed more than 50% within 24–48 hours.

Patient and public involvement
Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS
As of 15 May 2020, 79 studies on COVID-19-related AKI from around the world were selected, including 62 studies from Asia, 9 studies from Europe and 7 studies

| ID | Country | Study author(s) | Year | SS (N) | Age in years n (%) | AKI n (%) | CRRT n (%) | Severe disease n (%) | Deaths n (%) |
|----|---------|----------------|------|--------|-------------------|-----------|------------|---------------------|-------------|
| 69 | Spain   | Adrián Sánchez-Montalvá | 2020 | 82 NA  | 52/30 | 9 (10.0) | 0 (0) | 14 (17.1) | 22 (26.8) |
| 70 | USA     | Raef Fadel      | 2020 | 213 NA | 109/114 | 101 (47.4) | NA | 26 (12.2) | 39 (18.3) |
| 71 | Switzerland | Jean Regina | 2020 | 200 <65, 86 (43.0) | 65, 114 (57.0) | 120/80 | 30 (15.0) | NA | 36 (18.0) | 25 (12.5) |
| 72 | USA     | Leonidas Palaiodimos | 2020 | 200 <65, 104 (52.0) | 65, 96 (48.0) | 98/102 | 70 (3.50) | 16 (8.0) | 32 (16.0) | 48 (24.0) |
| 73 | Iran    | Ghasem Janbabaei | 2020 | 18754 <60, 7104 (37.9) | ≥60, 11650 (62.1) | NA | 300 (16.0) | 131 (0.7) | 1444 (7.7) | 2738 (14.6) |
| 74 | Global  | Rand Alattar | 2020 | 25 NA  | 23/2 | 2 (8.0) | NA | 21 (84.0) | 3 (12.0) |
| 75 | Italy   | Spinello Antinori | 2020 | 35 NA  | 26/9 | 8 (22.9) | NA | 18 (51.4) | 4 (11.4) |
| 76 | Germany | E M Junga      | 2020 | 5 NA   | 5/0 | 5 (100.0) | 3 (60.0) | 5 (100.0) | NA |
| 77 | Hong Kong, China | Lowell Ling | 2020 | 8 NA  | 4/4 | 2 (25.0) | 2 (25.0) | 8 (100.0) | 1 (12.5) |
| 78 | Portugal | Madanelo M     | 2020 | 122 NA | NA | 4 (3.3) | NA | NA | NA |
| 79 | USA     | Safiya Richardson | 2020 | 5700 NA | 3437/2263 | 1370 (24.0) | 225 (3.9) | 1281 (22.5) | 553 (9.7) |

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; NA, not available.
Table 3 Summary of clinical characteristics of patients with COVID-19

| Variable                | All patients (n=49692) |
|-------------------------|------------------------|
| Sex                     |                        |
| Male                    | 30555                  |
| Female                  | 16071 (52.6%)          |
| Age                     |                        |
| <50 years               | 144 (50.0%)            |
| ≥50 years               | 144 (50.0%)            |
| 55 years as the cut-off | 414                    |
| <55 years               | 268 (64.7%)            |
| ≥55 years               | 146 (35.3%)            |
| 60 years as the cut-off | 21340                  |
| <60 years               | 8384 (39.3%)           |
| ≥60 years               | 12966 (60.7%)          |
| 65 years as the cut-off | 9050                   |
| <65 years               | 3838 (42.4%)           |
| ≥65 years               | 5212 (57.6%)           |
| Country                 |                        |
| China                   | 49692                  |
| Non-China               | 38568 (77.6%)          |
| Disease type            |                        |
| Non-severe              | 35794 (86.4%)          |
| Severe                  | 5623 (14.6%)           |
| Death                   | 6259/47 078 (13.3%)    |

Analysis of risk factors for COVID-19 in conjunction with AKI

Eight studies investigated the risk factors for AKI in COVID-19, and no heterogeneity was found among the studies. The use of a fixed-effects model to combine the data showed that age ≥60 years old and having severe infection were independent risk factors for AKI during COVID-19 infection, with ORs of 3.53 (95% CI (2.92–4.25), p<0.001) and 6.07 (95% CI (2.53–14.58), p<0.001), respectively. The use of a random-effects model to combine the studies showed no correlation between male sex and incidence of AKI in patients with COVID-19, with an OR of 1.36 (95% CI (0.84–2.20), p=0.21). However, the probability of AKI complications in male patients with COVID-19, of which 14.6% (5623/41 417) were severe cases. Among all 49692 patients with COVID-19 included in this meta-analysis, the overall incidence of AKI was 10.6% (5249/49 692). The incidences of AKI in non-severe, severe and deceased cases of COVID-19 were 5.4% (94/1732), 22.1% (177/802) and 22.1% (1403/6357), respectively. Additionally, 2.4% (940/39 561) of patients received continuous renal replacement therapy (CRRT).

Comparison of demographic and clinical characteristics of patients with COVID-19 between different regions

This study included 11124 patients with COVID-19 described in 60 articles from China and 38568 patients with COVID-19 described in 20 articles from outside China. Table 4 shows the demographic and clinical characteristics of all included patients. The group of patients with COVID-19 from outside China had significantly higher proportions of patients aged ≥60 (62.3% vs 46.5%, p<0.05) and 65 years (62.6% vs 32.3%, p<0.05), and the proportion of those who died was higher than that of the Chinese patients (13.5% vs 12.4%, p<0.05). The incidences of AKI in all patients with COVID-19 and in those with severe COVID-19 were significantly higher outside of China than in China (10.9% vs 9.5%, 41.5% vs 20.4%, respectively, p<0.05). No significant difference was found in the incidence of AKI in patients with mild COVID-19 infection. The incidence of AKI in patients who died from COVID-19 and the rate of CRRT in China were significantly higher than those outside China (35.7% vs 20.7% and 4.4% vs 2.1%, respectively, p<0.05).

This study included 30974 Asian patients with COVID-19 from 62 articles; 3213 European patients with COVID-19 from 9 articles; and 15480 North American patients with COVID-19 from 7 articles. Table 5 shows the demographic and clinical characteristics of patients with COVID-19 among different regions. No difference in sex was found among all patients. The population of patients with COVID-19 from North America had significantly higher proportions of patients aged ≥65 years and a higher incidence of AKI (p<0.05) than the Asian patient population. European patients with COVID-19 in Europe had a significantly higher rate of both CRRT and mortality than patients with COVID-19 from the other regions.

from North America. Table 2 shows the demographic and clinical characteristics of these 79 COVID-19 studies.

Demographic and clinical characteristics

Table 3 shows the demographic and clinical characteristics of 49692 patients with COVID-19. Among these patients, 52.6% were men, with a 1.11:1 male-to-female ratio. A total of 414 cases were regrouped using the age of 55 years as a cut-off, with 146 (35.3%) of these cases involving patients ≥55 years old. A total of 21340 cases were regrouped using the age of 60 years as a cut-off, with 12966 (60.7%) of these cases involving patients ≥60 years old and having severe infection were independent risk factors for AKI during COVID-19 infection, with ORs of 3.53 (95% CI (2.92–4.25), p<0.001) and 6.07 (95% CI (2.53–14.58), p<0.001), respectively. The use of a random-effects model to combine the studies showed no correlation between male sex and incidence of AKI in patients with COVID-19, with an OR of 1.36 (95% CI (0.84–2.20), p=0.21). However, the probability of AKI complications in male patients with COVID-19, of which 14.6% (5623/41 417) were severe cases. Among all 49692 patients with COVID-19 included in this meta-analysis, the overall incidence of AKI was 10.6% (5249/49 692). The incidences of AKI in non-severe, severe and deceased cases of COVID-19 were 5.4% (94/1732), 22.1% (177/802) and 22.1% (1403/6357), respectively. Additionally, 2.4% (940/39 561) of patients received continuous renal replacement therapy (CRRT).
### Table 4  Comparison of clinical characteristics between Chinese and non-Chinese patients with COVID-19

| Variable                  | Patients from China (n=11124) | Patients from non-Chinese countries (n=38568) | $X^2$ | P value |
|---------------------------|-------------------------------|-----------------------------------------------|-------|---------|
| Sex                       |                               |                                               |       |         |
| Male                      | 5649                          | 10422                                         | 5.790 | 0.016   |
| Female                    | 5283                          | 9202                                          |       |         |
| Age                       |                               |                                               |       |         |
| 50 years as the cut-off   | 288                           | NA                                            |       |         |
| <50 years                 | 144                           | NA                                            |       |         |
| ≥50 years                 | 144                           | NA                                            |       |         |
| 60 years as the cut-off   | 2136                          | 19204                                         |       | <0.001  |
| <60 years                 | 1143                          | 11963                                         | 201.320 | <0.001 |
| ≥60 years                 | 993                           | 11963                                         |       |         |
| 65 years as the cut-off   | 1499                          | 8752                                          |       | <0.001  |
| <65 years                 | 1015                          | 2823                                          | 471.130 | <0.001 |
| ≥65 years                 | 484                           | 4729                                          |       | <0.001  |
| Death                     | 1056/8527                     | 5108/38 441                                   | 5.000 | 0.025   |

| Acute kidney injury       |                               |                                               |       |         |
| Incidence                 | 1052/11 124                   | 4188/38 568                                   | 17.980 | <0.001 |
| Non-severe                | 80/1540                       | 14/192                                        | 1.460 | 0.227   |
| Severe                    | 150/737                       | 27/65                                         | 15.590 | <0.001 |
| Death                     | 206/577                       | 1197/5780                                     | 68.560 | <0.001  |
| CRRT                      | 190/4286                      | 750/35 275                                    | 87.680 | <0.001  |

CRRT, continuous renal replacement therapy; NA, not available.

### Table 5  Comparison of clinical characteristics among different regions

| Variable                  | Asia (n=30974) | Europe (n=3213) | North America (n=15480) | P value |
|---------------------------|---------------|-----------------|--------------------------|---------|
| Sex                       | 11998         | 3091            | 15437                    | 0.148   |
| Male                      | 6507          | 1616            | 7918                     |         |
| Female                    | 5491          | 1475            | 7519                     |         |
| Age                       |               |                 |                          |         |
| 60 years as the cut-off   | 20900         | 489             | NA                       | <0.001  |
| <60 years                 | 8247          | 137             | NA                       |         |
| ≥60 years                 | 12653         | 313             | NA                       |         |
| 65 years as the cut-off   | 2676          | 200             | 7347                     |         |
| <65 years                 | 2047          | 86              | 1721                     | <0.001  |
| ≥65 years                 | 629           | 114             | 4534                     |         |
| Death                     | 4392/28 624 (15.3%) | 692/3086 (22.4%) | 1656/15 480 (10.6%) | <0.001  |
| Acute kidney injury       |               |                 |                          |         |
| Incidence                 | 1323/30 974 (4.3%) | 374/3213 (11.6%) | 3498/15 480 (22.6%) | <0.001  |
| Non-severe                | 84/1572 (5.3%) | 8/146 (5.5%)    | 2/14 (14.0%)             | 0.338   |
| Severe                    | 154/745 (20.7%) | 13/26 (50.0%)  | 10/31 (32.3%)            | <0.001  |
| Death                     | 226/678 (33.3%) | 97/330 (29.4%)  | 395/5349 (7.4%)         | <0.001  |
| CRRT                      | 326/24 136 (1.4%) | 9/158 (5.7%)    | 605/15 276 (4.0%)       | <0.001  |

CRRT, continuous renal replacement therapy; NA, not available.
COVID-19 was higher than that in female patients with COVID-19 (figure 2).

Incidence of need for CRRT during COVID-19 infection
Thirty-eight studies reported the administration of CRRT to 39,561 patients, but there was no statistical

heterogeneity among these studies (p>0.1). Nine studies reported administration of CRRT to 6,795 patients. The rate of CRRT in severe COVID-19 cases was significantly higher than the rate in non-severe COVID-19 cases, with an OR of 6.07 (95% CI (2.83–15.39)) (figure 3). Only one

Figure 2 Forest plot showing the subgroup analysis of AKI risk factors. (A) The Q test showed p>0.1, indicating no heterogeneity existed between studies. The fixed-effects model was used to combine the data, with an OR of 3.53 (95% CI (2.92–4.25), p<0.001), suggesting that age was a risk factor for AKI; the older the patient, the higher the risk of AKI. (B) The Q test showed p>0.1, indicating heterogeneity existed between studies. The random-effects model was used to combine the data, with an OR of 3.53 (95% CI (2.92–4.25), p<0.001), suggesting that age was a risk factor for AKI; the older the patient, the higher the risk of AKI. (C) The Q test showed p>0.1, indicating no heterogeneity existed between studies. The fixed-effects model was used to combine the data, with an OR of 6.07 (95% CI (2.83–15.39), p<0.001), suggesting that age was a risk factor for AKI; the older the patient, the higher the risk of AKI.

Figure 3 Forest plot showing the subgroup analysis of patients requiring CRRT during COVID-19 infection. The Q test showed p>0.1, indicating no heterogeneity existed between studies. The fixed-effects model was used to combine the data, with an OR of 6.07 (95% CI (2.83–15.39), p<0.001), suggesting that age was a risk factor for AKI; the older the patient, the higher the risk of AKI.
study analysed the effect of receiving CRRT on in-hospital mortality, but there was no statistical heterogeneity.

**Prognostic analysis of COVID-19 combined with AKI**

A total of five studies investigated the risk of death in patients with COVID-19 after development of AKI. The Q test showed $p>0.1$, indicating no heterogeneity between studies. The fixed-effects model was used to combine the data, with an OR of 11.05 (95% CI (9.13–13.36), $p<0.001$), suggesting that AKI incidence was a risk factor for death. The risk of death in patients with COVID-19 complicated by AKI was higher than that in patients with COVID-19 not complicated by AKI, COVID-19, acute kidney injury.

**DISCUSSION**

The retrospective analysis of our system showed that the incidence of kidney injury in patients with COVID-19 was 10.6%, which was higher than the incidence of AKI (8%) in hospitalised patients without COVID-19.18 Currently, the mechanism of kidney injury in patients with COVID-19 is believed to involve SARS-CoV-2 directly attacking intrinsic renal cells. SARS-CoV-2 is a cytopathic virus that passes through the membrane protein ACE2 to enter host cells.19 High ACE2 expression in proximal tubular epithelial cells may be a potential target for kidney injury. Cellular transmembrane serine proteases (TMPRSSs) act as co-receptors and activate the spike protein on the SARS-CoV-2 viral surface, enabling membrane fusion into host cells. Single-cell RNA sequencing analysis of kidney cells has revealed that ACE2 is expressed along with TMPRSSs in proximal straight tubule cells and podocytes, indicating that the kidney cells are exposed to SARS-CoV-2 infection.19 One study has shown that the main pathological changes in the kidneys of patients with COVID-19 are swelling, vacuolar degeneration, shedding of renal tubular epithelial cells, and showing visible protein casts and pigmented casts in the lumen.19 In addition, SARS-CoV-2 inclusion bodies have been found in renal tubular epithelial cells.19 These findings suggest that SARS-CoV-2 may directly attack renal tubular epithelial cells and cause AKI. In addition, SARS-CoV-2 can directly infect glomerular endothelia, podocytes and renal tubules, causing acute tubular injury, and occasionally collapsing focal segmental glomerulosclerosis in the kidney tissue. Renal biopsies of patients with COVID-19 have revealed global collapse of the glomerular capillary loops, accompanied by hyperplasia of overlying glomerular epithelial cells, many of which contain abundant eosinophilic intracytoplasmic protein droplets. Collapsing glomerulosclerosis (CG) is increasingly reported in African American patients with COVID-19 infection. It is possible that CG following COVID-19 infection in this population may be linked to underlying APOL1 kidney risk alleles, which are not uncommon in this ethnic group. This lesion should be considered in the differential diagnosis of rapidly declining renal function in association with heavy proteinuria in patients with COVID-19 disease, especially in patients of African ancestry.19–21

High-load SARS-CoV-2 infection induces cytokine storm, in which various inflammatory mediators are released, such as interleukin (IL)-6, IL-1β, tumour necrosis factor-alpha, inducible protein-10, monocyte chemotactic protein 1, granulocyte-colony stimulating factor and macrophage inflammatory protein-1α, leading to ischaemia, hypoxia, fibrosis and kidney injury.22–24 Furthermore, COVID-19 that is accompanied by high fever, shock, dehydration and hypoxemia, and treated with non-steroidal anti-inflammatory drugs, antiviral drugs, antibiotics and other potentially nephrotoxic drugs, may cause AKI. In addition, advanced age, diabetes and hypertension also induce or aggravate the incidence and progression of AKI.25

To our knowledge, this study presents the first systematic analysis of the risk factors of COVID-19 that lead to AKI. A recent report suggested that the incidence of AKI in patients with severe COVID-19 was significantly higher than in patients with non-severe COVID-19, with an OR of 11.02,26 which was consistent with our conclusion. In addition, our study showed that advanced age was an independent risk factor for AKI, with an OR of 3.53. After SARS-CoV-2 infected elderly patients, the morbidity and mortality rates increased significantly, possibly implicating that the weakened immune system function of elderly patients and the ageing of tissues lead to greater susceptibility to viral replication.27,28 Another study found that advanced age was an independent risk factor for AKI in hospitalised patients without COVID-19.29 The viral clearance ability of male patients with SARS-CoV-2

**Figure 4 Forest plot showing the subgroup analysis of risk of death.** The Q test showed $p>0.1$, indicating no heterogeneity existed between studies. The fixed-effects model was used to combine the data, with an OR of 11.05 (95% CI (9.13–13.36), $p<0.001$), suggesting that AKI incidence was a risk factor for death. The risk of death in patients with COVID-19 complicated by AKI was higher than that in patients with COVID-19 not complicated by AKI, COVID-19, acute kidney injury.
infection is significantly lower than that of female patients with SARS-CoV-2 infection, which may represent one potential reason for the increased severity of symptoms and incidence of complications observed in male patients with SARS-CoV-2 infection.\textsuperscript{30} Higher rates of smoking and alcohol consumption, as well as biological differences in the immune system between the sexes, could make men more vulnerable to AKI during SARS-CoV-2 infection.

The role of androgen-responsive elements (AREs) of the TMPRSS type II (TMPRSS2) gene has been underappreciated as one of the major players of male dominance in the severe COVID-19 category. AREs of the TMPRSS2 gene are responsible for higher expression of the TMPRSS2 enzyme on the epithelial cell membranes of the respiratory system, which facilitates the non-endosomal entry of SARS-CoV-2 into the lung tissue.\textsuperscript{31}

Our study found that the incidence of CRRT in patients with severe COVID-19 was significantly greater than that in patients with non-severe COVID-19. A recent report using increased SCr and urea nitrogen as the diagnostic standard for AKI had results consistent with our conclusion.\textsuperscript{32} Unfortunately, only one study used in this meta-analysis reported the relationship between CRRT and in-hospital death in patients with COVID-19 in China; therefore, strong evidence for COVID-19 treatment in these patients is lacking.

Also, this study was the first meta-analysis to assess the in-hospital mortality in patients with both COVID-19 and AKI. Our results showed that the mortality rate of patients with COVID-19 and AKI was 22.1%, and the risk of death in patients with COVID-19 and AKI was 11.05 times that of patients with COVID-19 not complicated by AKI. In hospitalised patients without COVID-19, the mortality rate of AKI was 1.0%–14.4%, and the mortality rate of severely ill patients in the intensive care unit with AKI as a complication was 21.8%,\textsuperscript{33} both of which were lower than the mortality rate of patients with COVID-19 in conjunction with AKI, suggesting that patients with both COVID-19 and AKI had a higher risk of death than patients with COVID-19 who did not have AKI.

In brief, this systematic analysis suggests that patients with COVID-19 were at risk for kidney injury, which was closely related to age, sex and disease type. Patients with COVID-19 in conjunction with AKI had a high risk of death. Thus, it is necessary to prevent the controllable factors related to AKI through diagnostic and treatment strategies. This includes providing full volume support, alleviation of hypoxemia and avoidance of nephrotoxic drug administration in patients with COVID-19 who are elderly and men, or in those who have severe COVID-19. In addition, early serum and urine tests to assess kidney function and early detection and treatment of AKI have been conducive to reducing the occurrence of AKI in patients with COVID-19 and to improving treatment success rates.

This study had several limitations related to the inclusion of patients with AKI who had been diagnosed according to the Kidney Disease Improving Global Outcomes guidelines in our analysis of AKI incidence. First, the baseline creatinine level was unknown in some patients, which may have led to missed AKI diagnoses. In some studies, the absolute level of increased SCr in patients as a standard for kidney injury may have overestimated the incidence of AKI.\textsuperscript{34} Second, due to the limitation of examining only objective conditions, the long-term prognosis of SARS-CoV-2 infection, which might directly attack the kidneys and cause AKI in patients with COVID-19, is not clear. This topic must be investigated further.
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