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Association of acute kidney injury with the severity and mortality of SARS-CoV-2 infection: A meta-analysis

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ABSTRACT

Background: we aimed to explore the relationship of acute kidney injury (AKI) with the severity and mortality of coronavirus disease 2019 (COVID-19).

Methods: A systematic literature search was conducted in PubMed, EMBASE, Scopus, Web of Science, MedRxiv Database. We compared the laboratory indicators of renal impairment and incidences of AKI in the severe versus non-severe cases, and survival versus non-survival cases, respectively.

Results: In 41 studies with 10,335 COVID-19 patients, the serum creatinine (sCr) in severe cases was much higher than that in non-severe cases (SMD = 0.34, 95% CI: 0.29–0.39), with a similar trend for blood urea nitrogen (BUN) (SMD = 0.66, 95%CI: 0.51–0.81), hematocrit (OR = 1.59, 95% CI: 1.15–2.19), and proteinuria (OR = 2.92, 95% CI: 1.58–5.38). The estimated glomerular filtration rate decreased significantly in severe cases compared with non-severe cases (SMD = -0.45, 95% CI: −0.67—−0.23). Moreover, the pooled OR of continuous renal replacement therapy (CRRT) and AKI prevalence for severe vs. non-severe cases was 12.99 (95%CI: 4.03–41.89) and 13.16 (95%CI: 10.16–17.05), respectively. Additionally, 11 studies with 3759 COVID-19 patients were included for analysis of disease mortality. The results showed the levels of sCr and BUN in non-survival cases remarkably elevated compared with survival patients, respectively (SMD = 0.97, SMD = 1.49). The pooled OR of CRRT and AKI prevalence for non-survival vs. survival cases was 31.51 (95%CI: 6.55–151.59) and 77.48 (95% CI: 24.52–244.85), respectively.

Conclusions: AKI is closely related with severity and mortality of COVID-19, which gives awareness for doctors to pay more attention for risk screening, early identification and timely treatment of AKI.

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1. Introduction

Coronavirus disease 2019 (COVID-19), a newly emerging acute respiratory disease, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and causes substantial morbidity and mortality [1]. As of 12 June 2020, 7,519,566 COVID-19 cases have been confirmed and 419,447 people died from COVID-19 in more than 200 countries around the world. Most patients with COVID-19 are considered as non-severe patients and recover from this infection. However, the symptoms in about 10% of COVID-19 patients are severe and progress rapidly to critical conditions, including organ dysfunctions, such as acute respiratory distress syndrome (ARDS), acute cardiac injury, acute kidney injury (AKI) and even death [2].

Recently, several clinical studies have demonstrated that AKI was one of the most common complications in patients with SARS-CoV-2 infection. For example, in one retrospective study of 193 patients from Wuhan in China, Li et al. reported that proteinuria, hematocrit, and elevated levels of blood urea nitrogen (BUN), as well as serum creatinine (sCr) were significantly associated with the death of COVID-19 patients [3]. In addition, an analysis of 355 inpatients in Wuhan showed that prevalence of AKI was 15.8% in admitted patients and 33.9% COVID-19 patients with AKI were died on mean 10.9 day after hospitalization [4]. However, the study of 116 hospitalized COVID-19 patients in Wuhan demonstrated that SARS-CoV-2 infection did not result in AKI [5]. A meta-analysis with large clinical samples is warranted to draw a
reliable conclusion. Therefore, we performed the present meta-analysis to investigate the association of AKI with the severity and mortality of SARS-CoV-2 infection.

2. Methods

The systematic review and meta-analysis were performed according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and reported based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [6,7]. This meta-analysis has no protocol.

2.1. Search strategy

Articles published from December 2019 to 8 June 2020 in Pubmed, EMBASE, Web of Science, Scopes, and MedRxiv Database were searched. To identify all the articles displaying the renal impairment in COVID-19, we used the following terms alone or in combination for literature search: “SARS-CoV-2”, “COVID-19”, “2019-nCoV”, “nCoV”, “COVID-19”, “coronavirus”, “severe acute respiratory syndrome coronavirus 2”, “renal”, “kidney”, “acute kidney”, “urology”, “urogential system”, “urea”, “urinalysis”, “creatinine”, “proteinuria”, “hematuria”, “blood urea nitrogen” and “serum creatinine”.

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) subjects: adult inpatients diagnosed with COVID-19 according to the guidelines for the diagnosis and treatment of novel coronavirus disease; (2) clinical features: definite disease severity or mortality according to the guidelines for the diagnosis and treatment of novel coronavirus disease; (3) outcomes: COVID-19 patients with exact values of renal impairment indicators including BUN, sCr or estimated glomerular filtration rate (eGFR), and the incidences of hematuria, proteinuria, continuous renal replacement therapy (CRRT) and AKI.

Exclusion criteria included: (1) studies with special populations, such as children, elderly, pregnant women, transplant recipients and cancer patients; (2) case reports, reviews, letters, meta-analysis, guidelines, editorials and comments; (3) studies without the data of renal impairment indicators (e.g., BUN, sCr or eGFR) or incidence of hematuria, proteinuria, CRRT and AKI for comparison between severe versus non-severe cases or survival versus non-survival cases; (4) sample size less than 20 patients. The flow chart of the study selection was drafted in accordance to the PRISMA principle.

2.3. Definitions

The degrees of COVID-19 severity were evaluated according to the guidelines for the diagnosis and treatment of novel coronavirus disease. The clinical subgroups of disease severity were described as follows: (1) non-severe group: the clinical symptoms were mild, and there was no or mild imaging signs of pneumonia [8]; (2) severe group (any of the following conditions): I, shortness of breath with respiratory rate ≥ 30 bpm; II, finger SpO\textsubscript{2} ≤ 93% at rest; III, ARDS or arterial partial pressure of oxygen/fraction of inspired oxygen ≤ 300 mmHg; IV, respiratory failure (requiring mechanical ventilation); V, shock; VI, other organ failure (requiring ICU monitoring and treatment) [9].

Fig. 1. Flowchart of study selection.
2.4. Data extraction and quality assessment

Two investigators worked independently to decide which studies should be included, and the disagreement was resolved by a third investigator. Data was extracted from selected studies including the first author’s name, publication data, sex, average age, numbers of patients and study type. In addition, laboratory examinations of renal impairments including BUN, sCr, eGFR, proteinuria and hematuria, and incidence of AKI and CRRT were also extracted. The data shown as median and interquartile range was transformed into mean and standard deviation (SD) according to the formula below (http://www.math.hkbu.edu.hk/tongt/papers/median2mean.html). The prevalence of proteinuria, hematuria, CRRT and AKI as well as average means of BUN, sCr and eGFR were evaluated between severe and non-severe group or survival and non-survival group, respectively.

The quality of studies was evaluated according to the Newcastle-Ottawa scale (NOS) containing three aspects (selection, comparability and outcomes). Scores ranging from 0 to 9, and studies with the score ≥6 were considered as high quality studies.

2.5. Statistical analysis

All data was analyzed by the Review Manager meta-analysis software (version 5.4). The standardized mean differences (SMDs) and 95% confidence intervals (CIs) were calculated for continuous data. The odds ratios (ORs) and 95% CIs were calculated for dichotomous data. The magnitude of heterogeneity between different studies was tested using I² statistics. If there was no evidence of between studies heterogeneity (I² ≤ 50%), a fixed-effects model was used to calculate. Otherwise, a random-effects model was selected [10]. The Z score was tested for overall effect, with significance considered as P < .05. Publication bias was evaluated by funnel plot if the number of included studies >10.

Table 1

| Study | Country | City | Type of study | Sample size, n | Male N.(%) | Age, years (mean (SD)/median(IQR)) | NOS score |
|-------|---------|------|---------------|---------------|------------|-----------------------------------|-----------|
| Antinori S [11] | Italy | Milan | Retrospective | 35           | 26(74.3)   | 63(51–69)                         | 6         |
| Argenziano MG [12] | US | New York | Retrospective | 850          | 511(60)    | 63(50–75)                         | 6         |
| Bi QF [13] | China | Shenzhen | Retrospective | 420          | 200(47.6)  | /                                 | 7         |
| Cai QX [14] | China | Shenzhen | Retrospective | 298          | 145(48.66) | 47.5(33–61)                       | 7         |
| Cao M [16] | China | Shanghai | Cohort | 198          | 101(51.0)  | 50.1(16.3)                        | 6         |
| Cao WL [17] | China | Xiangyang | Retrospective | 128          | 60(46.9)   | /                                 | 6         |
| Chen G [18] | China | Wuhan | Retrospective | 21           | 17(81)     | 56.3(14.3)                        | 5         |
| Duan J [23] | China | Guangzhou, Wuhan | Retrospective | 189          | 88(46.6)   | 49(35–63)                         | 5         |
| Dong J [26] | China | Guangzhou | Retrospective | 1099         | 637(58)    | 47(35–58)                         | 6         |
| Guan W [27] | China | Wuhan | Cohort | 41           | 30(73)     | 49(41–58)                         | 6         |
| Huang CL [30] | China | Wuhan | Retrospective | 213          | 126(56.5)  | 62(49–51)                         | 5         |
| Huang H [31] | China | Guangzhou | Retrospective | 125          | 63(50.4)   | 44.87(18.55)                     | 6         |
| Huang SP [32] | China | Shanghai | Retrospective | 125          | 63(50.4)   | 44.87(18.55)                     | 6         |
| Huang YS [2] | China | Wuhan | Cohort | 125          | 63(50.4)   | 44.87(18.55)                     | 6         |
| Hu L [29] | China | Wuhan | Retrospective | 125          | 63(50.4)   | 44.87(18.55)                     | 6         |
| Jiang XF [33] | China | Wuhan | Retrospective | 55           | 27(49.1)   | 45(27–60)                         | 7         |
| Liu R [37] | China | Wuhan | Retrospective | 119          | 40(33.61)  | /                                 | 8         |
| Li Z [3] | China | Wuhan | Retrospective | 193          | 95(49)     | 57(46–67)                         | 6         |
| Pei GC [41] | China | Wuhan | Retrospective | 333          | 182(54.7)  | 56.3(13.4)                        | 7         |
| PengTD [42] | China | Wuhan | Retrospective | 112          | 53(47.32)  | 62(55–67)                         | 6         |
| Perilli CM [43] | US | New York | Cross-sectional | 1999         | 125(62.6)  | 62(50–74)                         | 7         |
| Yan SJ [51] | China | Hainan | Retrospective | 168          | 81(48.2)   | 51(36–62)                         | 5         |
| Rika R [21] | Spain | / | Cohort | 48           | 32(67)     | 65.98(13.91)                     | 5         |
| Xu Y [50] | China | Wuhan | Retrospective | 189          | 88(46.6)   | 49(35–63)                         | 5         |
| Wang DW [47] | China | Wuhan | Retrospective | 138          | 75(54.3)   | 56(42–68)                         | 6         |
| Wang ZH [48] | China | Wuhan | Case-control | 116          | 65(56)     | 61(51–69)                         | 8         |
3. Results

3.1. Study selections

We searched a total of 2893 articles according to the search terms. Firstly, duplicated articles (n = 597) were excluded. After reviewing the titles and abstracts, case reports, reviews, letters, meta-analysis, editorials, guidelines, comments, not relevant studies and sample size less than 20 (n = 2150) were ruled out. 94 articles were excluded after thoroughly reviewing the full texts due to the following reasons: studies focused on special populations (n = 35); studies without available data (n = 47), studies with sample less than 20 (n = 12). Finally, 52 articles were included for the meta-analysis.

A. sCr

| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | Std. Mean Difference | IV, Random, 95% CI |
|-------------------|------|----|-------|------|----|-------|--------|----------------------|-------------------|
| Chen T 2020       | 89.4 | 36.0 | 113   | 68.1 | 22.4 | 161   | 16.0%  | 0.74 [0.49, 0.99]    |
| Deng Y 2020       | 98.7 | 46.2 | 109   | 66.1 | 18.1 | 116   | 14.9%  | 0.62 [0.44, 0.81]    |
| Fu L 2020         | 88.4 | 40.2 | 34    | 67.9 | 22.0 | 166   | 11.0%  | 0.61 [0.43, 0.80]    |
| Giacometti A 2020 | 111.0 | 48.6 | 48    | 82.2 | 22.2 | 185   | 12.7%  | 0.97 [0.64, 1.30]    |
| Li KY 2020        | 158.1 | 82.6 | 15    | 89.8 | 19.6 | 87    | 6.5%   | 1.06 [0.48, 1.65]    |
| Parangie I 2020   | 130.4 | 85.5 | 310   | 80.6 | 32.3 | 788   | 21.1%  | 0.69 [0.75, 1.03]    |
| Wang ZH 2020      | 117.1 | 34.3 | 15    | 74.0 | 16.0 | 401   | 5.9%   | 2.63 [1.43, 2.64]    |
| Yang JK 2020      | 86.0 | 26.8 | 16    | 62.3 | 16   | 53    | 6.0%   | 1.23 [0.64, 1.83]    |
| Zhang F 2020      | 120.5 | 87.3 | 17    | 77.7 | 20.2 | 31    | 5.6%   | 0.78 [0.17, 1.40]    |
| Total (95% CI)    | 677  |     |       | 1668 |     |       | 100.0% | 0.97 [0.80, 1.14]    |

Heterogeneity: Tau² = 0.03; Chi² = 17.16, df = 8 (P = 0.03); I² = 53%
Test for overall effect: Z = 11.21 (P < 0.00001)

B. BUN

| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | Std. Mean Difference | IV, Random, 95% CI |
|-------------------|------|----|-------|------|----|-------|--------|----------------------|-------------------|
| Chen T 2020       | 8.9  | 5.1 | 113   | 4.0  | 1.5 | 161   | 27.6%  | 1.36 [1.11, 1.65]    |
| Fu L 2020         | 8.1  | 4.0 | 34    | 4.3  | 1.8 | 166   | 22.7%  | 1.61 [1.21, 2.01]    |
| Li KY 2020        | 9.4  | 6.7 | 15    | 4.3  | 1.7 | 87    | 16.5%  | 1.60 [1.09, 2.28]    |
| Wang ZH 2020      | 10.0 | 3.6 | 15    | 5.3  | 1.6 | 101   | 16.2%  | 2.09 [1.48, 2.69]    |
| Yang JK 2020      | 6.0  | 3.9 | 16    | 4.5  | 2.0 | 53    | 17.1%  | 0.76 [0.20, 1.35]    |
| Total (95% CI)    | 193  |     |       | 568  |     |       | 100.0% | 1.49 [1.15, 1.84]    |

Heterogeneity: Tau² = 0.09; Chi² = 10.94, df = 4 (P = 0.03); I² = 63%
Test for overall effect: Z = 8.58 (P < 0.00001)

C. AKI

| Study or Subgroup | Non-survival | Survival | Odds Ratio | M-H, Fixed, 95% CI |
|-------------------|--------------|----------|------------|--------------------|
| Cao JL 2020       | 15           | 17       | 1          | 85                 | 13.1%  | 120.00 [21.27, 676.92] |
| Chen T 2020       | 28           | 113      | 1          | 161                | 41.5%  | 52.71 [7.05, 394.12]  |
| Deng Y 2020       | 20           | 109      | 0          | 116                | 26.4%  | 53.37 [3.18, 894.38]  |
| Zhou F 2020       | 27           | 54       | 1          | 137                | 18.9%  | 136.00 [17.72, 1044.04] |
| Total (95% CI)    | 293          | 499      | 100.0%     | 73.78 [24.52, 244.85] |
| Total events      | 90           | 7        |            |                   |

Heterogeneity: Chi² = 0.75, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 7.41 (P < 0.00001)

D. CRRT

| Study or Subgroup | Non-survival | Survival | Odds Ratio | M-H, Fixed, 95% CI |
|-------------------|--------------|----------|------------|--------------------|
| Cao JL 2020       | 5            | 17       | 1          | 85                 | 27.2%  | 36.00 [3.76, 332.69]  |
| Chen T 2020       | 3            | 113      | 0          | 161                | 46.2%  | 10.23 [0.52, 200.03]  |
| Zhou F 2020       | 10           | 54       | 0          | 137                | 26.6%  | 64.89 [3.73, 1129.76] |
| Total (95% CI)    | 184          | 383      | 100.0%     | 31.51 [6.55, 151.59] |
| Total events      | 18           | 1        |            |                   |

Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 4.30 (P < 0.00001)

Fig. 2. Meta-analysis of prevalence of AKI and CRRT as well as two laboratory indexes of kidney injury. Forest plots represent the comparisons of the prevalence of AKI and CRRT and standard mean differences (SMD) in two laboratory indicators between non-survival and survival cases. A, sCr (serum creatinine, μmol/L); B, BUN (blood urea nitrogen, mmol/L); C, AKI (acute kidney injury); D, CRRT (continuous renal replacement therapy).
with 14,094 patients were included in our meta-analysis. Fig. 1 showed the flow diagram of the studies selections.

3.2. Study characteristics

As shown in Table 1, most of studies were from China, and six studies were published from other countries [11,12,25,28,40,43]. Among of them, 41 studies with 10,335 patients were analyzed for the association of renal impairment with severity of COVID-19 [2-4,9,11-14,16-18,20,21,23,26-34,36-39,41-47,49-51,54-57]. In additions, 11 studies with 3759 patients reported the association of renal impairment with mortality of COVID-19 [1,15,19,22,24,25,35,40,48,52,53]. The incidence of AKI and CRRT during SARS-CoV-2 infections was evaluated between the severe versus non-severe cases or survival versus non-survival cases, respectively.

3.3. Association between AKI and mortality of COVID-19

As shown in Fig. 2A, sCr was measured in nine studies among 2345 patients. The heterogeneity test of sCr was shown as $I^2 = 53\%$, thus we applied the random-effects model for further investigation. The following results elucidated that sCr was significantly higher in non-survival group than that in survival group [$SMD = 0.97, 95\%CI (0.80, 1.14), Z = 11.21, P < 0.00001$]. There was moderate statistical heterogeneity between the studies to evaluate BUN ($I^2 = 63\%$). In Fig. 2B, the levels of BUN in five studies were remarkably elevated in non-survival group compared with survival group [$SMD = 1.49, 95\%CI (1.15, 1.84)$, $Z = 8.58, P < 0.00001$]. Furthermore, we compared the incidence of AKI between survival and non-survival group (Fig. 2C). The heterogeneity test of AKI was shown as $I^2 = 0$. Pooled analysis of four studies among 792 COVID-19 patients revealed that the incidence of AKI was statistically higher in non-survival group (30.72%) compared with survival group $(1.4\%)$ [OR 77.48, 95\%CI (24.52, 244.85), $Z = 7.41, P < 0.00001$]. Additionally, 3 studies reported the application rate of CRRT in non-survival vs. survival group without heterogeneity ($I^2 = 0$). As shown in Fig. 2D, non-survival group had higher application rate of CRRT than survival group [OR = 31.51, 95\% CI: 6.55 to 151.59, $P < 0.0001$].

3.4. Correlation between AKI and severity of COVID-19

As illustrated in Fig. 3, sCr was evaluated in 35 studies among 6949 patients, with no statistical heterogeneity ($I^2 = 37\%$). 35 studies reported that the level of sCr was significantly increased in severe group compared with non-severe group [SMD = 0.34, 95\%CI (0.29–0.39), $Z = 12.21, P < 0.00001$]. In Fig. 4A, the heterogeneity test of BUN in
23 studies was shown as $I^2 = 71\%$, thus we applied the random-effects model for further investigation. Sensitivity analysis by removing one study each time suggested the results were robust. Subgroup analysis by the country of study, sample size, age, male percentage and quality score of the studies failed to resolve the obvious heterogeneity. The level of BUN in severe group was remarkably higher than that in non-

| Study or Subgroup | Severe Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|-------------|----|-------|------|----|-------|--------|-------------------|-------------------|
| Cai QX 2020       | 5.2         | 1.94 | 58    | 3.91 | 1.22 | 240   | 5.4%   | 0.93 [0.63, 1.22] |                   |
| Cao M 2019        | 5.51        | 3.76 | 19    | 4.83 | 1.52 | 172   | 4.0%   | 0.83 [0.65, 1.01] |                   |
| Cao W 2020        | 6.06        | 13.03 | 21    | 5.4 | 9.63 | 107   | 4.1%   | 0.06 [0.40, 0.53] |                   |
| Chen G 2020       | 7.7          | 3.7 | 11    | 4.2 | 1.3 | 10 | 1.9% | 1.19 [0.24, 2.13] |                   |
| Chen X 2020       | 4.55        | 1.79 | 50    | 3.94 | 1.26 | 241   | 5.3%   | 0.45 [0.14, 0.75] |                   |
| Duan J 2020       | 4.1          | 2.6 | 20    | 4 | 4.4 | 328 | 4.2% | 0.07 [0.38, 0.52] |                   |
| Gong J 2020       | 5.02        | 3.2 | 28    | 3.9 | 1.05 | 161 | 4.5% | 0.72 [0.31, 1.12] |                   |
| Hong KS 2020      | 7.12        | 4.06 | 13    | 5.2 | 3.2 | 85 | 3.3% | 0.57 [-0.02, 1.16] |                   |
| Huang YS 2020     | 7.47        | 3.46 | 98    | 4.04 | 1.35 | 125   | 5.4% | 1.36 [1.07, 1.66] |                   |
| Jiang X 2020      | 6.61        | 5.99 | 8     | 4.01 | 0.99 | 47 | 2.4% | 1.08 [0.31, 1.86] |                   |
| Li Z 2020         | 6.37        | 2.96 | 65    | 4.01 | 1.57 | 128 | 5.2% | 1.10 [0.78, 1.42] |                   |
| Liu JY 2020       | 5.06        | 2.02 | 17    | 4.2 | 1.23 | 44 | 3.4% | 0.57 [0.00, 1.14] |                   |
| Liu L 2020        | 4.95        | 2.57 | 7     | 4.28 | 1.92 | 44 | 2.3% | 0.33 [-0.47, 1.13] |                   |
| Liu YL 2020       | 5.54        | 2.36 | 53    | 3.75 | 1.45 | 56 | 4.6% | 0.91 [0.52, 1.31] |                   |
| Ma KL 2020        | 4.89        | 2.71 | 20    | 4.04 | 1.14 | 64 | 3.8% | 0.51 [0.00, 1.02] |                   |
| Pei GC 2020       | 4.96        | 2.38 | 189   | 4.01 | 1.42 | 144 | 5.9% | 0.47 [0.25, 0.69] |                   |
| Peng YD 2020      | 6.42        | 4.54 | 16    | 5.07 | 2.93 | 96 | 3.7% | 0.42 [0.11, 0.95] |                   |
| Shi PY 2020       | 4.15        | 2.14 | 46    | 3.51 | 0.98 | 88 | 4.9% | 0.36 [0.00, 0.72] |                   |
| Wang DW 2020      | 6.65        | 4.09 | 36    | 4.07 | 1.5 | 102 | 4.6% | 1.05 [0.65, 1.45] |                   |
| Xu S 2020         | 5.93        | 4.29 | 131   | 4.3 | 2.3 | 224 | 5.9% | 0.51 [0.29, 0.73] |                   |
| Yan SJ 2020       | 4.71        | 3.2 | 36    | 3.6 | 1.05 | 132 | 4.8% | 0.63 [0.26, 1.01] |                   |
| Zhang GQ 2020     | 6.22        | 3.2 | 55    | 4.11 | 1.27 | 166 | 5.2% | 1.09 [0.77, 1.41] |                   |
| Zhou HF 2020      | 4.09        | 1.14 | 52    | 3.68 | 1.36 | 126 | 5.1% | 0.31 [-0.01, 0.64] |                   |

Total (95% CI) 1049 2937 100.0% 0.66 [0.51, 0.81]

Heterogeneity: Tau² = 0.09; Chi² = 75.56; df = 22 (P < 0.00001); I² = 71%

Test for overall effect: Z = 6.85 (P < 0.00001)

Fig. 4. Forest plots represent the comparisons of standard mean differences (SMD) in BUN and eGFR as well as the prevalence of CRRT between severe and non-severe cases. A, BUN (blood urea nitrogen, mmol/L); B, eGFR (estimated glomerular filtration rate, ml/min); C, CRRT (continuous renal replacement therapy).
severe group [SMD = 0.66, 95% CI (0.51 – 0.81), Z = 8.58, P < 0.00001]. As indicated in Fig. 4B, 4 studies reported the eGFR with no remarkable heterogeneity (I² = 44%). The eGFR decreased significantly in severe cases compared with non-severe cases [SMD = -0.45, 95% CI (-0.67 – -0.23), Z = 4.04, P < 0.0001]. Additionally, 10 studies reported the application rate of CRRT with moderate heterogeneity (I² = 62%). As shown in Fig. 4C, the application rate of CRRT in severe group was significantly higher than that in non-severe group [OR = 12.99, 95% CI: 4.03 to 41.89, P < 0.0001].

As severity of illness was related with complication in COVID-19, we also evaluated the incidence of AKI in severe and non-severe group (Fig. 5A). The heterogeneity test of AKI was shown as I² = 20%. 19 studies among 4968 COVID-19 patients reported that the incidence of AKI was shown to be 26.74% in severe group, which was significant higher.

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**A. AKI**

| Study or Subgroup | Severe Events | Non-severe Events | Total Events | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|---------------|-------------------|-------------|--------|-------------------------------|-------------------------------|
| Antinori S 2020   | 7             | 18                | 1           | 17     | 1.9%                          | 10.18 [1.09, 94.83]           |
| Argenziano MG 2020| 184           | 236               | 104         | 614    | 37.6%                         | 17.35 [11.95, 25.20]          |
| Bi QF 2020        | 9             | 93                | 2           | 327    | 2.4%                          | 17.41 [3.69, 82.10]           |
| Cai QX 2020       | 13            | 58                | 4           | 240    | 3.6%                          | 17.04 [5.32, 54.65]           |
| Guan W 2020       | 5             | 173               | 1           | 926    | 0.9%                          | 27.53 [3.20, 237.12]          |
| Hong KS 2020      | 8             | 13                | 1           | 85     | 0.3%                          | 134.40 [13.94, 1295.98]       |
| Hu L 2020         | 15            | 172               | 2           | 151    | 5.7%                          | 7.12 [1.60, 31.66]            |
| Huang CL 2020     | 3             | 13                | 0           | 28     | 0.7%                          | 19.00 [0.90, 399.79]          |
| Jiang XF 2020     | 2             | 8                 | 1            | 47     | 0.6%                          | 15.33 [1.20, 195.74]          |
| Li Z 2020         | 43            | 65                | 12           | 128    | 8.1%                          | 18.89 [6.61, 41.45]           |
| Pei GC 2020       | 30            | 189               | 5            | 144    | 14.1%                         | 5.25 [1.98, 13.69]            |
| Regina J 2020     | 17            | 36                | 13           | 164    | 7.3%                          | 10.39 [4.37, 24.70]           |
| Shi FY 2020       | 2             | 46                | 1            | 88     | 1.9%                          | 3.95 [0.35, 44.82]            |
| Wan SX 2020       | 1             | 40                | 4            | 95     | 6.8%                          | 0.58 [0.06, 5.39]             |
| Wang DiW 2020     | 3             | 36                | 2            | 102    | 2.8%                          | 4.55 [0.73, 28.39]            |
| Yan SJ 2020       | 3             | 36                | 0            | 132    | 0.6%                          | 27.69 [1.40, 549.10]          |
| Yang QX 2020      | 3             | 33                | 1            | 103    | 1.3%                          | 10.20 [1.02, 101.68]          |
| Zhang GQ 2020     | 8             | 55                | 2            | 166    | 2.5%                          | 13.96 [2.87, 67.97]           |
| Zhao XY 2020      | 5             | 30                | 0            | 61     | 0.8%                          | 26.53 [1.41, 497.65]          |

Total (95% CI) 361 | 156

Heterogeneity: Chi² = 22.51, df = 18 (P = 0.21); I² = 20%

Test for overall effect: Z = 19.54 (P < 0.00001)

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**B. Proteinuria**

| Study or Subgroup | Severe Events | Non-severe Events | Total Events | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|---------------|-------------------|-------------|--------|-------------------------------|-------------------------------|
| Cao M 2020        | 8             | 18                | 51          | 144    | 17.1%                         | 1.46 [0.54, 3.93]             |
| Li Z 2020         | 31            | 47                | 45          | 82     | 21.3%                         | 1.59 [0.76, 3.35]             |
| Liu R 2020        | 22            | 52                | 12          | 67     | 19.7%                         | 3.36 [1.46, 7.73]             |
| Pei GC 2020       | 156           | 189               | 63          | 144    | 25.8%                         | 6.08 [3.69, 10.02]            |
| Zhou HF 2020      | 11            | 19                | 18          | 64     | 16.1%                         | 3.51 [1.22, 10.16]            |

Total (95% CI) 228 | 189

Heterogeneity: Tau² = 0.31; Chi² = 11.99, df = 4 (P = 0.02); I² = 67%

Test for overall effect: Z = 3.43 (P = 0.0006)

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**C. Hematuria**

| Study or Subgroup | Severe Events | Non-severe Events | Total Events | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|---------------|-------------------|-------------|--------|-------------------------------|-------------------------------|
| Li Z 2020         | 21            | 47                | 36          | 82     | 24.4%                         | 1.03 [0.50, 2.12]             |
| Liu R 2020        | 22            | 52                | 27          | 67     | 22.9%                         | 1.09 [0.52, 2.27]             |
| Pei GC 2020       | 91            | 189               | 48          | 144    | 47.6%                         | 1.86 [1.19, 2.91]             |
| Zhou HF 2020      | 10            | 19                | 14          | 64     | 5.1%                          | 3.97 [1.35, 11.66]            |

Total (95% CI) 307 | 357

Heterogeneity: Chi² = 5.63, df = 3 (P = 0.13); I² = 47%

Test for overall effect: Z = 2.83 (P = 0.005)

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Fig. 5. Forest plots represent the comparisons of incidence of AKI and two clinical characteristics of kidney injury between severe and non-severe cases. A, AKI; B, Proteinuria; C, Hematuria.
than that in non-severe group (4.31%) [OR = 13.16, 95%CI (10.16–17.05), Z = 19.54, P < 0.00001].

As shown in Fig. 5B, based on the 5 studies with significant heterogeneity to evaluate proteinuria ($I^2 = 67$%), COVID-19 patients in severe cases had higher ratio of proteinuria than non-severe cases [OR = 2.92, 95% CI (1.58–5.38), Z = 3.43, P = 0.0006]. In addition, we also performed meta-analysis on the incidence of hematuria of 664 COVID-19 patients with no statistical heterogeneity among 4 studies ($I^2 = 47$%). The incidence of hematuria in severe group was statistically higher compared with non-severe group [OR = 1.59, 95% CI (1.15–2.19), Z = 2.83, P = 0.005] (Fig. 5C).

4. Discussion

Our meta-analysis including 14,094 subjects from 52 studies explored the potential relationship between renal impairment as well as AKI and the clinical outcome (severity and mortality) of COVID-19 patients. To our knowledge, this is the first systemic review and meta-analysis which evaluated the kidney function and prevalence of AKI between survival and non-survival cases. We found that the prevalence of AKI in non-survival cases was 30.72%, which was approximately 77.48-fold higher than that in survival cases. Furthermore, patients who died of COVID-19 displayed higher baseline of sCr and BUN as well as higher application rate of CRRT than the survival cases. Meanwhile, our results including severe and non-severe cases (41 studies, 10,335 patients) demonstrated that the overall rate of AKI in severe cases was 13.16-fold higher compared with non-severe cases. The levels of sCr and BUN were shown elevated, while eGFR was decreased in severe cases compared with non-severe cases. In addition, the average ratio of proteinuria, hematuria and CRRT were 2.92-fold, 1.59-fold and 12.99-fold in severe cases compared with those in non-severe cases, respectively.

Currently, the exact mechanism of renal impairment involved in COVID-19 remains unclear. One potential explanation is direct virus attack mediated via angiotensin-converting enzyme 2 (ACE2). RNA sequencing studies found that ACE2, the novel protein of coronavirus receptor, was highly expressed in proximal renal tubules, which could explain that the urinary analysis was obviously abnormal in COVID-19 patients [58]. Hence, early detection of urinary analysis is important for preventing the occurrence of AKI. In addition, hyper-activated immune response may be partly responsible for the development of kidney damage. Clinical studies have shown that the levels of inflammatory cytokines in severe patients are significantly increased compared with mild patients [30]. A recent biopsy pathology result of a COVID-19 patient with ARDS demonstrated that the numbers of immune response may be partly responsible for the development of kidney impairment and AKI are susceptible to occur in COVID-19 patients with worse clinical outcome. The risk of AKI dramatically increased in severe COVID-19. Therefore, it is necessary to establish the early identification for AKI, such as dynamic monitoring urine analysis, renal function, and biomarker detections of renal injury, which should be helpful for improvement for prognosis of COVID-19 patients.

In conclusions, our meta-analysis provides the further evidence that kidney impairment and AKI are susceptible to occur in COVID-19 patients with worse clinical outcome. The risk of AKI dramatically increased in severe COVID-19. Therefore, it is necessary to establish the early identification for AKI, such as dynamic monitoring urine analysis, renal function, and biomarker detections of renal injury, which should be helpful for improvement for prognosis of COVID-19 patients.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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