Risk Factors for Acute Kidney Injury in Patients with Coronavirus Disease 2019 (COVID-19): A Meta-Analysis

Lei Tian

Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital

Xinghua Shao

Renji Hospital, School of Medicine, Shanghai Jiao Tong University

Ying Hang

Renji Hospital, School of Medicine, Shanghai Jiao Tong University

Weiqiang Yang

Renji Hospital, School of Medicine, Shanghai Jiao Tong University

Shan Mou (✉ shan_mou@126.com)

Renji Hospital, School of Medicine, Shanghai Jiao Tong University

Changqing Zhu

Renji Hospital, School of Medicine, Shanghai Jiao Tong University

Research

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Abstract

Background

Acute kidney injury (AKI) frequently develops in patients with Coronavirus Disease 2019 and is associated with poor outcome. Unfortunately, risk factors for AKI in COVID-19 have not been clearly elucidated. Clinical evidence is required to identify risk factors for AKI and to adopt appropriate management strategies during early COVID-19 intervention.

Method

The PubMed, MEDLINE, Web of Science, EMBASE, Google Scholar, Scopus, and Elsevier Science direct were systematically searched up to September 2020. The studies that reported risk factors for AKI in patients with COVID-19 were included. Statistical analysis was performed using Review Manager Software (RevMan 5.3). Pool odds ratio (OR) with 95% confidence interval (CI) were assessed for each risk factor.

Results

Eleven studies with 8815 COVID-19 patients fulfilled eligibility criteria were incorporated into the meta-analysis, and sixteen risk factors related to AKI in patients with COVID-19 were included and analyzed. The following variables probably correlated with an increased risk of AKI in COVID-19 patients: male (OR=1.62, 95% CI, 1.24-2.13, $P<0.05$), mechanical ventilation (OR=9.44, 95% CI, 5.16-17.27, $P<0.05$), ICU admission (OR=10.57, 95%CI, 9.33-11.98, $P<0.00001$), use of vasopressor (OR=19.36, 95%CI, 16.77-22.34, $P<0.00001$), obesity (OR =1.75 ,95%CI, 1.58-1.95, $p<0.00001$), diabetes (OR= 1.73, 95% CI, 1.57-1.90, $p<0.00001$), hypertension (OR=1.53 , 95% CI, 1.04-2.20, $p=0.03$), cardiac disease (OR = 1.71, 95% CI, 1.51-1.94, $p<0.00001$), CKD (OR=2.86, 95%CI, 1.54-5.32, $p=0.0009$), and COPD (OR= 1.7 ,95% CI, 1.40-2.07, $p<0.00001$). The factors RAAS inhibitors use, cerebrovascular disease and malignancy were not significantly associated with AKI in patients with COVID-19.

Conclusions

Our meta-analysis revealed a variety of risk factors for AKI in patients with COVID-19. These findings strengthened clinical awareness of early warning to identify COVID-19 patients with high risk for AKI.

Background

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly evolved into a global pandemic. Most patients with COVID-19 have mild symptoms, but about 15.7%-26.0% develop severe symptoms, including acute respiratory distress syndrome, septic shock, and multiple organ failure [1,2]. The kidney may serve as a target for organ injury in COVID-19 because angiotensin-converting enzyme 2, the binding site for SARS-CoV-2, is highly expressed in proximal tubule cells and podocytes. Data from the single center studies in China

showed an incidence of AKI ranging from 0.5% to 29% in hospitalized patients with COVID-19 [2-4]. In contrast, early studies in the United States have reported a much higher incidence of AKI of 28%-46% [5,6]. AKI is more common among patients with more severe disease, particularly in those recovering in the intensive care unit (ICU), and is considered a negative prognostic factor for survival. In a retrospective study of 333 patients with COVID-19 those who presented with kidney dysfunction had higher mortality rates than patients without kidney involvement (11.2 and 1.2%, respectively) [7]. Attention must be paid to AKI in patients with COVID-19.

Indeed, the actual AKI incidence remains uncertain and may have been underestimated due to the retrospective design of the studies. Unfortunately, with the global outbreak of COVID-19, it is difficult to conduct prospective studies to explicit the incidence of AKI in patients with COVID-19. Therefore, identifying risk factors for AKI in COVID-19 patients will be conducive to early intervention.

To improve strategic intervention and prognosis, it is indispensable to make systemic analysis of factors contributing to AKI and clear identification of post-COVID-19 patients who are likely to have AKI. Thus, this meta-analysis was conducted to estimated risk factors and provide more reliable evidence for the clinical setting.

Methods

The protocol for this review was registered on the International Prospective Register of Systematic Reviews (PROSPERO)(ID :CRD42020211933) .

Data Sources and Searches

Relevant articles were identified from PubMed, ISI Web of Science, EMBASE, Google Scholar, Scopus and Cochrane library up to September 2020. Searches were conducted by combined text words and medical subject headings (MeSH), including all spellings of “novel coronavirus”, “COVID-19”, “SARS-COV-2”, “acute kidney injury”, “AKI”, and “risk factor”. The reference lists of retrieved articles were also checked to identify additional studies. The searches were performed by 2 investigators (Tian L and Shao X) independently, and eligible studies were verified by all authors to determine suitability for inclusion.

Study Selection

We included observational studies that reported risk factors for AKI in patients with COVID-19. Only articles published in the English language were included. We excluded studies that did not utilized the Kidney Disease Improving Global Outcomes (KDIGO) definition for AKI. Conference, abstracts and letters to journal editors were also excluded on account of the limited data.

Data Extraction and Quality Assessment

Data were reviewed and confirmed by all authors independently. We extracted data of study characteristics, including first author, the country of origin, year of publication, study design, the study

sample, and participant demographic characteristics.

The quality of all included studies was assessed independently by two authors (Tian L and Hang Y), using the validated Newcastle -Ottawa Scale (NOS) [8]. The NOS is based on an accumulative score in each of three categories: selection, comparability, and exposure or outcome. The NOS scores range between 0 and 9 stars. Each study was assigned a final quality rating of good (7-9 stars), fair (5-6 stars) or poor (0-4 stars). We excluded studies as poor quality.

Risk Factor Analysis

All statistical analyses were performed using the Review Manager Software (RevMan 5.3). Our meta-analysis examined risk factors identified in at least two studies. Odds ratio (OR) with 95% confidence interval (CI) were assessed for each risk factor. Heterogeneity of studies was measured using I^2 statistic. When $I^2 > 50\%$ or P value < 0.05 was identified for heterogeneity among studies, we used the random effect model; Otherwise, a fixed effects model was adopted. Publication bias was defined as visual asymmetry of the funnel plots.

Results

Study Selection

A total of 2364 potentially relevant citations were identified and screened from variable databases. Firstly, 466 repeated studies were rejected in our research. Then the majority was sifted out based on titles or abstracts. There were 125 articles retrieved for detailed evaluation. Finally, 11 studies (6, 9-18) with 8815 patients with COVID-19 fulfilled eligibility criteria (Fig 1).

Study Characteristics

Table 1 presents the summary characteristics of the 11 included studies [6, 9-18]. The prevalence of AKI ranged from 10.3% to 81%. Ten studies [6,9-14, 16-18] were single center, and one [15] was multicenter. Eight studies [6, 9-13, 15, 17] used retrospective cohorts, two [14, 18] were observational studies, and one [16] was a cohort trial. Studies were conducted in China [9, 10,13, 15], United States [6, 11, 17, 18], France [12, 16], and Australia [14]. We assessed the risk of bias of the studies included in the qualitative review based on Newcastle-Ottawa Scale criteria.

Risk Factor Analysis

Male

All included studies provided eligible data for demonstrating the relationship between gender and AKI. The pooled results showed that males had a higher risk of developing AKI than females in patients with COVID-19 (OR=1.62, 95% CI, 1.24-2.13, $P < 0.05$) (Fig S1). There was significant heterogeneity among these studies ($I^2 = 68\%$).

Race

Race was categorized into of the four groups: White, Black, Hispanic and Asian. The data for White and Black were available in four studies. Patients in White with COVID-19 had a significant increase in risk for AKI (OR=1.14, 95%CI, 1.03-1.26, $p<0.05$), whereas the pooled OR revealed a non-significant increase in Black (OR=1.29, 95%CI, 0.96-1.74, $P=0.09$). There studies reported the relationship between Hispanic and the risk of AKI. The results showed decreased risk of AKI in Hispanic patients with COVID-19, but the result was not statistically significant (OR=1.09, 95%CI, 0.46-1.046, $P=0.08$). Two papers reported information on Asian. The overall effect size was OR=1.18(95% CI, 0.75-1.12), $p=0.39$, with $I^2=0\%$, $P=0.05$ (Fig S2).

Mechanical Ventilation

We identified six studies that reported available data on mechanical ventilation as risk factor for AKI. Meta-analysis of the six studies showed increased risk of AKI with mechanical ventilation use (OR=9.44, 95% CI, 5.16-17.27, $p<0.05$) (Fig 2). There was significant heterogeneity among these studies ($I^2=98\%$).

ICU admission

There studies with 7026 patients about ICU admission were pooled in the analysis (Fig 3). No heterogeneity across studies was detected ($I^2=0\%$, $p=0.84$), so fixed-effect model was applied. Patients in ICU had a strong significant increase in risk for AKI (OR=10.57, 95%CI, 9.33-11.98, $p<0.00001$).

Renin-Angiotensin-Aldosterone System (RAAS) inhibitors

Five studies that included a total of patients provided available data on the association between RAAS inhibitors use and AKI. Heterogeneity across studies was detected ($I^2=70\%$, $p=0.009$), so random-effect model was applied. However, no significant difference was found between the combined estimates (OR=1.17, 95%CI, 0.77-1.80, $p=0.46$) (Fig S3).

Vasopressor

Seven studies with 8205 patients contributed to pooled outcome. Heterogeneity across studies was detected ($I^2=93\%$, $p<0.00001$), so random-effect model was applied. The use of vasopressor was associated with the risk of AKI (OR=19.36, 95%CI, 16.77-22.34, $p<0.00001$) (Fig S4).

Glucocorticoids

There studies provided extractable data to analyze the association between the risk of AKI and glucocorticoids use. Heterogeneity across studies was detected ($I^2=80\%$, $p=0.007$), so random-effect model was applied. However, no significant difference was found between the combined estimates (OR=1.64, 95%CI, 0.27-9.91, $p=0.59$) (Fig S5).

Comorbidity

Comorbidities related to AKI were analyzed, including obesity, hypertension, diabetes mellitus, cardiac disease, chronic kidney disease (CKD), cerebrovascular disease, chronic obstructive pulmonary disease (COPD) and malignancy, as showed in Table 2. Five included studies reported the impact of obesity on AKI in patients with COVID-19. The heterogeneity of these studies was detected, showing $I^2=43\%$ ($p=0.14$), under fixed-effect model. The synthesized OR was 1.75 (95%CI, 1.58-1.95, $p<0.00001$). Ten studies that explored the relationship between diabetes and AKI in patients with COVID-19 were included in the meta-analysis. The pooled data under fixed-effect model showed an OR of 1.73 (95% CI, 1.57-1.90, $p<0.00001$), with mild heterogeneity ($I^2=17\%$, $p=0.25$). Data on COVID-19 patients with hypertension were available from 9 studies with a pooled OR of 1.53 (95% CI, 1.04-2.20, $p=0.03$) from the random-fixed model with $I^2=83\%$ ($p<0.00001$). Cardiac disease was regarded as a risk factor associated with AKI in patients with COVID-19, based on ten included studies. Analysis was conducted by fixed-model ($I^2=46\%$, $p=0.05$), with an OR of 1.71 (95% CI, 1.51-1.94, $p<0.00001$). Investigators in eight studies reported on relationships between CKD and AKI among patients with COVID-19. With an OR of 2.86 (95%CI, 1.54-5.32, $p=0.0009$), the history of CKD showed a significant trend towards higher AKI risk, under random-effect model ($I^2=79\%$, $p<0.0001$). Four studies were pooled to investigate the effect of cerebrovascular disease on AKI, revealing no statistical significance (OR=1.11, 95%CI, 0.47-2.65, $p=0.06$, random-effect model). Significant heterogeneity was found, with $I^2=59\%$ ($p=0.06$). Six studies provided estimates for the relationship of between COPD and the incidence of AKI in patients with COVID-19, showing obvious statistical significance, with OR of 1.7 (95% CI, 1.40-2.07, $p<0.00001$) under fixed-effect model. Between-study heterogeneity was not apparent ($I^2=9\%$, $p=0.36$). Malignancy was not significantly associated with AKI in patients with COVID-19 (pooled OR=1.18, 95%CI, 0.97-1.45, $p=0.85$, under random-effect model), based on 5 studies. These studies showed a significant heterogeneity, with $I^2=66\%$ and $p=0.93$.

Publication Bias

Publication bias assessments were carried out on studies that examined male sex. The funnel plot suggested possible publication bias in studies reporting male and risk of AKI, as asymmetric graph was observed. (Fig S6)

Discussion

To better identify COVID-19 patients at risk of AKI, we conducted a comprehensive, systematic review of studies from the past one year. This review sought to identify risk factors associated with AKI in patients with COVID-19, and, as far as we are aware, is the first meta-analysis conducted to do so. Sixteen risk factors related to AKI in patients with COVID-19 were included and analyzed, of which male, white, mechanical ventilation, ICU admission, vasopressor, obesity, diabetes, hypertension, cardiac disease, CKD, and COPD were most likely associated with AKI in patients with COVID-19, with statistical significance.

Studies [19, 20] on ICU patients with COVID-19 suggested that male sex is the risk factor for death and disease severity associated with COVID-19. The findings of our study indicate a higher rate of AKI prevalence in male gender groups of COVID-19 patients. It may be explained by the study of Carrero et al

[21] that kidney function declines faster in men than women, possibly owing to unhealthier lifestyles in men and the protective effects of oestrogen or the damaging effects of testosterone. Data from the America and England reported on the disparities in the risk and outcomes of COVID-19, with a higher risk in black people than white people [22, 23]. Nimkar et al. also demonstrated African-American race showed higher odds of AKI than the White [11]. However, our study indicated patients in White with COVID-19 had a significant increase in risk for AKI, whereas the pooled OR revealed a non-significant increase in Black. It is difficult to have definitive views on the cause of ethnic disparities in COVID-19 until the overall infection rate has been established in different racial groups.

Mechanical ventilation is an important treatment for COVID-19 patients with respiratory failure. Our study indicated COVID-19 patients treated with mechanical ventilation were at a higher risk of AKI (OR=9.44, 95% CI, 5.16-17.27, $P<0.05$), which was consistent with the results of previous studies (6, 10,15,18). A recent study, which is by far the largest cohort of COVI-19 patients with a focus on AKI, reported the rate of AKI was 89.7% among patients on ventilators compared with 21.7% among other patients [6]. This might be explained by the largest cohort which implied AKI is a condition that occurs among COVID-19 patients with respiratory failure. In addition, ICU admission was confirmed as a risk factor of AKI in this meta-analysis. A multicenter prospective observational study, which investigated COVID-19 patients received in 19 ICUs of 16 hospitals, demonstrated the average incidence of AKI was 25.2% [24]. It is common knowledge that patients admitted in ICU are critically-ill. AKI is a common complication of patients in ICU, which can be caused by various conditions [24]. The pathophysiology of AKI in critically ill patients with COVID-19 currently relies on unspecific mechanisms (hypovolemia, nephrotoxic drugs, high PEEP, right heart failure), a direct viral injury, an imbalanced elevation of pro-inflammatory cytokines elicited by the viral infection, and a procoagulant state [25].

Angiotensin-converting enzyme-2(ACE-2), which has been described as the most likely “receptor” for viral entry into human cells, is abundantly expressed in kidney [26, 27]. Likewise, patients on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ARB) could be at a greater risk due to the mechanism by which SARS-CoV-2 enters the cell. Nevertheless, in our study, renal-angiotensin-aldosterone-inhibiting drugs were no longer an AKI predictor, which was consistent with the results of the study of Hirsch et al [6]. In addition, vasopressor treatment was confirmed as a risk factor of AKI in this meta-analysis. Pathologic studies performed in kidney tissues from ten deceased patient revealed AKI in COVID-19 patients was more likely caused by ischemia rather than viral infection [10]. Benjamin et al [28] have reported sepsis shock was the leading cause for AKI, and vasoactive agents were used to treat shock. This may be the main reason that vasopressor treatment was associated with AKI. Great attention should be paid to the hemodynamics and volume balance of patients with COVID-19.

A variety of comorbidities, obesity, diabetes, hypertension, cardiac disease, CKD and COPD, did present evidence to correlate with AKI in COVID-19 patients. The association between morbid obesity and risk for AKI in individuals with ARDS in the ICU has been previously recognized [29] Our observation of higher odds of AKI in COVID-19 patients with CKD is not surprising, as CKD is a well-known risk factor for AKI [30]. Diabetes and hypertension frequent co-exist with CKD, and can modify kidney disease outcomes

[31]. Importantly, both of these conditions have been associated with heightened risks of AKI in several clinical setting [32, 33]. Cardiac and renal disease interact in complex bidirectional and interdependent manner in both acute and chronic settings, as shown by a pathophysiological perspective that cardiac and renal disease share a number of common pathways [34]. A COPD cohort has reported the incidence and prevalence of AKI is relatively high in COPD patients [35], which was similar to our research trends.

Our study still had some limitations to consider. The standard for estimating risk factors differed with the study design in variable studies, which could have led to discrepant results. Furthermore, the study inclusion was restricted to published studies, there was a risk for overestimating effects of risk domains due to publication bias. In addition, our study only evaluated the relationship between clinical characteristics of AKI in COVID-19 patients, not the laboratory findings. The previous studies have reported elevated D-dimer, higher serum interleukin-6, and higher Sequential Organ Failure Assessment (SOFA) scores were associated with AKI [10, 36]. Unfortunately, there was no way to extract available biochemical data from included studies. Nonetheless, to the best of our knowledge, the present study is the first meta-analysis to investigate the risk factors of AKI in COVID-19 patients.

Conclusion

In conclusion, this meta-analysis has revealed statistically significant increases in risk of AKI in COVID-19 patients with mechanical ventilation treatment, ICU admission, use of vasopressor, and CKD. For patients with male sex, obesity, diabetes, cardiac disease, hypertension, and COPD were identified as the contributing risk factors. Future molecular epidemiology studies are also warranted to establish the underlying mechanisms linking these risk factors with AKI in COVID patients. Our study strengthened clinical awareness of early warning to identify COVID-19 patients with high-risk for AKI.

Abbreviations

AKI: Acute kidney injury; ACE-2: Angiotensin-converting enzyme-2; ARB: Angiotensin receptor blockers; CI: Confidence interval; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; NOS: Newcastle -Ottawa Scale; OR: Odds ratio; RAAS: Renin-Angiotensin-Aldosterone System; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SOFA: Sequential Organ Failure Assessment; ICU: Intensive care unit.

Declarations

Authors' contributions

Lei Tian, Xinghua Shao, Ying Hang, Changqing Zhu, and Shan Mou developed the original concept of the meta-analysis. Lei Tian, Xinghua Shao, Ying Hang, and Weiqiang Yang contributed to the screening of eligible studies, data extraction, and data synthesis. Lei Tian, Xinghua Shao, Weiqiang Yang, Changqing Zhu, and Shan Mou drafted the first version of manuscript. All authors read and approved the final

manuscript and take public responsibility for it. Lei Tian and Xinghua Shao contributed equally to this study.

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Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of supporting data

All data generated or analyzed during this study are included in this article and its supplementary information files.

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Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristic of included studies

Study	Year	Country	Study design	Number of participants	Age(year)	Sex ♂M/♀F	NOS Stars
Hirsch et al [6]	2020	USA	A retrospective observational cohort study	5449	64	3317/2232	7
Yan et al [9]	2020	China	A retrospective observational cohort study	882	71	440/882	7
Xia et al [10]	2020	China	A retrospective cohort study	81	66.6±11.4	54/27	9
Nimkar et al [11]	2020	USA	A retrospective study	327	71(59-82)	181/146	7
Joseph et al [12]	2020	France	Retrospective monocenter study	100	59(53-67)	70/30	8
Wang et al [13]	2020	China	A retrospective cohort study	116	62(55-69)	62/54	9
Fominskiy et al [14]	2020	Australia	Observational study	96	NR	80/16	7
Cui et al [15]	2020	China	A multicenter retrospective observational study	116	NR	66/50	9
Rubin et al [16]	2020	France	Single-centre cohort study	71	61.2±12.2	55/16	9
Lee et al [17]	2020	USA	A retrospective cohort study	1002	66(53-76)	619/383	7
Mohamed et al [18]	2020	USA	An observational single-cent study	575	65.72	312/263	7

NR=not reported, NOS= Newcastle-Ottawa Scale, USA= United States of America

Table 2 Meta-analysis of comorbidities related to AKI in patients with COVID-19

Comorbidity	Pooled analysis						
	No. of studies	OR	95%CI	p-Value	Q	p-Value	I ²
Obesity	5	1.75	1.58-1.95	p<0.00001	6.98	p=0.14	43%
CKD	8	2.86	1.54-5.32	p=0.0009	32.66	p<0.0001	79%
Diabetes	10	1.73	1.57-1.90	p<0.00001	10.82	p=0.25	17%
Hypertension	9	1.53	1.04-2.20	P=0.03	46.5	p<0.00001	83%
Cardiac disease	10	1.71	1.51-1.94	p<0.00001	16.82	p=0.05	46%
Cerebrovascular disease	4	1.11	0.47-2.65	p=0.81	7.38	p=0.06	59%
COPD	6	1.7	1.40-2.07	p<0.00001	5.51	p=0.36	9%
Malignancy	5	1.18	0.97-1.45	p=0.11	0.85	p=0.93	66%

CKD= Chronic kidney disease, COPD= Chronic obstructive pulmonary disease, OR=odds ratio, CI=confidence intervals.

Figures

Figure 1

Identification process for eligible articles.

Figure 1

Identification process for eligible articles.

Figure 2

Forest plot: effect of mechanical ventilation on AKI in patients with COVID-19.

Figure 2

Forest plot: effect of mechanical ventilation on AKI in patients with COVID-19.

Figure 3

Forest plot: effect of ICU admission on AKI in patients with COVID-19.

Figure 3

Forest plot: effect of ICU admission on AKI in patients with COVID-19.

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