Blood Purification

Meta-Analysis

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Acute Kidney Injury in Coronavirus Disease 2019 Infected Patients: A Meta-Analytic Study

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Keywords
COVID-19 · Acute kidney injury · Continuous renal replacement therapy · Mortality

Abstract
Introduction: In clinical reports on coronavirus disease 2019 (COVID-19), the incidence of acute kidney injury (AKI) is extremely variable, although AKI is described as an independent risk factor for mortality. A meta-analysis was performed to clarify the incidence and the impact of COVID-19-related AKI on mortality. ***Methods:*** All trials reporting the incidence of AKI in COVID-19 patients were searched using MEDLINE, the Cochrane Library, and EMBASE databases (last update April 26, 2020). ***Results:*** Ten trials with a sample of 5,166 patients were included. AKI occurred in 947 out of 5,166 (18.3%) patients. AKI incidence was higher in severe cases: 62/305 severe patients developed AKI (20%) versus 27/1,268 nonsevere patients (2%) ($p = 0.00001$). AKI occurred in 475 out of 915 (52%) deceased patients versus 183 out of 2,678 (7%) survivors ($p = 0.00001$). Continuous renal replacement therapy was significantly more frequent in severe cases and in dead patients. ***Conclusion:*** A significant increase in mortality rate was observed in COVID patients who developed AKI, and AKI incidence was also higher in severe cases. Any supportive strategies to protect kidney could represent valuable intervention to reduce mortality in severe COVID-19 patients.

Introduction

In December 2019, a series of unknown origin cases of acute respiratory illness occurred in Wuhan, Hubei Province, China [1]. High sequencing showed that the disease was caused by named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) [2]. On February 11, 2020, the World Health Organization officially changed the name of the disease caused by SARS-CoV-2 to coronavirus disease 2019 (COVID-19). The disease rapidly spread from Wuhan to other areas worldwide. As of April 14, 2020, 1,844,863 cases of COVID-19 have been reported worldwide with 111,828 deaths [3], and numbers are still growing up.

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The common clinical presentations of COVID-19 are fever (98%), cough (76%), and myalgia and fatigue (18% each), with accompanying leukopenia (25%) and lymphopenia (63%) [4–6]. Symptoms of upper respiratory infection with rhinorrhea and productive cough are uncommon, except in children. About 16–20% of cases have been classified as severe or critical. Of the 41 patients described by Huang et al. [7], all had pneumonia with abnormalities on computerized tomographic examination of the chest (bilateral lobular and subsegmental areas of consolidation), and 32% required care from the intensive care unit.

Although diffuse alveolar damage and acute respiratory failure are the main features of COVID-19, the involvement of other organs needs to be explored. After lung infection, the virus may enter the blood, accumulate in kidney, and cause damage to resident renal cells. Indeed, COVID-19 RNA was found in the plasma of 15% of patients by real-time polymerase chain reaction [7]. Of note, it is reported that 6.7% of patients with SARS developed acute kidney injury (AKI), and the mortality of those with AKI was 91.7% [8]. Cohort studies suggested a 3–11% incidence of AKI in those with COVID-19 infection [5, 9], although a recent report has shown higher frequency of renal abnormalities [9]. Computed tomography scan of the kidneys showed reduced density, suggestive of inflammation and edema [10]. Recently, AKI was described as an independent risk factor for patient mortality [11]. Therefore, we performed a meta-analysis of published trials to clarify the incidence and the impact of COVID-19-related AKI on mortality.

Methods

Eligibility Criteria

According to PRISMA and MOOSE [12, 13], studies were searched using the following eligibility criteria. Participants were adult (age 18 years or over) hospitalized patients and outpatients with laboratory-confirmed COVID-19. Studies involving pediatric patients were excluded. All trials reporting the incidence of AKI in COVID-19 patients were analyzed. No publication date or publication status restrictions were imposed when selecting studies. Primary outcome measure was mortality.

Information Sources

Different search strategies were performed to retrieve relevant studies by using MEDLINE, the Cochrane Library, and EMBASE databases (last update April 26, 2020). No date restriction was applied. Additional trials were searched in the DARE database and the reference lists of previously published reviews and retrieved articles.

Search

We used the following terms to search for studies: Covid-19, AKI, kidney failure, renal injury.

Study Selection

Two investigators examined at first each title and abstract to identify potentially relevant articles, and therefore the eligibility of the retrieved full-text articles was independently determined by 2 investigators.

Data Collection Process

Data were independently collected by 2 investigators with any discrepancy resolved by reinspection of the original article. To avoid transcription errors, the data were input into statistical software and rechecked by a third investigator.

Data Items

Data abstraction included type and number of patients, AKI rate and definition, mortality and severity of patients (defined as need of ICU and/or definitions provided by authors), and the use of continuous renal replacement therapy (CRRT).

Risk of Bias in Individual Studies

Although observational studies and downgraded randomized trials generally yield a low rating for quality of evidence, there might be unusual circumstances in which authors could "upgrade" such evidence to moderate or even high quality. Moreover, in some instances, observational studies might better reflect actual patient care. Case-control and cohort studies are potentially susceptible to bias, and any limitations of the data should therefore be critically discussed. Bias may be present in findings from nonrandomized trials as well as in poorly designed or conducted randomized trials. For example, numbers of exclusions in nonrandomized trials are frequently unclear, intervention and outcome assessment are often not performed according to standardized protocols, and outcomes may not be blindly assessed. The biases caused by these problems are likely similar to those occurring in randomized trials. The Cochrane collaboration proposed a 16 (or 15)-item scale that consists of 4 headings: "Was there a comparison? How were groups created? Which parts of the study were prospective? On which variables was comparability assessed?" [13]. The items were designed to characterize key features of studies which, on the basis of the experiences of Non-Randomised Studies Methods Group (NRSMG) of the Cochrane Collaboration and "first principles" (rather than evidence), are suspected to define the major study design categories or to be associated with susceptibility to bias. Therefore, we used this scale to evaluate the risk of bias in trials included.

Summary Measures and Planned Method of Analysis

Meta-analytic techniques (analysis software RevMan, version 5.3 Cochrane Collaboration, Oxford, England, UK) were used to combine studies and obtain odds ratios (ORs) and 95% confidence intervals (CIs) for dichotomous variables. A statistical difference between groups was considered to occur if the pooled 95% CI did not include 1 for the OR. An OR >1 indicates a harmful effect. Two-sided p values were calculated. Statistical heterogeneity and inconsistency were assessed by using the Q and I^2 tests, respectively. When the p value of the Q-test was <0.10 and/or the I^2 was >40%, heterogeneity and inconsistency were considered significant. Random-effects was used for all analyses.

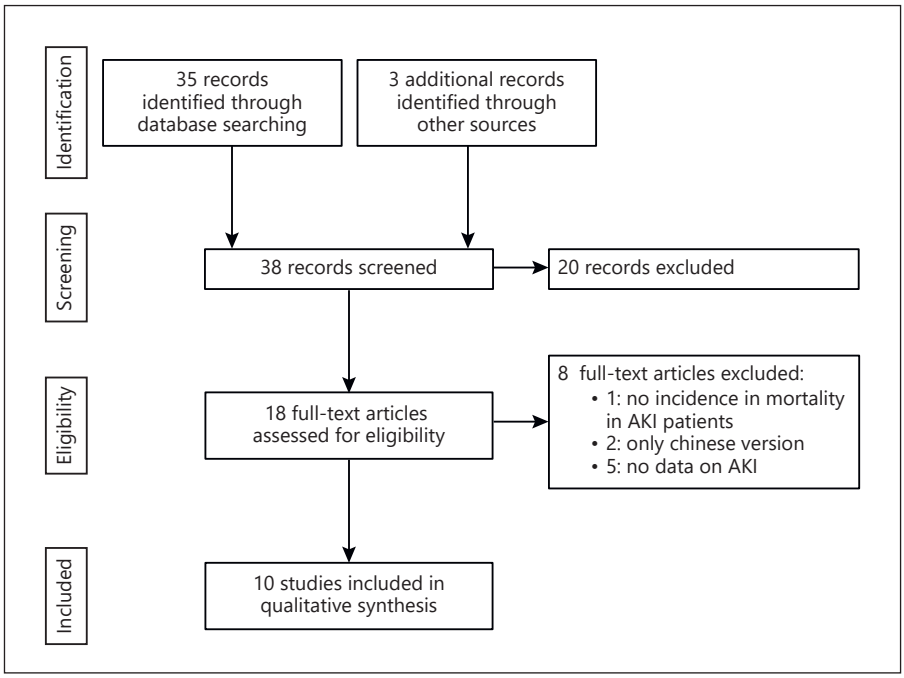

Fig. 1. Overview of study selection.

Table 1. Clinical trials included in the meta-analysis

Study	Country, year	Trial design	Patients, *n*	AKI definition	AKI	Mortality	Severe cases	Severity definition	ICU admission
Cao et al. [20]	China, 2020	Retrospective	102	Not stated	20	17	18	Respiratory rate >30/min, oxygen saturation ≤93%, or PaO_2/FiO_2 ratio ≤300 mm Hg	18
Cheng et al. [11]	China, 2020	Retrospective	274	AKIN	29	113	N/A	Respiratory rate >30/min, oxygen saturation ≤93%, or PaO_2/FiO_2 ratio ≤300 mm Hg	N/A
Deng et al. [15]	China, 2020	Retrospective	225	N/A	20	109	N/A	Respiratory rate >30/min, oxygen saturation ≤93%, or PaO_2/FiO_2 ratio ≤300 mm Hg	N/A
Guan et al. [6]	China, 2020	Retrospective	1,099	AKIN	6	15	173	American Thoracic Society guidelines for community-acquired pneumonia	55
Huang et al. [7]	China, 2020	Retrospective	41	KIDGO	3	6	13	ICU admission	13
Li et al. [10]	China, 2020	Retrospective	153	KIDGO	95	32	65	Respiratory rate >30/min, oxygen saturation ≤93%, or PaO_2/FiO_2 ratio ≤300 mm Hg	N/A
Richardson et al. [19]	USA, 2020	Retrospective	2,500	KIDGO	553	523	320	N/A	373
Wang et al. [16]	China, 2020	Retrospective	138	KIDGO	5	6	36	ICU admission for organ dysfunction	36
Wang et al. [17]	China, 2020	Retrospective	116	KIDGO	0	7	N/A	N/A	11
Wang et al. [18]	China, 2020	Retrospective	344	KIDGO	86	133	344	Respiratory rate >30/min, oxygen saturation ≤93%, or PaO_2/FiO_2 ratio ≤300 mm Hg	344

AKI, acute kidney injury; KIDGO, Kidney Disease Improving Global Outcomes; PaO_2, arterial oxygen partial pressure; FiO_2, oxygen inspired fraction.

Results

Study Selection

The search strategy identified 38 articles. Three articles were identified from the reference list of other articles. After initial screening and subsequent selection, a pool of 18 potentially relevant trials was identified. The subsequent eligibility process excluded 8 articles. Overall, 10 articles with a total sample of 5,166 patients [6, 7, 10, 14–20] were considered for analysis (Fig. 1).

Study Characteristics

All studies were published in 2020. Table 1 depicts the characteristic of included studies, AKI definition, num-

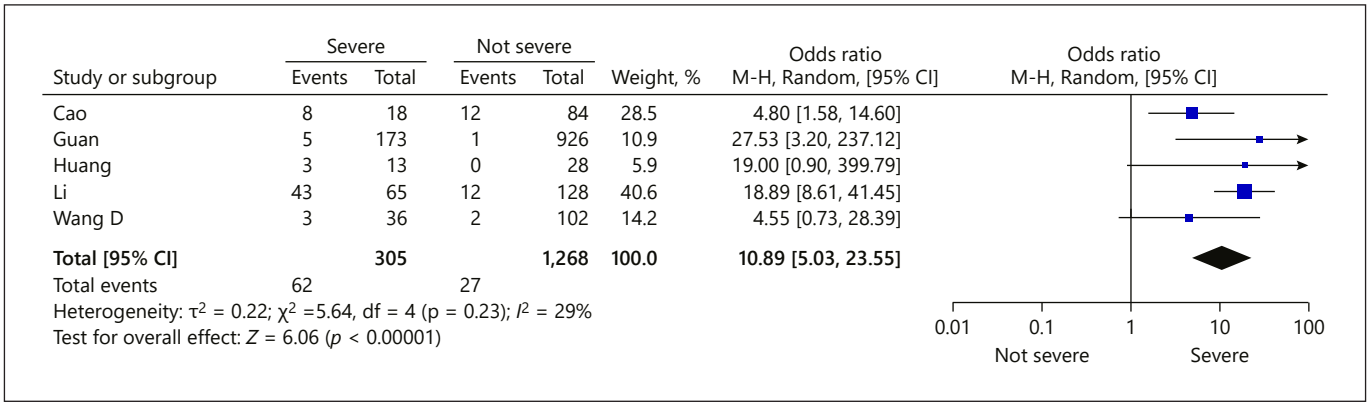

Fig. 2. Rates of AKI in severe and nonsevere patients for each of the studies with ORs and 95% CIs. The pooled OR and 95% CI are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamond represents the point estimate of the pooled OR, and the length of the diamond is proportional to the CI. AKI, acute kidney injury; OR, odds ratio; CI, confidence interval.

Table 2. Risk of bias evaluation in nonrandomized trials as proposed by the Cochrane collaboration

Study	Was there a comparison?	How were groups created?	Which parts of the study were prospective?	On which variables was comparability assessed?
Cao et al. [20]	N	N		N
Cheng et al. [11]	N	N	Outcomes	N
Deng et al. [15]	N	N		N
Guan et al. [6]	N	N	Outcomes	N
Huang et al. [7]	N	N	Outcomes	N
Li et al. [10]	N	N	Outcomes	N
Richardson et al. [19]	N	N	Outcomes	N
Wang et al. [16]	N	N	Outcomes	N
Wang et al. [17]	N	N	Outcomes	N
Wang et al. [18]	N	N	Outcomes	N

ber of patients, severity (e.g., ICU admission), and mortality. All trials were retrospective, but adopted a clear definition of severity of cases and AKI (except 2) (Table 2).

AKI, Severity of Patients and Mortality

Considering all trials, AKI occurred in 947 out of 5,166 (18.3%) patients, while CRRT was performed in 111 out of 4,597 (2.4%) COVID-19 patients. Nine out of 10 studies [6, 7, 10, 14–18, 20] derived from oriental experience with a prevalence of AKI of 866 cases out of 2,532 patients (34%), whereas in the only nonoriental study [19] AKI occurred in 81 out of 2,634 patients (3%).

AKI incidence was higher in severe cases: 62/305 severe patients developed AKI (20%) versus 27/1,268 in nonsevere patients (2%) (OR 10.89, 95% CI 5.03–23.6, $p = 0.00001$, Q statistic $p = 0.23$, $I^2 = 29\%$, 5 trials) (Fig. 2). In severe patients, CRRT was performed in 23 out of 305 patients (7.5%) versus 4 out of 1,268 nonsevere patients (0.3%) (OR 14.75, 95% CI 3.4–64.8, $p = 0.0004$, Q statistic $p = 0.18$, $I^2 = 36\%$, 5 trials).

A significant increase in AKI rate was observed in COVID deceased patients: 475/915 patients with AKI died (52%) versus 183/2678 non-AKI patients (7%) (OR = 31.03, 95% CI 13.95–69.02, $p = 0.00001$, Q statistic $p = 0.08$, $I^2 = 56\%$, 5 trials) (Fig. 3). Excluding the largest trial [19], similar results were found (OR 51.87, 95% CI 23.85–112.84, $p = 0.00001$, Q statistic $p = 1$, $I^2 = 0\%$, 4 trials), with no statistical heterogeneity and inconsistency. Eighty-one out of 673 dead patients underwent CRRT in comparison with 3 out of 2351 survivors (OR 51.1, 95% CI 5.5–473, $p = 0.0005$, Q statistic $p = 0.14$, $I^2 = 54\%$, 3 trials).

Discussion

The result of the present meta-analysis suggests that AKI was found in a significant fraction of severe COVID-19 patients and that the presence of AKI was significantly associated with the death of COVID-19 patients. The etiology of AKI in COVID-19 is thought to be multifactorial, and the mechanism of kidney involvement may include direct cellular injury due to the virus or sepsis leading to cytokine storm syndrome [21]. Angiotensin-converting enzyme 2 (ACE2) is a carboxypeptidase that preferentially removes carboxy-terminal hydrophobic or basic amino acids [22]. After infection,

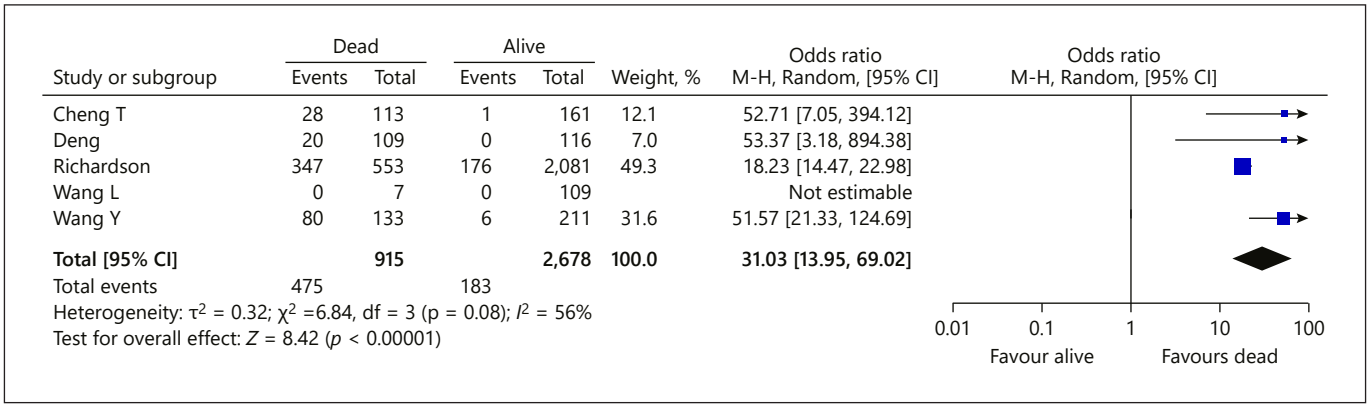

Fig. 3. Rates of AKI in alive and dead patients for each of the studies with ORs and 95% CIs. The pooled OR and 95% CI are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamond represents the point estimate of the pooled OR, and the length of the diamond is proportional to the CI. AKI, acute kidney injury; OR, odds ratio; CI, confidence interval.

SARS-CoV-2 entry starts with the binding of the spike glycoprotein expressed on the viral envelope to ACE2 on the alveolar surface [23]. ACE-2 expression has been reported in other organs, such as the gut, kidneys, and heart [24], and the incidence of abdominal symptoms, cardiac dysfunction, and AKI in COVID-19 patients may suggest that the virus could have a tropism for these organs. A very recent autoptic study shows that the infection may involve kidney causing formation of hyaline thrombi in small vessels [25]. Pathogen-induced lung injury produce a "cytokine storm" [26] in which strong proinflammatory response spills over into the systemic circulation, causing hypotension, hyper- or hypothermia, leukocytosis or leukopenia, and often thrombocytopenia. The fall in glomerular filtration secondary to hypotension, hypoxia, vasoconstriction, and sepsis plausibly could contribute to the development of acute tubular necrosis. Other causes of AKI in COVID-19 patients with interstitial pneumonia treated with mechanical ventilation can be related to recruitment maneuvers, higher positive end-expiratory pressure (PEEP), and peak and mean airway pressure, despite it is common to use protective ventilation [27], which may contribute to increase venous pressure and foster kidney congestion. Moreover, bidirectional interaction between lung injury and AKI, mediated by several pathophysiologic, molecular, and cellular mechanisms (e.g., upregulation of cytokine production, deranged nitric oxide metabolism, leukocyte trafficking, increased vascular permeability, pulmonary hemorrhage, and pulmonary hypertension), could contribute to the multifaceted kidney and lung interactions and comorbidity [28].

Cox proportional hazard regression confirmed that elevated baseline serum creatinine and blood urea nitrogen, proteinuria, and hematuria were independent risk factors for in-hospital death after adjusting for age, sex, disease severity, comorbidity, and leukocyte count [11]. Our results confirm the link between AKI and mortality in COVID-19. Of note, the incidence of AKI and use of CRRT were significantly higher in sicker and dead patients. This finding is not surprising, since severely sick patients are more prone to develop organ dysfunctions, and kidney failure can initiate and perpetuate heart and lung injury, but once more underlines the potential multifaceted impact of lung-kidney crosstalk. Therefore, monitoring kidney function must be emphasized even in patients with mild respiratory symptoms, and altered kidney function should be given particular attention after admission in clinical practice. Early detection and treatment of renal abnormalities, including adequate hemodynamic support and avoidance of nephrotoxic drugs, and, if possible, blood purification therapies in severely ill patients, particularly when cytokine release actually plays a role in sustaining inflammation and multiorgan involvement, may help to improve the vital prognosis of COVID-19.

Most of medicines currently prescribed to treat COVID-19 (i.e., oseltamivir, lopinavir/ritonavir, ribavirin, and chloroquine phosphate or hydroxychloroquine sulfate) are metabolized in the liver, and some of their metabolites are found in the urine due to renal excretion. Therefore, injury to the liver and kidneys by impairing metabolism and excretion may affect dosing and concentrations of the above drugs, increasing the risk of toxicity [29]. As a result, frequent and careful monitoring of kidney function might

help in achieving optimal drug therapeutic concentrations while reducing the risk of adverse drug reaction [29].

Our study has several limitations. Due to the understandable urgency in producing, synthesizing, and disseminating data during the current pandemic, there has been a noticeable increase in fast track publication of studies. All studies were retrospective, and the risk of reporting, selecting, and publication bias was high, even if all except one adopted well-established AKI definition, assuring at least consistent result for this outcome. At this moment, however, these retrospective trials are the only available evidences and we can only infer data from their results.

Moreover, they included a limited number of patients and were not designed to explore the link between AKI, mortality, and severity of patients. We did not know, for example, what are the risk factors more involved in AKI pathogenesis in COVID-19 patients and which pre-existing condition could more contribute to AKI incidence.

Although we could retrieve consistent definition of AKI according to KDIGO in 9 out of 10 studies and results about CRRT utilization, data regarding AKI severity, presumed pathophysiology, and preventive measure are still lacking. Difference in AKI prevalence between oriental and nonoriental studies (although there was only 1 nonoriental study) is another matter of debate.

Conclusions

Our meta-analytic study, within the limits of the studies included, shows that a significant increase in mortality rate was observed in COVID patients who developed AKI and that AKI incidence was also higher in severe cases. Taken together, these results suggest exercising a high degree of attention in monitoring kidney function of COVID-19 patients particularly in critically ill. Any supportive strategies that are potentially protective for kidney functions (hemodynamic monitoring and optimization, avoiding fluid overload and nephrotoxic drugs, and also considering blood purification treatments) could represent valuable intervention in order to reduce mortality in severe COVID-19 patients.

Statement of Ethics

Ethical approval was not required being a meta-analytic study based on already published studies.

Disclosure Statement

The authors have no conflicts of interest to declare.

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The authors did not receive any funding.

Author Contributions

N.B.: conceptualization, data curation, writing, and editing. F.P.: data collection, writing, and review. S.R.: data collection and review. L.T.: data curation and review.

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