Blood Purification

Systematic Review

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DOI: 10.1159/000514940

Received: August 23, 2020
Accepted: February 3, 2021
Published online: June 15, 2021

Incidence and Outcomes of Acute Kidney Injury in COVID-19: A Systematic Review

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Keywords
COVID-19 · Acute kidney injury · Kidney replacement therapy · Epidemiology · Nephrology

Abstract
Background and Objectives: The recent worldwide pandemic of COVID-19 has been a serious, multidimensional problem that has left a detrimental worldwide impact on individuals of all ages and several organ systems. The typical manifestation of kidney involvement is acute kidney injury (AKI); however, there is a lack of consensus data regarding AKI epidemiology in COVID-19. This systematic literature review aims to bridge this knowledge gap. ***Design, Setting, Participants, and Measurements:*** MEDLINE and Cochrane library were systematically searched for the literature related to AKI in COVID-19 patients of all ages. MedRxIV was searched for relevant unpublished manuscripts. Two reviewers independently assessed the literature on the incidence of AKI and mortality, extracting the need for kidney replacement therapy (KRT). ***Results:*** Sixty studies (n = 43,871 patients) were included in this review. The pooled incidence of AKI among COVID-19 patients was 19.45% (95% confidence intervals [95% CI]: 14.63–24.77%), while the pooled incidence of AKI COVID-19 patients requiring KRT was 39.04% (16.38–64.57%). The pooled proportion of COVID+ patients was significantly lower at 8.83% (5.64% to 12/66%). The overall mortality of COVID-19 patients was calculated to be 17.71% (95% CI: 11.49–24.93%), while the mortality among patients with AKI was higher at 54.24% (95% CI: 44.70–63.63%). ***Conclusion:*** This comprehensive systematic review summarizes the available literature pertaining to AKI epidemiology in COVID-19 patients and highlights the incidence, associated mortality, and the need for KRT in this susceptible population.

Introduction

The COVID-19 pandemic is a serious, multidimensional problem with tremendous detrimental consequences for healthcare, occupation, and economy [1–3]. First identified as a cluster of pneumonia cases of unknown origin in Wuhan, China in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-

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CoV-2) has rapidly spread worldwide leading the WHO to declare the coronavirus disease outbreak as a public health emergency of international concern [4].

The clinical spectrum of the SARS-CoV-2 infection appear to be wide, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and death. Although COVID-19 cardinally manifests as diffuse alveolar damage, the involvement of other organ systems merits discussion. Recent literature suggests that the kidney is a vulnerable organ in COVID-19 patients with evidence of acute kidney injury (AKI) in up to 37.5% of fatal cases of COVID-19 [5]. Despite the recognition of AKI as a frequent complication of COVID-19, there is a lack of consensus data regarding its incidence and outcomes. This systematic literature review aims to bridge this knowledge gap and help establish widespread consensus using worldwide data.

Methodology

Outcomes

The primary outcome of this systematic literature review, conducted according to the preferred reporting items for systematic reviews and meta-analyses "PRISMA" checklist (Appendix 1), was with the objective to identify evidence regarding acute kidney involvement in COVID-19, focusing on the incidence and outcomes of COVID-19 patients with AKI.

Database Sources and Search Strategy

A systematic search was conducted in PubMed/MEDLINE and Cochrane Center Trials databases to identify all published literature relevant to AKI in COVID-19 patients from November 1, 2019 to June 5, 2020. Search terms such as "COVID," "Coronavirus," "Betacoronavirus," "kidney," "renal," and "creatinine" were included in the search criteria (Appendix 2). The search strategy was modified as per the search engine, as appropriate. Study identification was done in 2 phases: first, all the literature retrieved from the search strategy was imported into Rayyan QCRI via EndNote and reviewed using the inclusion and exclusion criteria. Second, the reference lists of the selected studies were reviewed to identify other relevant publications.

Study Selection

The inclusion criteria included prospective and retrospective cohort studies and case series assessing AKI in both adult and pediatric COVID-19 patients. All included studies needed to demonstrate laboratory-confirmed SARS-CoV-2 infection (including detection of SARS-CoV-2 nucleic acid via transcriptase polymerase chain reaction and CT scanning of the lung) and include demographic data, epidemiological data (incidence of AKI, severity, and comorbidities), laboratory and radiological data, treatment, and outcome. Case reports, systematic reviews, meta-analyses, randomized clinical trials, animal studies, and studies not in English were excluded. Studies exclusively on kidney transplant patients were also excluded from this analysis.

Data Extraction

The titles, abstracts, full-texts, and reference lists of the collected manuscripts were independently reviewed by 2 investigators (Z.M. and P.V.) to identify relevant studies for inclusion. Any disagreements or conflicts were resolved either via a consensus of the 2 reviewers or by the opinion of a third independent reviewer (R.C.). The schema for the selection of studies is shown in online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000514940. The data regarding patient demographics, presence of comorbidities, AKI incidence and severity, presence of hematuria and/or proteinuria, mortality rates, need for kidney replacement therapy (KRT), and outcomes were recorded electronically.

Statistical Methods

The outcomes included the incidence of AKI among COVID-19 patients, the proportion of COVID-19 patients with AKI receiving KRT over the study period, and mortality among COVID-19 patients with incident AKI. These outcomes and their 95% confidence intervals (95% CI) were calculated for each study. A meta-analysis of these outcomes was conducted. The degree of between-study heterogeneity was assessed using the I^2 test, where $I^2 \geq 50\%$ indicated high heterogeneity. Overall (pooled) estimates were calculated with random effects models for high heterogeneity and fixed effects models for low heterogeneity. Forest plots were used to visualize these outcomes in each study and the combined estimated outcomes with their 95% CI. Publication bias was assessed graphically using funnel plots. To determine the source of heterogeneity, sensitivity analyses and random-effects meta-regression were performed based on these parameters (criteria used for defining AKI, the study design, the geographic location of the study, age of the studied population, and the sample size of the study). A p-value ≤ 0.05 was considered for statistical significance. All statistical analyses were performed with R software version 3.1.0.

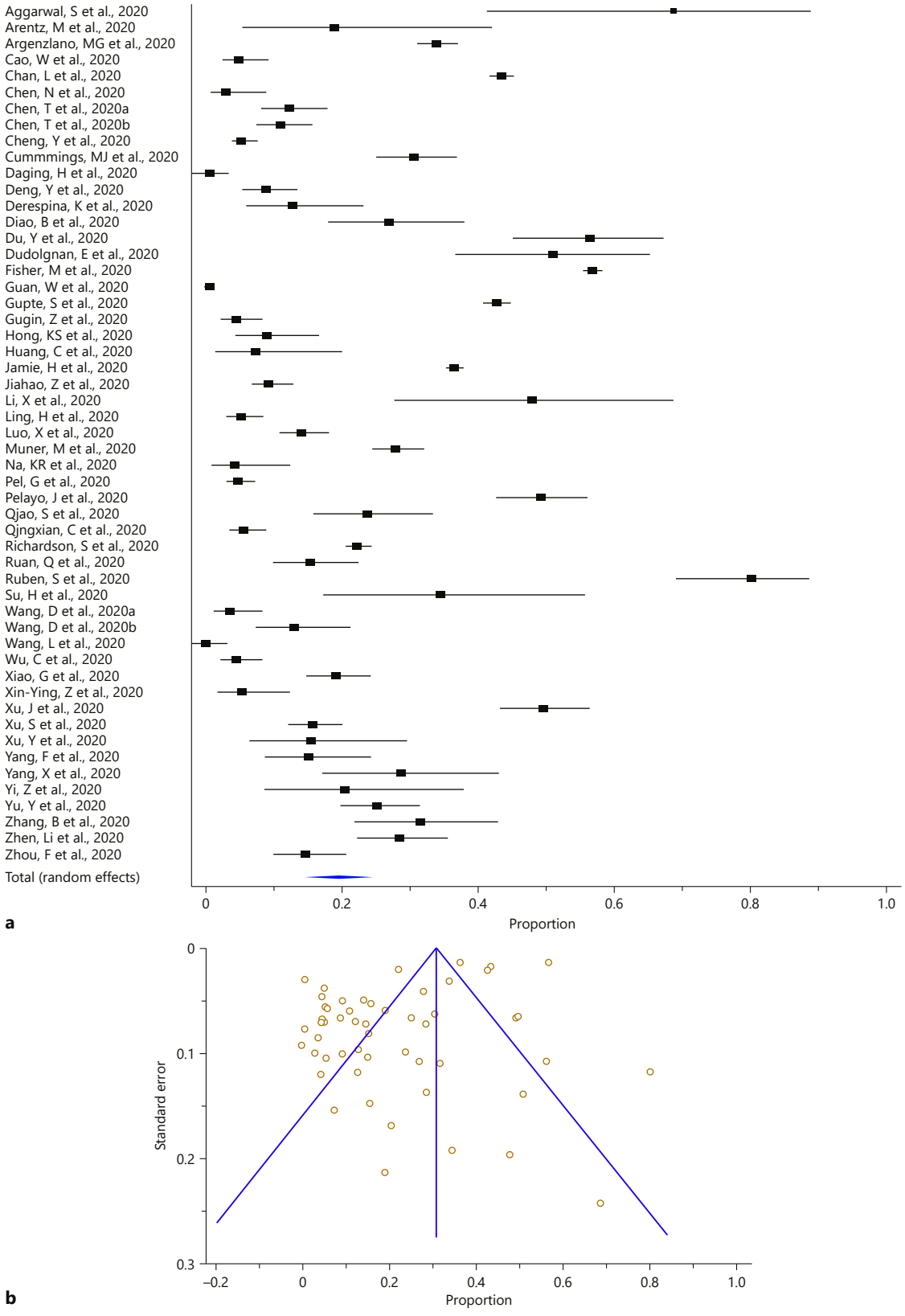
Results

Study Selection and Details

The initial database search yielded 146 potential articles and considered 31 additional studies by searching through citation lists and unpublished manuscripts (online suppl. Fig. 1). A total of 177 studies were screened, of which 113 were excluded. After screening titles and abstracts, 61 full-text articles were obtained for detailed evaluation based on the inclusion criteria. One study was excluded after the full-text review, yielding a total of 60

Fig. 1. AKI incidence among COVID positive patients. **a** Forest plot of the meta-analysis different studies. The lower diamond in the graph represents the pooled estimate. **b** Funnel plot for AKI incidence among COVID positive patients. AKI, acute kidney injury.

(For figure see next page.)



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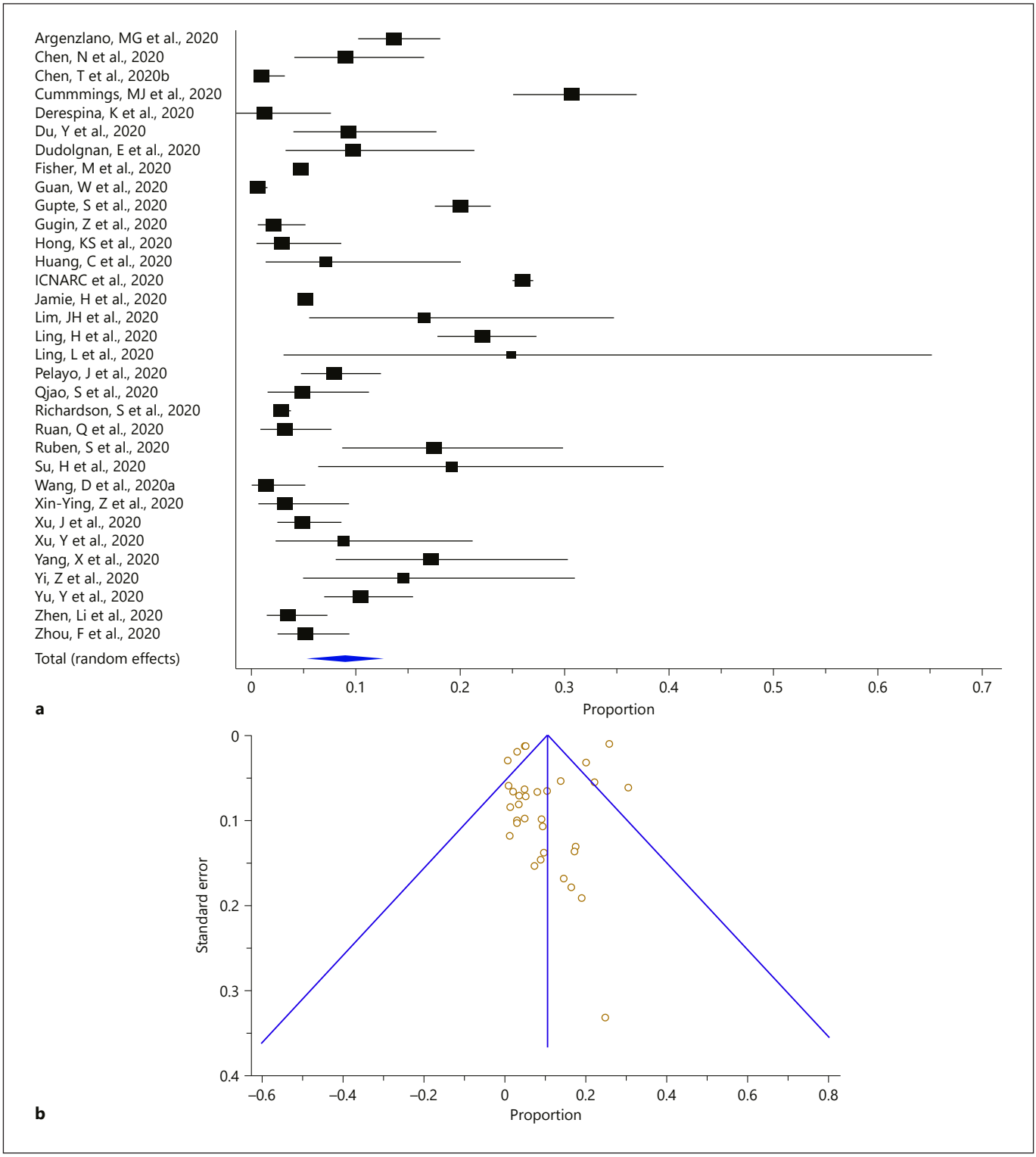

Fig. 2. Incidence of KRT in COVID positive patients. **a** Forest plot of the meta-analysis across different studies. The lower diamond in the graph represents the pooled estimate. **b** Funnel plot for KRT incidence among COVID positive patients. KRT, kidney replacement therapy.

studies reporting the outcomes of interest. Of these, 40 were retrospective studies, 12 were prospective, and 8 were case series. Most of the studies (n = 40) were conducted in China, followed by 14 studies in USA, 3 in Korea, 2 in France, and 1 in UK.

The overall sample size of COVID-19 patients evaluated was 42,612. The pooled median age of these patients was 61.1 years (median of 45.6–73 years) and 60.9% (n = 25,936) were men. Pediatric patients were included in only one study (<2% of overall sample size). The most common comorbidities reported among these patients were hypertension (28.4% [n = 12,112]), diabetes mellitus (20.8% [n = 8,844]), obesity (17.8% [n = 7,590]), chronic kidney disease (5.2% [n = 2,237]), coronary artery disease (3.5% [n = 1,481]), malignancy (2.8% [n = 1,190]), asthma (2.5% [n = 1,082]), CHF (2.4% [n = 1,040]), and COPD (2.1% [n = 914]). The majority of the studies (n = 29) had used KDIGO AKI guidelines, followed by elevated serum creatinine level in 2 studies, elevated blood urea nitrogen or creatinine in 2, elevated creatinine/uric acid in 1, and AKIN in 1, while 25 studies did not specify the criteria. Details of the studies are given in online suppl. Table 1 [5–64].

Data Analysis

Incidence of AKI among COVID-19 Patients

The pooled (95% CI) incidence of AKI among COVID+ patients was 19.45% (95% CI: 14.63–24.77%) (I^2 = 99.10% [99.01–99.18%]; p < 0.0001; random effects; 53 studies; n = 29,142) (online suppl. Table 2; Fig. 1).

Proportion of COVID-19 Patients Requiring KRT

Only 4 studies reported the data on AKI COVID patients receiving KRT. The pooled proportion (95% CI) of AKI COVID+ patients receiving KRT was 39.04% (16.38–64.57%) (I^2 = 96.75% [94.12–98.20%]; p < 0.001; random effects; 4 studies; n = 1,608) (online suppl. Table 3). As expected, the pooled proportion (95% CI) of COVID+ patients receiving KRT was much lower at 8.83% (5.64–12.66%) (I^2 = 98.85% [98.69–99.00%]; p < 0.0001; random effects; 33 studies; n = 27,996) (online suppl. Table 4; Fig. 2).

Mortality among COVID-19 Patients with AKI

The pooled proportion (95% CI) of mortality among AKI COVID+ patients was 54.24% (95% CI: 44.70–63.63%) (I^2 = 97.53% [96.74–98.12%]; p < 0.001; random effects; 13 studies; n = 6,302) (online suppl. Table 5; Fig. 3). While the pooled proportion (95% CI) of mortality among COVID+ patients was 19.35% (95% CI: 12.40–27.42%) (I^2 = 99.11% [98.97–99.22%]; p < 0.0001; random effects; 25 studies; n = 17,470) (online suppl. Table 6; Fig. 4). Moreover, AKI COVID+ patients (n = 1,369) had significantly higher odds of mortality as compared with non-AKI COVID+ patients (n = 3,932) (pooled odds ratio: 18.63 [95% CI: 15.67–22.15] [I^2 = 0.00% (0.00–67.78%); p = 0.6571; fixed effects; 5 studies) (online suppl. Table 7; Fig. 5). Visual inspection of the funnel plot showed an asymmetrical distribution, which indicated the presence of publication bias for all the above outcome measures (Fig. 1–5).

Proteinuria and Hematuria

The pooled proportion (95% CI) of proteinuria among COVID+ patients was 52.47% (95% CI: 27.97–76.34%) (I^2 = 99.65% [99.59–99.70%]; p < 0.0001; random effects; 11 studies; n = 7,794). While the pooled proportion (95% CI) of hematuria among COVID+ patients was 35.89% (95% CI: 25.94–46.50%) (I^2 = 95.55% [93.14–97.11%]; p < 0.0001; random effects; 8 studies; n = 2,007).

Sensitivity Analyses and Meta-regression

The I^2 value for sensitivity analyses was like that obtained without excluding the studies based on the previously mentioned parameters (online suppl. Table 8). Also, the proportion (%) of the outcomes obtained from the sensitivity analyses was within the 95% CI of the overall proportion for all the parameters (except for age and geography), indicating that the results of this meta-analysis are robust enough. To further explore the impact of these parameters on the outcomes, the meta-regression analyses were conducted (online suppl. Table 9). The meta-regression analyses reported that the pooled incidence of AKI among COVID+ patients was significantly higher among studies from geography other than China (OR: 2.34 [95% CI: 1.50–3.64]), the prospective/retrospective study design (1.80 [1.07–3.02]), and studies with a mean/median age ≥60 years (3.87 [2.53–5.91]), but significantly lower among studies with a sample size ≥175 (0.62 [0.42–0.91]). Regarding mortality among COVID+ patients, higher mortality was observed in studies with a mean/median age ≥60 years (3.94 [1.55–9.99]), the only significant parameter observed. None of the parameters were significantly associated with the incidence of KRT among COVID+ patients. These analyses were not conducted for other outcomes due to insufficient data.

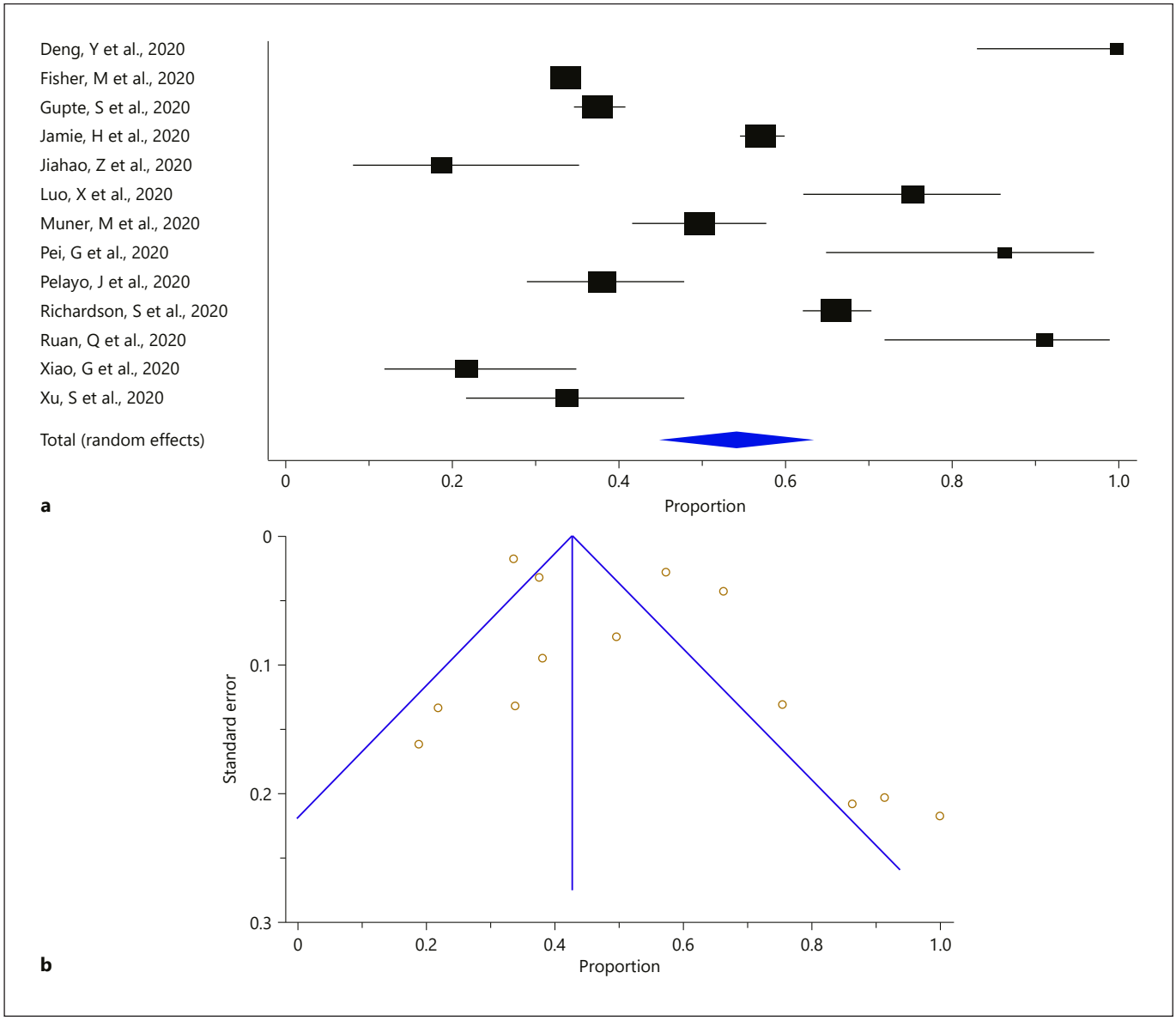

Fig. 3. Mortality among COVID positive patients with AKI. **a** Forest plot of the meta-analysis across different studies. The lower diamond in the graph represents the pooled estimate. **b** Funnel plot for mortality among overall COVID positive patients with AKI. AKI, acute kidney injury.

Discussion

COVID-19 primarily manifests as an acute respiratory illness with interstitial or alveolar pneumonia, but can also affect multiple organs, such as the kidneys, heart, liver, blood, and nervous system [65, 66]. Recent literature suggests that kidneys are especially vulnerable in COVID-19 patients, with AKI being the most frequent manifestation [5]. There is a dearth of accurate consensus regarding incidence, pathogenesis, diagnosis, management, and outcomes of AKI. This systematic literature review and meta-analysis specifically aims to address incidence and outcomes of AKI in COVID-19 patients. Our findings revealed that AKI was a frequently observed complication of COVID-19 infection, with a cumulative incidence of 19.76%. COVID-19 patients had an overall mortality rate of 17.51%. This is in line with the historical mortality estimates of the SERS and MERS epidemics (10

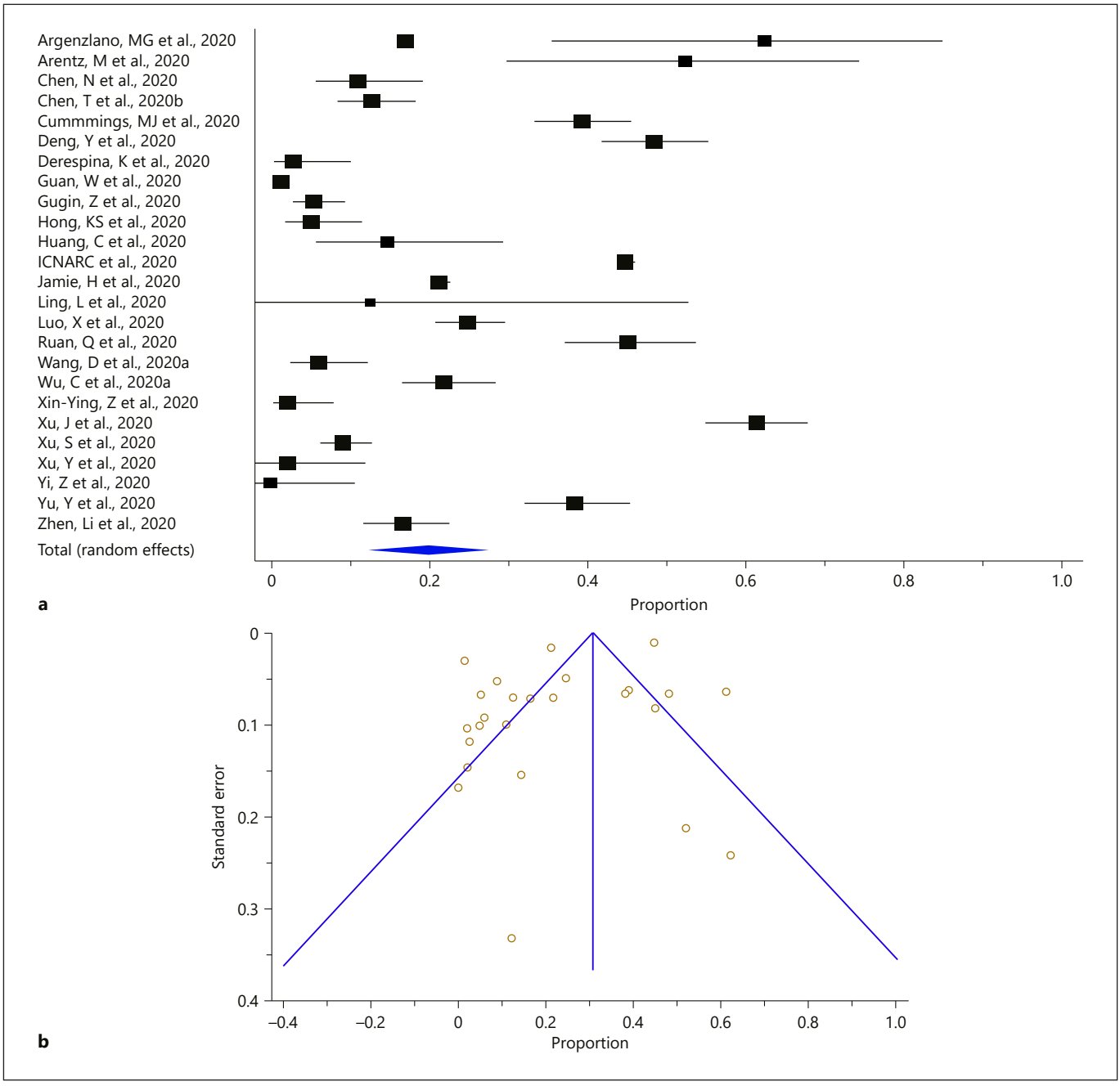

Fig. 4. Mortality among overall COVID positive patients. **a** Forest plot of the meta-analysis across different studies. The lower diamond in the graph represents the pooled estimate. **b** Funnel plot for mortality among overall COVID positive patients.

and 40%, respectively) [65, 66]. COVID-19 patients with AKI had a significantly higher mortality rate of 54.24% and, overall, 18 times higher risk of death when compared to COVID-19 patients without AKI. Thus, AKI is a major negative prognostic factor in COVID-19 patients with dire need of prevention and management in this susceptible population.

The pathophysiology of AKI in COVID-19 is complex, suggestive of a biphasic pattern with volume responsive AKI occurring in early stages of the disease and kidney

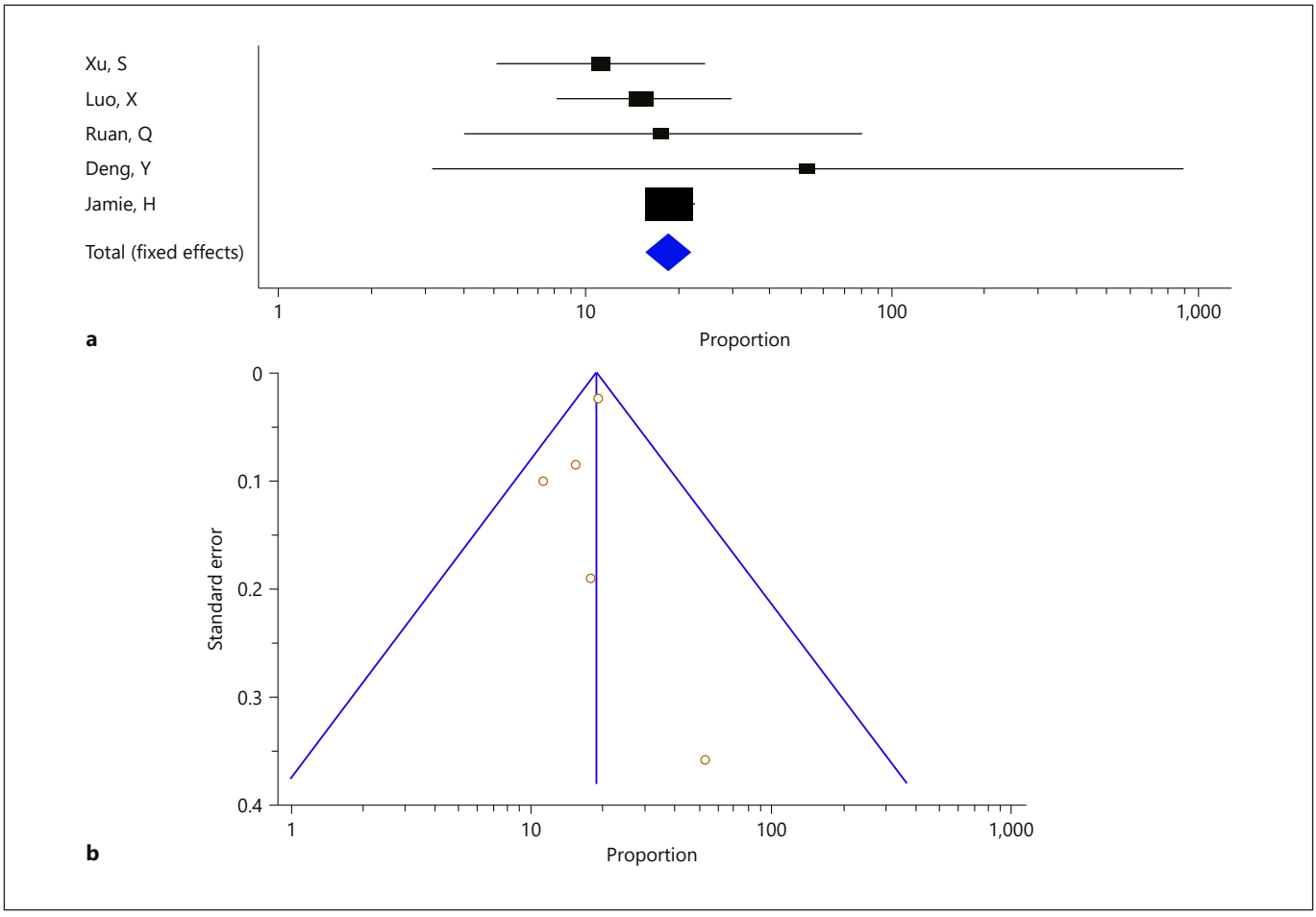

Fig. 5. Comparison of mortality among AKI versus Non-AKI COVID+ patients. **a** Forest plot of the meta-analysis of mortality among AKI versus non-AKI COVID+ patients across different studies. The lower diamond in the graph represents the pooled estimate. **b** Funnel plot of mortality among AKI versus non-AKI COVID+ patients across different studies. AKI, acute kidney injury.

injury occurring in later stages of the disease [67]. Acute lung injury that ensues in COVID-19 patients can effectuate impairment of the kidney function through its effect on gas exchange, release of pro-inflammatory mediators (IL-2, IL-7, IL-10, IFN-γ, IP10, GCSF, and MCP1), and cardiopulmonary interactions [67, 68]. The lung-kidney crosstalk may be bidirectionally deleterious, due to a cascade of irreversible cytokine release [67, 69]. A transient febrile/illness-related proteinuria may also be seen, like the MERS CoV infection [6, 70]. The cellular entry of SARS-CoV-2 is mediated by angiotensin-converting enzyme II, which is highly expressed in the podocytes and proximal tubules (100× levels compared to the lungs) and upregulated in patients with COVID-19 [7, 71–73]. An autopsy series conducted by Puelles et al. [74] (n = 27), showed that SARS-CoV-2 has organotropism beyond the pulmonary tract. Recent postmortem kidney pathology findings in patients with COVID-19 suggests that although there are little signs of viral nephropathy, noted acute tubular injury in the setting of creatinine elevation is reversible with appropriate care such as aggressive fluid management [75]. Mechanical ventilation may be provided to patients which affects the renal and systemic hemodynamics, stimulates sympathetic pathways, and causes biotrauma [9, 76]. Recent studies in London indicate that COVID-19 may present as multisystem inflammatory syndrome; however, there is still limited information regarding this COVID-19 associated condition.

In terms of management of patients with COVID-19 and AKI, discussion of goals of supportive care (e.g.,

KRT) among clinicians and patients/families is recommended. Standard recommendations by KDIGO include nutritional and fluid support, avoidance of nephrotoxins, maintenance of oxygenation saturation, and hemodynamic stability for the management of AKI. KRT may reduce the burden of inflammatory mediators and cytokines as supported by a study with Ghani et al. [77–80] particularly to patients with AKI; however, more studies are required. Various modalities such as peritoneal dialysis, hemodialysis, CKRT, and sustained low-efficiency dialysis can be utilized for AKI management. Although CKRT is the preferred modality in most ICU settings, the choice of modality should be based on the hemodynamic status, patient characteristics and needs, available resources, and health-care expertise [81–83]. Newer modalities such as CytoSorb (an extracorporeal cytokine filter) and Oxiris (a blood purification device for cytokine clearance) have received expedited FDA approval for use in adult COVID-19 patients (≥18 years old) with AKI [84, 85], where the provider can obtain an exploratory investigational new drug for use in the pediatric population. Evidence is actively evolving but insufficient for widespread application in COVID-19 patients with AKI.

Limitations

This systematic literature review is constrained due to the paucity of relevant peer reviewed studies and data. Our review excludes studies that are not in the English language. In several studies, baseline creatinine levels were unavailable and data of kidney recovery, drug exposure, or long-term kidney outcomes were not reported. Renal pathology data were sparse, and it was difficult to assess the precise etiology of AKI in COVID-19 patients. Additionally, visual inspection of the funnel plots for the incidence of AKI, need of KRT, and mortality showed an asymmetrical distribution, which indicates the possibility of publication bias (Fig. 2–5). The differences between this systematic review and recently published work helps address the prior lack of generalizability; this study includes data spanning Asia, Europe, and USA in addition to including a broader scope of studies as highlighted in online suppl. Table 10. Additionally, this systematic review reports higher incidence of AKI with COVID-19 patients (results = 19.76%, range in literature = 2–11%) and delves into a possible explanation with the results on the need for KRT [83, 86–95]. Future studies should assess risk stratification, specific management strategies, and long-term outcomes of COVID-19 patients with AKI.

Conclusion

AKI is increasingly being recognized as a negative prognostic factor in patients with COVID-19. Its high incidence (19.76%) and mortality rate (54.24%) mandated routine and standardized monitoring of the kidney function during hospitalization. Supportive measures, fluid management, and prevention of immune dysregulation are necessary to potentially improve outcomes in these patients. Effective use of KRT should be considered with evolving multiorgan failure, especially in patients with concomitant mechanical ventilation. Therapeutic options in COVID-19 patients with AKI require further exploration with randomized controlled trials. Improved awareness among health-care providers and proactive prevention and management of AKI are key to improve the high mortality observed in these patients.

Statement of Ethics

This review was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

J.A.N. has received consulting fees from Baxter Healthcare and Renibus Therapeutics.

Funding Sources

The authors did not receive any funding.

Author Contributions

R.R., Z.M., P.V., R.C., and J.N. contributed to the conception and design of the study. Z.M., P.V., K.M., A.T., and J.N. performed data and statistical analysis. All the authors wrote sections of the manuscript, contributed to manuscript revision, and read and approved the submitted version.

Appendix 1

Preferred reporting items for systematic reviews and meta-analyses checklist

Section and topic	No.	Checklist item	Inclusion (page #)
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria; participants and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	1, 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	1, 2
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., web address), and, if available, provide registration information including registration number	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	2
Data collection process	10	Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	2–5
Summary measures	13	State the principle summary measures (e.g., risk ratio, difference in means)	2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	2
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	2–5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified	N/A
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	2–5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, and follow-up period) and provide the citations	2–5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12)	2–5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	2–5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	2–5

Section and topic	No.	Checklist item	Inclusion (page #)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	2–5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16])	N/A
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health-care providers, users, and policy makers)	5–9
Limitations	25	Discuss limitations at the study and outcome level (e.g., risk of bias), and review level (e.g., incomplete retrieval of identified research, reporting bias)	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	9
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	9

Appendix 2

Database search strategy

Database	MEDLINE/PubMed
Date	05/19/2020
Strategy	1. Covid* OR Coronavirus OR Betacoronavirus 2. Kidney OR Renal OR Creatinine 3. "2019/11/01"[Date - Entry]: "2020/07/28"[Date – Entry] 4. #1 AND #2 AND #3 5. #4 Filters: humans, English

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