Acute kidney injury and kidney replacement therapy in COVID-19: a systematic review and meta-analysis

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ABSTRACT

Background. Acute kidney injury (AKI) can affect hospitalized patients with coronavirus disease 2019 (COVID-19), with estimates ranging between 0.5% and 40%. We performed a systematic review and meta-analysis of studies reporting incidence, mortality and risk factors for AKI in hospitalized COVID-19 patients.

Methods. We systematically searched 11 electronic databases until 29 May 2020 for studies in English reporting original data on AKI and kidney replacement therapy (KRT) in hospitalized COVID-19 patients. Incidences of AKI and KRT and risk ratios for mortality associated with AKI were pooled using generalized linear mixed and random-effects models. Potential risk factors for AKI were assessed using meta-regression. Incidences were stratified by geographic location and disease severity.

Results. A total of 3042 articles were identified, of which 142 studies were included, with 49,048 hospitalized COVID-19 patients including 5152 AKI events. The risk of bias of included studies was generally low. The pooled incidence of AKI was 28.6% [95% confidence interval (CI) 19.8–39.5] among hospitalized COVID-19 patients from the USA and Europe (20 studies) and 5.5% (95% CI 4.1–7.4) among patients from China (62 studies), whereas the pooled incidence of KRT was 7.7% (95% CI 5.1–11.4; 18 studies) and 2.2% (95% CI 1.5–3.3; 52 studies), respectively. Among patients admitted to the intensive care unit, the incidence of KRT was 20.6% (95% CI 15.7–26.7; 38 studies). Meta-regression analyses showed that age, male sex, cardiovascular disease, diabetes mellitus, hypertension and chronic kidney disease were associated with the occurrence of AKI; in itself, AKI was associated with an increased risk of mortality, with a pooled risk ratio of 4.6 (95% CI 3.3–6.5).

Conclusions. AKI and KRT are common events in hospitalized COVID-19 patients, with estimates varying across geographic locations. Additional studies are needed to better understand the underlying mechanisms and optimal treatment of AKI in these patients.

Keywords: acute kidney injury, COVID-19, kidney replacement therapy, meta-analysis, SARS-CoV-2
INTRODUCTION

Although coronavirus disease 2019 (COVID-19) primarily manifests as an acute pulmonary infection, multiple organs can be affected, including the kidney [1, 2]. Preliminary data suggest that acute kidney injury (AKI) and kidney abnormalities such as proteinuria and haematuria may be common among patients with COVID-19 [3-5]. This also became apparent in certain epicentres such as New York that faced a critical shortage of dialysis equipment due to the high incidence and severity of AKI caused by COVID-19 [6]. Furthermore, recent autopsy studies show direct pathological evidence of invasion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into kidney tissue as well as significant acute tubular injury and endothelial damage [7-9].

The estimated incidence of AKI and the need for kidney replacement therapy (KRT) among hospitalized COVID-19 patients varies between studies, ranging from 0.5% to as high as 40% [10, 11]. Two of the largest studies exemplify this wide variation: Guan et al. [10] reported an AKI incidence of only 0.5% in an analysis of 1099 hospitalized patients across China, while a recent analysis from New York reported an AKI incidence of 26.9% among 5700 hospitalized COVID-19 patients [12].

It is critical to provide an accurate estimation of the incidence of AKI and KRT in COVID-19 patients as well as exploration of differences in these estimations to improve treatment strategies, facilitate healthcare planning and gain pathophysiological insight into this novel disease. We therefore performed a systematic review and meta-analysis of studies reporting incidence, outcomes and risk factors for AKI in hospitalized COVID-19 patients. In addition, we determined the incidence of KRT in this population.

MATERIALS AND METHODS

This systematic review and meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines [13]. The protocol was not registered in any database of systematic reviews.

Literature search

According to the predetermined protocol, a systematic literature search of 11 databases (PubMed, PMC PubMed Central, WHO COVID-19 database, MEDLINE, Embase, Web of Science, Cochrane Library, Emcare, Academic Search Premier, ScienceDirect and Google Scholar) was performed from 1 December 2019 to 29 May 2020 in cooperation with a trained librarian. Keywords such as ‘AKI’, ‘KRT’ and ‘COVID-19’ were used. As AKI and KRT are often secondary outcome measures and may not always be mentioned in the title or abstract, we additionally included keywords such as ‘endpoint’, ‘outcome’ and ‘clinical characteristics’. The full search string and details of the search strategy are detailed in the Supplementary Material.

Study selection

Studies written in English with original data for at least 10 hospitalized patients with COVID-19 were eligible for inclusion. To be included, studies had to report data on the incidence of AKI or KRT and the majority of patients (>80%) had to be ≥18 years of age. Eligible study designs were cohort studies, case–control studies, case series and clinical trials. Cross-sectional studies, case reports, reviews without original data, preprints and reports for which no full text could be found were excluded. Two reviewers (E.L.F. and R.J.J.) independently screened titles and abstracts of all identified articles. Full-text screening of potential articles was thereafter performed independently by pairs of reviewers (composed from E.L.F., R.J.J., Y.d.J., V.v.d.E., J.M., E.v.d.W. and E.d.R.). Manual cross-referencing of included studies was performed. Discrepancies between the investigators were resolved through mutual discussion or, if necessary, by referring to the senior author (M.v.D.).

Data extraction and quality assessment

The same seven reviewers independently extracted relevant data using a custom-made, presdesigned data extraction form. Bibliographic details, eligibility criteria, details about the study population, study design, risk of bias and results were extracted. If necessary, authors of included studies were contacted for additional information. We assessed the risk of bias by focusing on study elements that could potentially bias the estimation of the incidence of AKI or KRT using a set of predefined questions [14]. A detailed explanation for these questions and the assessment of risk of bias is given in the Supplementary Methods.

Statistical analysis

The primary outcome of the meta-analysis was the incidence of AKI and KRT. As we anticipated clinical heterogeneity, incidences are presented stratified by geographic location with similar admission policies (China or South Korea versus the USA or Europe) [15–17]. Weighted incidences are also reported separately for hospitalized patients and patients admitted to the intensive care unit (ICU). Estimates for the ICU were not stratified by geographic location, as we hypothesized that patients admitted to the ICU would have similar disease severity. A generalized linear mixed model (random intercept logistic regression model) was used to pool incidences of AKI and KRT and the maximum likelihood was used to estimate the between-study variance [18]. This method has been recommended over the double arcsine transformation but does not provide individual study weights [19, 20]. A continuity correction was applied for studies with zero events. We used random-effects models since heterogeneity between included studies was expected even after stratification for geographic location and types of patients. Heterogeneity was visually assessed with forest plots and quantified by I². Potential small study bias was assessed using funnel plots and more formally with Egger’s test when sufficient studies were available (n = 10) [21]. It should be kept in mind that AKI was not the main outcome parameter of most included studies, which makes it unlikely that the incidence of AKI per se is a reason for not publishing the study [22].

For the association between AKI and subsequent mortality, we summarized relative risk estimates ([risk ratios or hazard ratios (HRs)] using random-effects models. Between-study variance was estimated using restricted maximum likelihood and we used a continuity correction for cells with zero counts. When studies did not report these measures but provided relevant numbers, we calculated crude risk ratios and their 95% confidence intervals (CIs). A continuity correction was applied for studies with a zero cell count, adding 0.5 to all cells.

In exploratory analyses, we investigated possible risk factors for AKI using random-effects meta-regression. Incidences were...
logit transformed, restricted maximum likelihood was used for calculating between-study variance and results were pooled using inverse variance weighting. Risk factors were prespecified and included age, sex, history of cardiovascular disease, diabetes mellitus, chronic kidney disease (CKD) and hypertension.

We performed a sensitivity analysis for the pooled incidence to test the robustness of our result, using a random-effects model with the inverse variance method and logit transformation instead of generalized linear mixed models. Second, we repeated our analyses but excluded studies for which there was suspected overlap of patients. This was predominantly the case for studies from China; reasons for exclusion are listed in the Supplementary data, Table S1. All data were analysed using R version 3.6.2 using the packages meta and metafor (R Foundation, Vienna, Austria) [23, 24].

Data availability
The data underlying this article will be shared on reasonable request to the corresponding author.

RESULTS
Search results
The literature search yielded 3042 potentially eligible publications after deduplication. Of these, 2442 were excluded after screening titles and abstracts. Full-text assessment was performed of the remaining 600 publications. Through cross-referencing, 24 additional studies were identified, of which 4 were included. A total of 142 studies [3, 4, 10, 11, 28–38, 42–44, 46–53, 55, 56, 58–77, 85, 87, 88, 90, 107–109, 112, 118–123, 132–135, 137–140, 142, 143, 146–148, 150–160], 27 studies were conducted in the USA [11, 12, 25, 27, 40, 57, 78, 81, 84, 94, 98–101, 103, 105, 111, 114, 116, 124, 129–131, 136, 141, 145, 149, 163], 23 studies reported data from Europe [26, 39, 45, 54, 80, 82, 83, 86, 89, 91–93, 95–97, 104, 110, 115, 125, 128, 144, 161, 162], 3 studies from South Korea [106, 113, 117], 1 study from Qatar [79], 1 study from Canada [126] and 3 studies reported data from multiple countries [41, 102, 127]. Sample size ranged from 10 to 7337 patients. Sample size was <300 patients in 117 studies and 7 studies (4 from China, 2 from the USA and 1 from South Korea) contained a sample size >1000 patients [10, 12, 34, 73, 105, 113, 159]. The majority of studies (85 studies) reported data on general hospitalized patients [3, 4, 10, 12, 28, 30–38, 40–42, 44, 46–50, 52, 53, 55, 56, 58–63, 65–67, 69–75, 77, 78, 80, 84, 85, 87, 88, 90–92, 97, 99–103, 105–107, 109, 110, 112, 113, 118, 119, 121, 123, 128, 129, 131, 132, 134–136, 138–140, 143, 147, 148, 153, 155, 157, 159], 32 studies solely included ICU patients [27, 39, 45, 54, 64, 68, 79, 81–83, 86, 94–96, 98, 104, 111, 115, 117, 120, 122, 124, 126, 130, 141, 149, 154, 158, 160–163] and 25 studies were on populations with specific characteristics, including 5 studies on kidney transplant patients and 3 studies on dialysis patients [11, 25, 26, 29, 43, 51, 57, 76, 89, 93, 108, 114, 116, 125, 127, 133, 137, 142, 144–146, 150–152, 156].

The reported mean or median age ranged from 30 to 85 years and 0–100% of participants were male (one study included pregnant women only and one study included only male heart failure patients). The median prevalence of prior cardiovascular disease was 12.7% (range 0–69), 25.8% for hypertension (range 6–100), 17.9% for diabetes (range 0–100) and 4% for CKD (range 0–100). The mean age and proportion of patients with

Study characteristics
A detailed overview of study characteristics is presented in the Supplementary data, Table S2. Most studies (84 studies) reported data on COVID-19 patients from China [3, 4, 10, 11, 28–38, 42–44, 46–53, 55, 56, 58–77, 85, 87, 88, 90, 107–109, 112, 118–123, 132–135, 137–140, 142, 143, 146–148, 150–160], 27 studies were conducted in the USA [11, 12, 25, 27, 40, 57, 78, 81, 84, 94, 98–101, 103, 105, 111, 114, 116, 124, 129–131, 136, 141, 145, 149, 163], 23 studies reported data from Europe [26, 39, 45, 54, 80, 82, 83, 86, 89, 91–93, 95–97, 104, 110, 115, 125, 128, 144, 161, 162], 3 studies from South Korea [106, 113, 117], 1 study from Qatar [79], 1 study from Canada [126] and 3 studies reported data from multiple countries [41, 102, 127]. Sample size ranged from 10 to 7337 patients. Sample size was <300 patients in 117 studies and 7 studies (4 from China, 2 from the USA and 1 from South Korea) contained a sample size >1000 patients [10, 12, 34, 73, 105, 113, 159]. The majority of studies (85 studies) reported data on general hospitalized patients [3, 4, 10, 12, 28, 30–38, 40–42, 44, 46–50, 52, 53, 55, 56, 58–63, 65–67, 69–75, 77, 78, 80, 84, 85, 87, 88, 90–92, 97, 99–103, 105–107, 109, 110, 112, 113, 118, 119, 121, 123, 128, 129, 131, 132, 134–136, 138–140, 143, 147, 148, 153, 155, 157, 159], 32 studies solely included ICU patients [27, 39, 45, 54, 64, 68, 79, 81–83, 86, 94–96, 98, 104, 111, 115, 117, 120, 122, 124, 126, 130, 141, 149, 154, 158, 160–163] and 25 studies were on populations with specific characteristics, including 5 studies on kidney transplant patients and 3 studies on dialysis patients [11, 25, 26, 29, 43, 51, 57, 76, 89, 93, 108, 114, 116, 125, 127, 133, 137, 142, 144–146, 150–152, 156].

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FIGURE 1: Incidence of AKI (%) among hospitalized COVID-19 patients stratified by geographic location.
FIGURE 1: (Continued)

[^1] Heterogeneity: $I^2 = 95\%$, $\chi^2 = 1.4097, p < 0.01$

| Study   | Events | Total | Incidence | 95% CI |
|---------|--------|-------|-----------|--------|
| Cai 2020a | 17     | 296   | 5.7       | 3.4; 9.0 |
| Cai 2020b | 8      | 417   | 1.9       | 0.8; 3.7 |
| Cao 2020a | 16     | 194   | 8.2       | 4.8; 13.0 |
| Cao 2020b | 20     | 102   | 19.6      | 12.4; 28.6 |
| Chen 2020a | 3      | 99    | 3.0       | 0.6; 8.6 |
| Chen 2020c | 29     | 274   | 10.6      | 7.2; 14.8 |
| Cheng 2020 | 36    | 701   | 5.1       | 3.6; 7.0 |
| Ding 2020 | 20     | 226   | 8.9       | 5.5; 13.4 |
| Guan 2020 | 6      | 1099  | 0.5       | 0.2; 1.2 |
| Guo 2020  | 18     | 187   | 9.6       | 5.8; 14.8 |
| He 2020   | 1      | 24    | 4.2       | 0.1; 21.1 |
| Huang 2020 | 3   | 41    | 7.3       | 1.5; 19.9 |
| Lei 2020  | 0      | 20    | 0.0       | 0.0; 16.8 |
| Li 2020a  | 95     | 548   | 17.3      | 14.3; 20.8 |
| Li 2020a  | 13     | 788   | 1.6       | 0.9; 2.8 |
| Liu 2020a | 0      | 10    | 0.0       | 0.0; 30.8 |
| Liu 2020b | 10     | 56    | 17.9      | 8.9; 30.4 |
| Liu 2020c | 1      | 13    | 7.7       | 0.2; 36.0 |
| Liu 2020d | 1      | 12    | 16.7      | 2.1; 48.4 |
| Wang 2020a | 14  | 107   | 13.1      | 7.3; 21.0 |
| Ruan 2020 | 23     | 150   | 15.3      | 10.0; 22.1 |
| Shi 2020a | 8      | 416   | 1.9       | 0.8; 3.8 |
| Tang 2020a | 13   | 73    | 17.6      | 9.8; 28.5 |
| Tu 2020   | 7      | 174   | 15.5      | 10.6; 21.8 |
| Wan 2020  | 5      | 135   | 3.7       | 1.2; 8.4 |
| Wang 2020b | 5     | 138   | 3.6       | 1.2; 8.3 |
| Wang 2020c | 27    | 332   | 8.1       | 5.4; 11.6 |
| Wang 2020d | 0     | 111   | 0.0       | 0.0; 3.3 |
| Yang 2020a | 11    | 91    | 12.1      | 6.2; 20.6 |
| Yang 2020b | 0     | 149   | 0.0       | 0.0; 2.4 |
| Yao 2020  | 16     | 108   | 14.8      | 8.7; 22.9 |
| Zhang 2020a | 10  | 221   | 4.5       | 2.2; 8.2 |
| Zhang 2020b | 68    | 663   | 10.3      | 8.1; 12.8 |
| Zhang 2020c | 28    | 290   | 9.7       | 6.5; 13.7 |
| Zhang 2020e | 2    | 643   | 0.3       | 0.0; 1.1 |
| Zhou 2020 | 28     | 191   | 14.7      | 10.0; 20.5 |
| Zou 2020a | 6      | 10    | 60.0      | 26.2; 87.8 |
| Wu 2020a | 9      | 198   | 4.5       | 2.1; 8.5 |
| Chen 2020d | 2      | 21    | 9.5       | 1.2; 30.4 |
| Chu 2020  | 0      | 149   | 0.0       | 0.0; 2.4 |
| Hong 2020 | 9      | 98    | 9.2       | 4.3; 16.7 |
| Hou 2020  | 12     | 101   | 11.9      | 6.3; 19.8 |
| Hu 2020b | 17     | 323   | 5.3       | 3.1; 8.3 |
| Li 2020b  | 6      | 27    | 22.2      | 8.6; 42.3 |
| Liao 2020 | 2      | 32    | 6.2       | 0.8; 20.8 |
| Ma 2020   | 25     | 93    | 30.1      | 21.0; 40.8 |
| Pei 2020  | 11     | 70    | 13.9      | 7.2; 23.5 |
| Qi 2020a  | 1      | 147   | 0.7       | 0.0; 3.7 |
| Qi 2020b  | 1      | 21    | 4.8       | 0.1; 23.8 |
| Qiu 200    | 2      | 104   | 1.9       | 0.2; 6.8 |
| Ren 2020  | 11     | 150   | 7.3       | 3.7; 12.7 |
| Shi 2020b | 19     | 153   | 12.4      | 7.6; 17.9 |
| Tan 2020a | 6      | 100   | 6.0       | 2.2; 12.6 |
| Tang 2020b | 1     | 150   | 0.7       | 0.0; 3.7 |
| Wang 2020f | 14    | 107   | 13.1      | 7.3; 21.0 |
| Wang 2020g | 1     | 156   | 0.6       | 0.0; 3.6 |
| Wang 2020h | 236   | 0.4    | 0.0; 2.3 |
| Yang 2020d | 4     | 52    | 7.7       | 2.1; 18.5 |
| Yang 2020e | 24    | 200   | 12.0      | 7.8; 17.3 |
| Zhang 2020f | 23   | 143   | 16.1      | 10.5; 23.1 |
| Zhao 2020 | 5      | 91    | 5.5       | 1.8; 12.4 |
| Zhu 2020b | 86     | 7337  | 1.2       | 0.9; 1.4 |
hypertension and diabetes tended to be higher in studies from the USA and Europe compared with those from Asia (Supplementary data, Figure S2).

Laboratory characteristics at hospital admission are reported in the Supplementary data, Table S3. Thirteen studies reported eGFR [3, 26, 63, 64, 66, 92, 102, 105, 107, 112, 137, 138, 140]. Reported mean serum creatinine varied from 0.54 to 11.8 (haemodialysis population) mg/dL. Seven studies reported data about haematuria and proteinuria [3, 4, 35, 47, 94, 105, 140]. The prevalence of proteinuria ranged from 31.2 to 87% and the prevalence of haematuria between 26.7 and 51%.

Incidence of AKI and KRT

Among studies from Asia, the pooled incidence of AKI was 5.5% (95% CI 4.1–7.4, $I^2 = 94%$, 62 studies, N = 19,378, 884 AKI events; Figure 1). For studies from the USA and Europe, the pooled incidence of AKI was 28.6% (95% CI 19.8–39.5, $I^2 = 97%$, 20 studies, N = 8061, 2545 AKI events).

Among studies from China, the pooled incidence of KRT was 2.2% (95% CI 1.5–3.3, $I^2 = 92%$, 52 studies, N = 24,135, 426 KRT events; Figure 2). For the USA and Europe, the pooled incidence was 7.7% (95% CI 5.1–11.4, $I^2 = 80%$, 18 studies, N = 7335, 426 KRT events).

Five studies reported data from kidney transplant patients [11, 25, 26, 76, 144], reporting an incidence of AKI between 30 and 69% and an incidence of KRT between 0 and 21%. Among patients admitted to the ICU, the pooled incidence of AKI was 29.2% (95% CI 20.1–40.3, $I^2 = 97%$, 23 studies, N = 4330, 1701 AKI events; Figure 3). The pooled incidence of KRT was 20.6% (95% CI 15.7–26.7, $I^2 = 90%$, 38 studies, N = 3001, 539 KRT events; Figure 4).

Risk factors for AKI

Meta-regression demonstrated that studies including subjects with higher age, a higher percentage of males, cardiovascular disease, diabetes or hypertension tended to have a greater incidence of AKI (Supplementary data, Figure S3, Table 1). The associated odds ratios (ORs) for AKI incidence were 2.15 (95% CI 1.54–3.00) per mean/median 10-year increase in age, 1.36 (95% CI 1.07–1.73) per 10% increase in male sex proportion, 1.53 (95% CI 1.13–2.08) per 10% increase in cardiovascular disease, 1.48 (95% CI 1.24–1.77) per 10% increase in diabetes, 1.64 (95% CI 1.40–1.93) per 10% increase in CKD and 1.50 (95% CI 1.33–1.69) per 10% increase in hypertension.

Association between AKI and mortality

We identified 21 studies that reported mortality for AKI for which crude risk ratios could be calculated [4, 11, 31, 35, 36, 53, 55, 59, 64, 68, 69, 71, 75, 96, 105, 123, 128, 133, 137, 146, 160]. In addition, two studies reported adjusted effect estimates for the association between AKI and mortality. Cheng et al. [3] found that, compared with no AKI, patients with Stage 1 AKI had an HR of 1.9 (95% CI 0.8–4.8), those with Stage 2 AKI had an HR of 3.5 (95% CI 1.5–8.3) and those with Stage 3 AKI had an HR of 4.7 (95% CI 2.6–8.8), with a pooled HR of AKI versus no AKI of 3.5 (95% CI 2.3–5.5, own calculations). Wang et al. [62] reported outcomes for 339 patients with COVID-19 admitted to hospital in Wuhan. After adjustment for age the HR for AKI was 1.2 (95% CI 0.6–2.4). The pooled risk ratio for mortality associated with AKI was 4.6 (95% CI 3.3–6.5, $I^2 = 90%$, 23 studies) (Supplementary data, Figure S4).

Sensitivity analyses

Inverse variance weighting with a logit transformation gave slightly higher estimates (~0.5%) of AKI and KRT incidence compared with generalized linear mixed models (Supplementary data, Figure S5). When studies with potential overlap in patients were excluded, a similar incidence of AKI and KRT to the main analysis was observed (Supplementary data, Figure S6).

FIGURE 2: Incidence of KRT (%) among hospitalized COVID-19 patients stratified by geographic location.
| Study         | Events | Total | Incidence | 95% CI |
|--------------|--------|-------|-----------|--------|
| Cai 2020a    | 4      | 298   | 1.3       | [0.4; 3.4] |
| Cao 2020a    | 9      | 199   | 4.5       | [2.1; 8.4] |
| Cao 2020b    | 6      | 102   | 5.9       | [2.2; 12.4] |
| Chen 2020a   | 9      | 99    | 9.1       | [4.2; 16.6] |
| Chen 2020b   | 17     | 937   | 1.8       | [1.1; 2.9] |
| Chen 2020c   | 3      | 274   | 1.1       | [0.2; 3.2] |
| Du 2020a     | 12     | 109   | 11.0      | [5.8; 18.4] |
| Du 2020b     | 8      | 85    | 9.4       | [4.2; 17.7] |
| Guan 2020    | 9      | 1099  | 0.8       | [0.4; 1.5] |
| Huang 2020   | 3      | 41    | 7.3       | [1.5; 19.8] |
| Lei 2020     | 0      | 20    | 0.0       | [0.0; 6.8] |
| Li 2020a     | 2      | 548   | 0.4       | [0.0; 1.3] |
| Lian 2020a   | 0      | 788   | 0.0       | [0.0; 0.5] |
| Liu 202b     | 5      | 56    | 8.9       | [3.0; 19.6] |
| Wang 2020a   | 4      | 107   | 3.7       | [1.0; 9.3] |
| Ruan 2020    | 5      | 150   | 3.3       | [1.1; 7.6] |
| Shi 2020a    | 2      | 416   | 0.5       | [0.1; 1.7] |
| Tu 2020      | 8      | 174   | 4.6       | [2.0; 9.5] |
| Wan 2020     | 5      | 135   | 3.7       | [1.2; 8.4] |
| Wang 2020b   | 2      | 138   | 1.4       | [0.2; 5.1] |
| Yao 2020     | 1      | 108   | 0.9       | [0.0; 5.1] |
| Zhang 2020a  | 5      | 221   | 2.3       | [0.7; 5.2] |
| Zhang 2020d  | 15     | 3430  | 0.4       | [0.2; 0.7] |
| Zhang 2020e  | 0      | 645   | 0.0       | [0.0; 0.6] |
| Zhou 2020    | 10     | 191   | 5.2       | [2.5; 9.4] |
| Wu 2020b     | 1      | 80    | 1.2       | [0.0; 6.8] |
| Cao 2020c    | 2      | 41    | 4.9       | [0.6; 16.5] |
| Chen 2020e   | 3      | 51    | 5.9       | [1.2; 16.2] |
| Cui 2020     | 1      | 20    | 5.0       | [0.1; 24.9] |
| Hong 2020    | 3      | 98    | 3.1       | [0.6; 8.7] |
| Hou 2020     | 5      | 101   | 5.0       | [1.6; 11.2] |
| Hu 2020a     | 4      | 884   | 0.5       | [0.1; 1.2] |
| Hu 2020b     | 72     | 323   | 22.3      | [7.9; 57.2] |
| Jin 2020     | 3      | 45    | 6.7       | [1.4; 18.3] |
| Jung 2020    | 13     | 1954  | 0.7       | [0.4; 1.1] |
| Lian 202b    | 0      | 465   | 0.0       | [0.0; 0.8] |
| Pei 2020     | 6      | 198   | 3.0       | [1.1; 8.5] |
| Qi 2020b     | 0      | 22    | 9.5       | [1.2; 30.4] |
| Ren 2020     | 4      | 150   | 2.7       | [0.7; 8.7] |
| Shi 2020b    | 3      | 153   | 2.0       | [0.4; 5.6] |
| Shi 2020c    | 4      | 671   | 0.6       | [0.2; 1.5] |
| Su 2020      | 3      | 116   | 2.6       | [0.5; 7.4] |
| Sun 2020b    | 1      | 32    | 3.1       | [0.1; 16.2] |
| Tan 2020     | 6      | 100   | 6.0       | [2.2; 12.6] |
| Wang 2020h   | 6      | 236   | 2.5       | [0.9; 5.5] |
| Wu 2020c     | 17     | 49    | 34.7      | [21.7; 56.1] |
| Xiong 2020   | 36     | 131   | 27.5      | [20.0; 36.0] |
| Yang 2002d   | 1      | 52    | 1.9       | [0.0; 10.3] |
| Yang 200e    | 2      | 200   | 1.0       | [0.1; 3.6] |
| Zhang 2020g  | 2      | 166   | 1.2       | [0.1; 4.3] |
| Zhao 2020    | 3      | 91    | 3.3       | [0.7; 9.3] |
| Zhu 2020b    | 57     | 7337  | 0.8       | [0.6; 1.0] |

Random effects model | 24135
Heterogeneity: $I^2 = 92\%$, $t^2 = 1.7259$, $p < 0.01$

Incidence KRT

2.2 [1.5; 3.3]

**FIGURE 2:** (Continued)

**Risk of bias**

The risk of bias assessment is presented in the Supplementary data, Tables S4–S5 and Supplementary data, Figure S7. Most studies (82%) included solely laboratory-confirmed SARS-CoV-2 patients who were diagnosed with positive reverse transcription polymerase chain reaction nasal or oropharyngeal swab. The majority of studies had a loss to follow-up <20% (96%) and sampled consecutive hospitalized patients (75%). Fifty-four percent of studies used the Kidney Disease: Improving Global Outcomes (KDIGO) definition for assessment...
of AKI. A definitive outcome (death or hospital discharge) in >80% of patients occurred in 39% of studies, as most initial studies on COVID-19 only had a short follow-up. In addition, 15% of studies presented results only for the subsample with a definitive outcome and excluded patients that were still in hospital. Overall, 81% of studies reporting AKI (for which all risk of bias questions could be answered) scored ≥5 points and were judged to be at low risk of bias. Of the studies reporting only KRT (for which five of the seven questions could be answered), 80% scored ≥3.5 points.

Publication bias
Funnel plots and Egger’s test for the incidence of AKI provided some evidence that in smaller studies the incidence estimates were slightly lower (Supplementary data, Figure S8). No firm evidence for small sample bias was present for KRT incidence and the association between AKI and mortality.

DISCUSSION
To our knowledge, this is the most comprehensive systematic review and meta-analysis of studies conducted to date focusing on kidney involvement in patients infected with SARS-CoV-2. We found that the incidence of AKI and KRT was high among hospitalized patients with COVID-19 and varied considerably according to geographic location. In addition, mortality risk was higher in COVID-19 patients with AKI and exploratory analyses suggested that higher age, the presence of diabetes and hypertension may increase the risk of AKI.

An important observation from our systematic review is that the incidence of AKI varies considerably according to geographic location, a finding that was noted earlier [164]. Among studies from Asia, we found a pooled incidence of AKI of 5.5% compared with 28.6% among studies from the USA and Europe. This may be caused by differences in guideline recommendations regarding hospital admission and hence differing patient populations [15–17]. For example, Chinese guidelines by the National Health Commission state that all ‘suspected and confirmed cases should be isolated and treated in designated hospitals with effective isolation and protection conditions’ [16]. Other countries, such as the USA and The Netherlands, only admit symptomatic patients with moderate to severe illness [15, 17]. Indeed, patients admitted for COVID-19 from the USA and Europe tended to be older and have more comorbidities compared with patients from China. We similarly observed differences in KRT incidence according to geographic location among hospitalized patients. The incidence of KRT was ~20.6% among patients admitted to the ICU, which is somewhat higher than the 17.4% incidence reported by the Intensive Care National Audit & Research Centre among 8250 critically ill patients across ICUs in England, Wales and Northern Ireland [165]. In addition, we included five studies on kidney transplant patients [11, 25, 26] that reported AKI incidences between 30 and 69%, indicating that certain groups may be especially vulnerable for adverse kidney outcomes.

To date, studies specifically investigating risk factors and outcomes associated with AKI are limited. We found that patients who developed AKI had a strongly increased risk for mortality, with a pooled risk ratio of 4.6. However, these findings should be regarded as hypothesis-generating since most studies only provided crude numbers and our estimates were not adjusted for confounding. The recent study by Hirsch et al. [164], which studied 5449 individuals admitted to hospitals across New York and was included in our meta-analysis, found that 35% of patients who developed AKI died. A recent preprint shows an adjusted OR for mortality of 9.6 [5]. These findings underline that AKI portends a poor prognosis. In meta-regression
analyses, we found that age, male sex and history of cardiovascular disease, diabetes, hypertension and CKD were significantly associated with a higher incidence of AKI. These findings are consistent with studies investigating risk factors for COVID-19-related mortality [35, 75, 166]. Future studies should confirm our observations.

Studies included in our review [3, 35] indicate that up to 60% of patients present with haematuria and proteinuria. A recent study showed that 75% of patients admitted to hospital had kidney abnormalities, with either haematuria (42%), proteinuria (66%) or AKI (5%) [4]. There are several plausible mechanisms for the kidney involvement in COVID-19 [2]. Recent autopsy reports showed evidence of SARS-CoV-2 nucleocapsid proteins in kidney tubules, including significant acute tubular injury, endothelial damage, pigment casts related to rhabdomyolysis and inflammation [7–9]. The limited studies to date suggest acute

### Table 1. ORs for the association between risk factors and AKI incidence in meta-regression analyses

| Study level variables | Studies included, n | OR (95% CI) per 10 years or 10% increase | P-value | \( I^2 \) (%) | \( R^2 \) (%) |
|----------------------|---------------------|------------------------------------------|---------|-------------|-------------|
| Age (years)          | 83                  | 2.15 (1.54–3.00)                         | <0.001  | 96.16       | 22.71       |
| Male (%)             | 83                  | 1.36 (1.07–1.73)                         | 0.01    | 96.48       | 7.04        |
| Cardiovascular disease (%) | 64              | 1.53 (1.13–2.08)                         | 0.01    | 97.14       | 11.48       |
| Diabetes (%)         | 72                  | 1.48 (1.24–1.77)                         | <0.001  | 95.85       | 22.87       |
| CKD (%)              | 46                  | 1.64 (1.40–1.93)                         | <0.001  | 92.85       | 49.21       |
| Hypertension (%)     | 72                  | 1.50 (1.33–1.69)                         | <0.001  | 94.49       | 43.64       |

ORs are interpreted as the OR associated with a 10-year or 10% increase in the prevalence of the risk factor. \( I^2 \) is the amount of heterogeneity present. \( R^2 \) is interpreted as the amount of heterogeneity explained by the risk factor.

FIGURE 4: Incidence of KRT (%) among COVID-19 patients admitted to the ICU.
tubular necrosis as the major cause of AKI, although cytokine storm, a prothrombotic state, organ crosstalk between lungs and kidneys and rhabdomyolysis may also contribute to the development of AKI [2, 4, 163].

To our knowledge, this is the most comprehensive overview of AKI and KRT among hospitalized COVID-19 patients to date. The strengths of this systematic review include the large number of studies included that allowed for precise estimation of incidences and the rich diversity of the populations included. Our results can be used to support decision-making and workforce planning. In addition, the systematic overview of all published studies allowed the discernment of patterns of geographic variability in AKI incidence that were previously not well understood. Our study has some limitations. First, most studies had only a short follow-up and in less than half of studies >80% of patients were discharged or had died. This could potentially underestimate the incidence of AKI since patients in hospital can still develop AKI. Second, our estimates for risk factors and outcomes associated with AKI were not adjusted for confounders. These findings should therefore be considered as hypothesis-generating. Third, we did not include non-English publications. Fourth, the definition of AKI was unclear in 31% of studies. When contacting the authors of studies that did not report the definition of AKI, the majority acknowledged that KDIGO criteria were used. For the remaining studies, only the most severe cases could have been reported, leading to an underestimate of AKI incidence. We therefore urge researchers to report definitions according to KDIGO criteria. Lastly, it is possible that some studies from China included overlapping patients. However, our sensitivity analysis excluding all studies with suspicion of potential overlap showed very similar estimates to our main analyses.

In conclusion, AKI and KRT are common among individuals hospitalized for COVID-19 and are associated with a poor prognosis. Future studies need to further elucidate the long-term outcomes of COVID-19-associated AKI.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

ACKNOWLEDGEMENTS

The authors would like to thank Jan Schoones, biomedical information specialist of the Walaeus Library, Leiden University Medical Center, for his assistance with the systematic literature search.

AUTHORS’ CONTRIBUTIONS

E.L.F., O.M.D., J.I.R. and M.v.D. contributed to the research idea and study design. E.L.F., R.J.J., Y.d.J., V.v.d.E., J.M., E.v.d.W. and E.d.R. contributed to data acquisition. E.L.F., O.M.D., J.I.R. and M.v.D. contributed to data analysis/interpretation. E.L.F. performed statistical analysis. M.v.D. provided supervision and mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest related to this work.

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