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A Systematic Review and Meta-Analysis Of Outcomes for Patients with COVID-19 and Acute Kidney Injury

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PII: S2468-0249(20)31336-X
DOI: https://doi.org/10.1016/j.ekir.2020.06.013
Reference: EKIR 1018

To appear in: Kidney International Reports

Received Date: 12 June 2020
Accepted Date: 17 June 2020

Please cite this article as: Robbins-Juarez SY, Qian L, King KL, Stevens JS, Husain SA, Radhakrishnan J, Mohan S, A Systematic Review and Meta-Analysis Of Outcomes for Patients with COVID-19 and Acute Kidney Injury Kidney International Reports (2020), doi: https://doi.org/10.1016/j.ekir.2020.06.013.

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Conclusions:

Kidney dysfunction is common among patients with COVID-19, and patients who develop AKI have inferior outcomes. Additional research into management and potential mechanism of this association is needed.
A Systematic Review and Meta-Analysis

Of Outcomes for Patients with COVID-19 and Acute Kidney Injury

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Word count abstract: 250

Word count text: 2620

Running Headline: COVID-19 Kidney
Abstract:

Introduction: There is limited data on the association of kidney dysfunction with prognosis in COVID-19, and the extent to which acute kidney injury (AKI) predisposes patients to severe illness and inferior outcomes is unclear. We aim to assess the incidence of AKI among patients with COVID-19 and examine their associations with patient outcomes as reported in the available literature thus far.

Methods: We systematically searched MEDLINE, EMBASE, SCOPUS, and MedRxiv databases for full-text articles available in English published from December 1, 2019 to May 24, 2020. Clinical information was extracted and examined from 20 cohorts that met inclusion criteria, covering 13137 mostly hospitalized patients confirmed to have COVID-19. Two authors independently extracted study characteristics, results, outcomes, study-level risk of bias, and strength of evidence across studies. Neither reviewer was blind to journal titles, study authors, or institutions.

Results: Median age was 56 years, with 55% male patients. Approximately 43% of patients had severe COVID-19 infection, and approximately 11% died. Prevalence of AKI was 17%; 77% of patients with AKI experienced severe COVID-19 infection, and 52% died. AKI was associated with increased odds of death among COVID-19 patients (pooled odds ratio 15.27, 95% CI 4.82-48.36), although there was considerable heterogeneity across studies and among different regions in the world. Approximately 5% of all patients required use of renal replacement therapy (RRT).

Conclusions: Kidney dysfunction is common among patients with COVID-19, and patients who develop AKI have inferior outcomes. Additional research into management and potential mechanisms of this association is needed.
Key words: COVID-19, acute kidney injury, renal replacement therapy, mortality, systematic review, meta-analysis
Introduction:

Following the emergence of a cluster of infections causing respiratory failure in Wuhan, Hubei Province, China in December 2019, researchers identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the causative pathogen for the respiratory disease later named COVID-19 by the World Health Organization.\textsuperscript{1} Morbidity and mortality from COVID-19 have been primarily attributed to respiratory failure and acute respiratory distress syndrome (ARDS), often in the setting of multi-organ failure.\textsuperscript{2,3,4}

The incidence of acute kidney injury and impact on the patient outcomes with COVID-19 remains unclear but is of particular interest given the need to plan for deploying limited renal replacement therapy options in an acute clinical setting and questions about prognosis. Reports from previous outbreaks of SARS and MERS-CoV described notable rates of acute renal failure, ranging from 5-15\% of total cases and utilization of continuous renal replacement therapy (CRRT) for 5-58\% of critically ill patients.\textsuperscript{5,6,7,8} The extent to which pre-existing chronic kidney disease (CKD), including end-stage kidney disease (ESKD), or the development of acute kidney injury (AKI), are associated with severe COVID-19 and inferior outcomes is not clear either given their association with relative immune dysregulation and exaggerated inflammatory responses.\textsuperscript{9} Acute kidney injury can lead to impaired acid-base, fluid, and electrolyte homeostasis, all of which may contribute to worse outcomes for patients with COVID-19. Given the high prevalence of kidney disease in the United States, which currently has more cases of COVID-19 than any other nation, an improved understanding of the associated risks as well as the need for the resources and the impact on outcomes are needed to inform clinical management and resource planning during the pandemic. Given the relative paucity of reports focused on
kidney-related outcomes, in this systematic review we assess the incidence of AKI among
patients with COVID-19 and examine their associations with patient outcomes as reported in the
available literature thus far.

**Methods:**

*Data Source and Searches*

The review was conducted in accordance with the Preferred Reporting Items for Systematic
Reviews and Meta-Analyses (PRISMA) statement (Supplemental Figure 1). Literature for this
review was identified by searching MEDLINE, SCOPUS, EMBASE, and medRxiv databases.
The following search terms were used: (“COVID” OR "SARS-COV-2") AND (“outcomes” OR
“clinical features” OR “clinical characteristics”) AND (“acute kidney injury" OR "acute renal
injury" OR "acute kidney failure" OR "acute renal failure" OR "chronic kidney disease" OR
"chronic renal disease" OR "chronic kidney insufficiency" OR "chronic renal insufficiency").
The search was limited to original research published between December 1, 2019 and May 24,
2020 with full text available in English.

*Study Selection*

Articles were initially screened by title and abstract to assess for relevance; those with
specialized populations such as pediatric, pregnant, transplant, ESKD, or cancer patients were
excluded, as were reviews, case reports, cross-sectional studies, and randomized controlled trials
for drug therapies. The full texts of the remaining studies were then assessed for the following
inclusion criteria: retrospective and prospective cohort studies and case series with more than 20
patients, with extractable quantitative data on patient demographics, as well as data on acute
kidney injury (AKI), chronic kidney disease (CKD), interventions used, and outcomes. We stringently excluded all studies that did not specify use of the Kidney Disease Improving Global Outcomes (KDIGO) criteria to define AKI. When multiple studies were published from the same institution with data from similar time periods with likely overlapping cohorts, we selected one study for inclusion in the meta-analysis, based on the following criteria in order of priority: the most general population, most detailed extractable kidney-related data, and largest number of patients included. Two authors independently screened all retrieved studies and assessed full text articles for inclusion; disagreements were resolved through consensus. Neither reviewer was blind to journal titles, study authors, or institutions.

**Data Extraction and Quality Assessment**

Clinical information including cohort demographics and prevalence of comorbidities including CKD were extracted. Similarly, information on all kidney related complications and outcomes including incidence of AKI, need for renal replacement therapy (RRT), and mortality, were identified and extracted. The primary outcomes of interest were mortality and severe illness, each modeled as a binary outcome. Definitions of severe COVID-19 infection were inconsistent across studies, with European and U.S. studies using admission to an intensive care unit (ICU) to stratify patients, while most studies from China used the National Health Commission of the People’s Republic of China (NHC of PRC) Clinical Severity Definitions. We defined “severe illness” as either admitted to an ICU or categorized as severe or critical based on the NHC of PRC criteria. The quality of individual studies was assessed based on the National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool for Case Series Studies.
(Supplementary Table 1). Small-study effects and publication bias were assessed visually using a random-effects model funnel plot (Supplementary Figure 3).

Data Synthesis and Analysis

Medians, interquartile ranges, and overall ranges were calculated for continuous demographic and clinical variables from all reported study-level values among the 20 studies meeting inclusion criteria. Random-effects meta-analyses were performed to obtain pooled prevalence, pooled odds ratio estimates, and 95% confidence intervals for categorical variables as well as for severe illness and mortality outcomes using the meta and metaprop commands. After the initial analysis, heterogeneity in mortality outcomes was investigated by excluding cohorts with particularly high mortality, as well as by conducting stratified analyses. We stratified studies based on pre-print versus peer-reviewed status, geographic location (Europe, Asia, or United States), and illness severity (<50% or ≥50% of the cohort severely ill). All analyses were performed using Stata 16 (College Station, TX), and an alpha of 0.05 determined statistical significance.

Results

We screened a total of 512 articles, of which 59 full-text articles were assessed for eligibility and 30 met our inclusion criteria (Figure 1). The included studies encompassed 21,591 patients from hospitals in Asia, Europe, and the United States, and took place in a time period spanning from Dec 11, 2019 through May 24, 2020. All studies included only hospitalized patients except for Guan, et. al, which included both outpatients and inpatients. Four studies were limited to patients admitted to the ICU only. Five studies included only deceased
and/or discharged patients. After accounting for potential overlapping patient cohorts in these smaller studies, we identified 20 unique cohorts encompassing 13,137 patients with available kidney disease related information. Of these 20 cohorts included in the statistical analysis, 13 were from China, 1 was from Korea, 3 were from the U.S., and 3 were from Europe. The quality of peer-reviewed studies and pre-print studies were similar (Supplemental Table 1).

Across the 20 cohorts, the median age was 56 years (range 43 to 72 years) with 55% male patients (Table 1). Forty-three percent (range 13.3-100%) of patients either required an ICU admission or were reported to have severe infection, and 11% (range 0-52.4%) of patients died. Only 5% (range 0.6-57.1%) of all patients were reported to have evidence of CKD at baseline; however, one ICU cohort from the United States reported a CKD prevalence of 57.1%. The prevalence of diabetes was 17% (range 6-33.3%) and the prevalence of hypertension was 33% (range 11.5-64.7%). Only one study, Pei et al, reported presence of proteinuria (43.9%) or hematuria (26.7%) on admission. Four studies reported the prevalence of use of renin-angiotensin-aldosterone-system (RAAS) inhibition prior to admission (24%, range 11.5-32%).

The prevalence of AKI across the 20 cohorts was 17% with a range of 0.5 to 80.3% (Table 2). Six studies provided a breakdown of the severity of AKI using KDIGO staging (15% stage 1, 7% stage 2, 11% stage 3), with Xiao et al not differentiating between stage 2 and stage 3 (data was only used for stage 1). Approximately 77% (range 39.3-100%) of patients with AKI either had evidence of severe infection or needed ICU level of care according to the 14
studies that reported on the association of AKI and severity of illness. Among the 8 studies that reported use of RRT for any indication, 5% (range 0.8-14.7%) of total patients required RRT.

Nine studies provided enough details in their reported outcomes to determine the association of AKI with subsequent mortality (Figure 2). The mortality rate of patients with AKI was 52% (range 7-100%). Across the 9 studies, AKI was associated with significantly higher mortality among COVID-19 patients, with a pooled odds ratio of 15.27 (95% CI 4.82 – 48.36) compared to patients without AKI. A sensitivity analysis that excluded data from three cohorts with particularly high mortality (among 64 patients with AKI from the Pei et al, Wang et al, and Zhou et al cohorts, only 4 survived) showed a higher mortality associated with AKI albeit with a lower OR of 6.20 (95% CI 3.63-10.59). Heterogeneity was high across studies ($I^2$ 97.9%), although lower after stratifying based on the proportion of severely ill patients (Figure 3). Cohorts with $\geq$50% severely or critically ill patients had a higher pooled OR (14.18, 95% CI 1.91-105.44) with more heterogeneity ($I^2$ 87.7%), compared to cohorts with <50% severely or critically ill patients (pOR 9.66, 95% CI 8.23-11.34, $I^2$ 31.4%). Heterogeneity was also reduced after stratifying studies by region (Figure 2). Studies conducted in China had very high heterogeneity ($I^2$ 89.7%), compared to those from Europe or from the U.S. ($I^2$ of 0% and 31.4%, respectively). Studies from China had a high pooled OR (39.0, 95% CI 5.34-284.97) and heterogeneity ($I^2$ 89.7%), whereas those from Europe (3.56, 95% CI 2.19-5.8, with $I^2$ 0.0%) or the U.S. (9.66, 95% CI 8.23-11.34, with $I^2$ 31.4%) were considerably lower. Subgroup analysis conducted using only pre-printed studies found a similar OR of 6.62 (95% CI 3.33-13.15) with less heterogeneity compared to peer-reviewed studies only ($I^2$ 77.4% versus 93.8%; Figure 4). Figure 5 shows a funnel plot including all 9 studies used to calculate the OR of death among patients with AKI.
Discussion:

Across 20 cohorts encompassing 13,137 patients with confirmed COVID-19 infection from Asia, Europe, and the United States, we identified a wide range of AKI prevalence and associated mortality. AKI prevalence was 17%, but ranged from 0.5 to 80.3%, perhaps reflecting varied disease severity thresholds for hospitalization across the globe as well as potential differences in clinical practices in monitoring for renal dysfunction. Nine cohorts reported data on mortality and AKI, with a pooled odds ratio of 15.27 (95% CI 4.82 – 48.36) for death compared to those without AKI. Although heterogeneity across all studies was extremely high, it was reduced after excluding cohorts with particularly high mortality, and the association between patient mortality and AKI persists even after elimination of these studies. While the development of AKI among patients with COVID-19 portended a worse prognosis across all the cohorts, the extent to which this represented an increased risk for mortality was somewhat variable. This variability may result from differences in the severity of the AKI observed as well as differences in the availability of RRT resources for those with the most severe forms of AKI.

Differences in COVID-19 disease severity likely also contribute to the observed heterogeneity. We found a stronger association between AKI and death among cohorts reporting a higher proportion of severely ill patients, suggesting that AKI may have a more pronounced adverse effect for patients with more severe pulmonary disease, as opposed to patients who are not critically ill. However, it is worth noting that what defines “severe” disease varied across the studies, with most studies from China classifying severity by the NHC of PRC Clinical Severity Definitions 7th Edition, while others used the American Thoracic Society Guidelines for
Community-Acquired Pneumonia definitions, or ICU admission itself, and some studies did not specify what “severe” meant. Such inconsistent definitions of “severe” disease likely contributed to the high heterogeneity that persisted in the subgroup of cohorts with ≥50% severe or critical patients. The absence of adequately granular details on several aspects of the AKI that patients experienced including information on severity, treatment choices as well as temporal relationship to pulmonary disease limited our ability to draw further conclusions about the prognostic implication of varying degrees of AKI.

We also observed a substantial need for RRT among hospitalized patients with COVID-19. Among the 8 cohorts that reported use of RRT, 5% of all patients required RRT. However, it is unclear from these studies whether RRT was used to treat AKI alone, or for other indications such as volume overload or ESKD, as demonstrated by in the Guan et al. study where the number of patients who needed RRT exceeded the combined number of patients with CKD or AKI. Additionally, it is unclear how utilization rates for RRT were influenced by local resource availability or local clinical practices such as the thresholds at which RRT is initiated (or not) for patients with AKI. The high proportion of patients with AKI requiring RRT across the cohorts underscores the need for resource planning to focus on the ability to provide adequate renal support as well during the pandemic particularly given the grim prognosis associated with AKI among patients with COVID-19.

Further investigation is needed to elucidate the risk conferred by AKI among patients with specific comorbidities of interest, such as diabetes or hypertension. Among the cohorts we identified, such data was extremely limited. Data for proteinuria, hematuria, or home use of
RAAS inhibitors were also extremely limited, despite current clinical interest and their potential to affect clinical outcomes. In addition, we were only able to study the association between renal disease and severe illness or death; other pertinent clinical questions including the apparent temporal association of AKI with intubation or the association of AKI with time to extubation, hospitalization time, and overall disease-related morbidity could not be examined using the currently available data. Absent data about renal recovery from the cohorts prevented any estimation of the extent of renal recovery among patients who survived to discharge.

Our study has several limitations. While our inclusion criteria requiring explicit adherence to the KDIGO definition of AKI enabled us to compute meaningful analyses across cohorts, this also resulted in excluding studies that did not specify using the KDIGO definition from our final analysis. In addition, given the rapid continuous expansion of the COVID-19 literature, many cohorts had relatively short follow up periods and limitations in their description of details, and there are new cohorts being reported continuously. Furthermore, as with any review, despite a detailed, comprehensive search strategy by 2 independent reviewers, it remains possible that some studies were missed. Finally, we allowed non-peer-reviewed literature to be more inclusive. However, the lack of peer review of these analyses may adversely impact the stability of our estimates. Nevertheless, analysis based on the NHLBI Study Quality Assessment Tool showed similar quality among the pre-print and peer-reviewed studies, and heterogeneity among the 4 pre-print studies used for meta-analysis was actually lower than that of the peer-reviewed studies.
In conclusion, there is a growing body of evidence that AKI occurs in a substantial number of COVID-19 cases, and that developing AKI is associated with significantly worse outcomes for patients with COVID-19. Given the extent of the adverse impact of AKI, it is imperative that future studies provide more detailed information the extent and severity of the renal injury as well as the need for RRT to allow for a more nuanced understanding of the prognosis for patients with COVID-19 and appropriate resource planning in this pandemic.

**Disclosure:**

All the authors declared no competing interests

**Author Contributions:**

SRJ, AH, JS, and SM conceived of the study. SRJ and LQ collected the data. SRJ, LQ, KK, JS, SAH, JR, and SM interpreted the data. SRJ, LQ, KK, JS, SAH, JR, and SM prepared the manuscript and approved the submitted version of the manuscript.
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Table 1. Demographic characteristics of cohorts selected for quantitative or qualitative analysis

| Cohort/Study       | Hospital and Location | Population          | N     | Demographics | ICU or Severe CoV (%)* | Creatinine | Comorbidities | Other | Home RAAS Inhibitor (%)* |
|-------------------|-----------------------|---------------------|-------|--------------|------------------------|------------|---------------|-------|--------------------------|
|                   |                       |                     |       | Age (median) | Sex (% male)          | All        | ICU or Severe CoV | CKD (%) | HTN (%) | DM (%) | Proteinuria (%) | Hematuria (%) | |
| Arentz et al, JAMA | Evergreen, Washington, USA | ICU                 | 21    | 70          | 52                     | 21 (100)** | 1.45          | 1.45   | 12 (57.1) | -       | 7 (33.3)        | -             | |
| Brill et al., preprint | Barnett Hospital, London, UK | Hospitalized       | 450   | 72          | 60.4                   | -          | -             | -      | (195) 43 | (134) 30 | -       | -               | -             | |
| Cai et al, Eur J All & Clinical Immunology | Third People’s, Shenzhen, China | Hospitalized       | 298   | 47          | 49                     | 58 (20) imaging | 0.71         | 0.81   | 41 (15.8) | 18 (6) | -       | -               | -             | |
| Chan et al., NEJM | Mt. Sinai, New York, USA | Hospitalized       | 3235  | 66.5        | 57.7                   | 815 (25.2) | 0.95          | -      | (323) 10 | (1193) 36.9 | (800) 24.7 | -       | -               | -             | |
| Guan et al, NEJM | 522 hospitals, China | All                | 1099  | 47          | 58.1*                  | 173 (15.7) | -             | -      | 8 (0.7)  | 165 (14.9) | 81 (7.4) | -       | -               | -             | |
| Hirsch et al, KI | 13 hospitals, New York, USA | Severe + Critical | 5449  | 64          | 60.9                   | 1395 (25.6) | 1.01         | -      | -         | 3037 (55.7) | 1797 (33) | -       | -               | 1556 (28.6) | |
| Hong et al, YMJ | Yeungnam, Daegu, Korea | Hospitalized + ICU | 98    | 55.4        | 38.8                   | 13 (13.3)** | 0.9          | 1.0    | -         | 30 (30.6) | 9 (9.2)  | -       | -               | -             | |
| Jiang et al., preprint | Wuxi 5th People’s Hospital, Jiangsu, China | Hospitalized       | 55    | 45          | 49.1                   | 8 (14.5)** | 0.63         | 0.75   | (1) 1.8   | (17) 30.9 | (9) 16.4 | -       | -               | -             | |
| Pei et al, JASN | Tongji (Sino-French), Wuhan, China | Hospitalized, CKD excluded | 333   | 56.3        | 54.7                   | 189 (56.8)** | 0.80         | 0.88   | -         | 107 (32.2) | 76 (22.9) | 219 (65.8) | 139 (41.7) | 37/321 (11.5) | |
| Qiu et al, JMV | 2 hospitals, Hunan, China | Hospitalized       | 104   | 43          | 47.1                   | 16 (15.4)** | 0.75         | -      | (12) 11.5 | (15) 14.4 | -       | -               | -             | |
| Regina et al., preprint | Lausanne University Hospital, Switzerland | Hospitalized       | 200   | 70          | 60                     | -          | 1.01         | -      | (28) 14   | (87) 43.5 | (43) 21.5 | -       | -               | 51 (26.2)    | |
| Rubin et al., preprint | University Hospital of Bordeaux, France | ICU                | 71    | 61.2        | 77                     | 71 (100)** | 1.31         | 1.31   | (4) 6      | (43) 61   | (21) 30  | -       | -               | 23 (32)      | |
| Cohort/Study | Hospital and Location | Population | N | Demographics | Creatinine | Comorbidities | Other | Home RAAS Inhibitor (%) |
|--------------|-----------------------|------------|---|--------------|------------|---------------|-------|------------------------|
| Chen et al, BMJ | Tongji, Wuhan, China | Deceased + Discharged | 274 | 62 | 62 | - | 0.86 | - | 4 (1) | 93 (34) | 47 (17) | - | - | - |
| Chen et al, JCI | Tongji, Wuhan, China | Hospitalized | 21 | 56 | 81 | 11 (52.4) | 0.92 | 0.93 | - | 5 (23.8) | 3 (14.3) | - | - | - |
| Cheng et al, KI | Tongji & Huazhong, Wuhan, China | Hospitalized | 701 | 63 | 52.4 | 297 (42.4) | 0.88 | - | 101 (14.4) | 233 (33.4) | 100 (14.3) | 194/442 (43.9) | 118/442 (26.7) | 33 (4.7) |
| Huang et al, Lancet | Jinyintan, Wuhan, China | Hospitalized | 41 | 49 | 73 | 13 (31.7) | 0.84 | 0.9 | 4 (9.8) | 6 (14.6) | 8 (19.5) | - | - | - |
| Richardson et al, JAMA | 12 hospitals, New York, USA | Hospitalized | 5700 | 63 | 60.3 | 1281 (22.5) | - | - | 454 (8.0) | 3026 (56.6) | 1808 (33.8) | - | - | 456/2411 (18.9) |
| Shi et al, Renmin | Hospitalized | Deceased + Discharged | 416 | 64 | 49.3 | - | 0.67 | - | 14 (3.4) | 127 | 60 (14.4) | - | - | - |
| Wang et al, Crit Care | Zhongnan & Xishui, Wuhan, China | Deceased + Discharged | 107 | 51 | 53.3 | - | 0.81 | - | 3 (2.8) | 26 (24.3) | 11 (10.3) | - | - | - |
| Xiao et al., preprint | Hankou Hospital, Wuhan, China | Hospitalized | 287 | 62 | 55.7 | 124 (43) | - | - | (5) 1.7 | (87) 30.3 | (45) 15.7 | - | - | - |
| Yan et al., preprint | Multiple hospitals, Hainan, China | Hospitalized | 168 | 51 | 48.2 | 36 (21.4) | 0.7 | 0.65 | (1) 0.6 | (24) 14.3 | (12) 7.1 | - | - | - |
| Zhang et al, Clin Micr Inf | Renmin, Wuhan, China | Hospitalized | 663 | 55.6 | 48.4 | 409 (61.7) | - | - | - | - | - | - | - |
| Zhao et al., preprint | You’an Hospital, Beijing, China | Hospitalized | 77 | 52 | 44.2 | 20 (26) | 0.72 | 0.77 | (5) 6.5 | (16) 20.8 | (6) 7.8 | - | - | - |
| Zheng et al, J Zhejiang University | 1st Aff. Hosp. of Zhejiang U. Coll. of Medicine, Hangzhou, China | ICU | 34 | 66 | 67.6 | 34 (100) | 0.95 | 0.95 | (2) 5.9 | (22) 64.7 | (8) 23.5 | - | - | - |
| Zhou et al, Lancet | Jinyintan, Wuhan, China | Deceased + Discharged | 191 | 56 | 62 | 119 (62.3) | - | - | 2 (1) | 58 (30.4) | 36 (18.8) | - | - | - |
| Zhou et al, preprint | 2 Hospitals, Yichang, China | Discharged | 197 | 56 | 50.3 | 56 (28.4) | 1.21 | (3) 1.5 | - | (18) 9.1 | - | - | - |

**Cohorts for qualitative analysis only**
### Table 1 Notes:
Some studies separated cohorts into ICU or non-ICU hospitalized populations, while other studies separated cohorts based on the National Health Commission of the People’s Republic of China (NHC of PRC) COVID-19 clinical guidelines, where severe disease was defined as any one of the following: tachypnea with RR >=30, SpO2 <= 93% at rest, or PaO2/FiO2 <= 300mmHg. Cai et al. used imaging criteria to define severity, while Guan et al., used the American Thoracic Society (ATS) community-acquired pneumonia (CAP) guidelines.

### Table 2. Outcomes of cohorts selected for quantitative or qualitative analysis
| Study                                  | Setting          | Sample Size | Stage 0 (%) | Stage 1 (%) | Stage 2 (%) | Stage 3 (%) | ICU (%) | Mortality Rate (%) |
|----------------------------------------|------------------|-------------|-------------|-------------|-------------|-------------|---------|-------------------|
| Cai et al, Eur J all & Clinical Imm    | Hospitalized     | 298         | 3 (1)       | 17 (5.7)    | 13 (22.4)   | -           | -       | -                 |
| Chan et al., preprint                  | Hospitalized     | 3235        | 771 (23.8)  | 1406 (44)   | 39.3        | 638 (45)    | 323 (10) | -                 |
| Guan et al, NEJM                       | All              | 1099        | 15 (1.4)    | 6 (0.5)     | 5 (83.3)    | -           | 8 (0.7) | 3 (37.5)          |
| Hirsch et al, KI                       | Severe + Critical| 5449        | 888 (16.3)  | 1993 (37)   | 1060 (53.2) | 694 (34.8)  | -       | 285 (5.2)         |
| Hong et al, YMJ                        | Hospitalized + ICU| 98          | 5 (5.1)     | 9 (9.2)     | 8 (88.9)    | -           | -       | 3 (3.1)           |
| Jiang et al., preprint                 | Hospitalized     | 55          | 0 (0)       | 3 (69.5)    | 66.7        | -           | 1 (1.8) | -                 |
| Pei et al, JASN                        | Hospitalized , CKD excluded | 333          | 29 (8.7)    | 22 (6.6)    | -           | 3 (13.6)    | -       | -                 |
| Qiu et al., JMV                        | Hospitalized     | 104         | 1 (1)       | 2 (1.9)     | -           | -           | -       | -                 |
| Regina et al., preprint                | Hospitalized     | 200         | 25 (12.5)   | 48 (24)     | -           | 28 (14)     | -       | -                 |
| Rubin et al., preprint                 | ICU              | 71          | 4 (6)       | 57 (80)     | 100         | 4 (7)       | 4 (6)   | 4 (100)           |
| Wang et al, Crit Care                  | Deceased + Discharged | 107         | 19 (17.8)   | 14 (13.1)   | -           | 14 (100)    | 3 (2.8) | -                 |
| Xiao et al., preprint                  | Hospitalized     | 287         | 19 (6.6)    | 55 (19)     | 61.8        | 12 (22)     | 5 (1.7) | -                 |
| Yan et al., preprint                   | Hospitalized     | 168         | 6 (3.6)     | 6 (3.6)     | 50          | -           | 1 (0.6) | 1 (100)           |
| Zhang et al, Clin Micr Inf             | Hospitalized     | 663         | 25 (3.8)    | 68 (10)     | 56 (82.3)   | 5 (7.4)     | -       | -                 |
| Zhao et al., preprint                  | Hospitalized     | 77          | 5 (6.5)     | 2 (2.6)     | 50          | -           | 5 (6.5) | -                 |
| Zheng et al., J Zheijang University    | ICU              | 34          | 0 (0)       | 7 (20.6)    | 100         | -           | 2 (5.9) | 2 (100)           |
| Zhou et al, Lancet                    | Deceased +       | 191         | 54 (28.3)   | 28 (14.7)   | 28 (100)    | 27 (96.4)   | 2 (1)   | 2 (100)           |
### Cohorts for qualitative analysis only

| Cohort/Study | Population | N   | Mortality (%) | AKI | CKD | RRT Used (%) |
|--------------|------------|-----|---------------|-----|-----|--------------|
| AKI (ICD)    |            |     |               |     |     |              |
| ICU or Severe CoV (% total AKI) |     |     |               |     |     |              |
| Death (% total AKI) |     |     |               |     |     |              |
| ICU or Severe CoV (% total CKD) |     |     |               |     |     |              |
| Death (% total CKD) |     |     |               |     |     |              |

| Chen et al, BMJ | Deceased + Discharged | 274 | 113 (14) | 29 (11) | 28 (96.6) | 4 (1) | - |
| Chen et al, JCI | Hospitalized | 21 | 4 (19) | 2 (9.5) | 101 (14.4) | - | - |
| Cheng et al, KI | Hospitalized | 701 | 113 (16.1) | 36 (5.1) | 101 (14.4) | - | - |
| Huang et al, Lancet | Hospitalized | 41 | 6 (14.6) | 3 (7.3) | 4 (9.8) | - | 3 (7.3) |
| Richardson et al, JAMA | Hospitalized | 5700 | 553 (9.7) | 1370 (24) | - | 454 (8.0) | - | 225 (3.9) |
| Shi et al, JAMA | Hospitalized | 416 | 57 (13.7) | 8 (1.9) | 14 (3.4) | - | 2 (0.5) |
| Shi et al, preprint | Deceased | 101 | 101 (100) | 24 (23.8) | 10 (9.9) | - | 5 (5) |
| Wang et al, Infection | Hospitalized + age >60 | 339 | 65 (19.2) | 27 (8.1) | 17 (3.9) | - | 4 (30.8) |
| Wang et al, JAMA | Hospitalized | 138 | 6 (4.3) | 5 (3.6) | 4 (2.9) | 2 (50) | - |
| Yang et al, Lancet | ICU | 52 | 32 (61.5) | 15 (28.8) | 12 (80) | - | 9 |
Records identified through database searching (n = 558)

Records after duplicates removed (n = 512)

Titles and abstracts screened (n = 512)

Excluded based on title or abstract (n = 453)

Full-text articles assessed (n = 59)

Full-text articles excluded:
- Not using KDIGO definition of AKI (n=21)
- Insufficient relevant data (n=8)

Studies included in qualitative synthesis (n = 30)

Duplicate cohorts excluded for quantitative meta-analysis (n=10)

Studies included in quantitative synthesis (meta-analysis) (n = 20)
ICU/Severe <50%

| Study                  | AKI Dead | AKI Alive | No AKI Dead | No AKI Alive | OR with 95% CI | Weight (%) |
|------------------------|----------|-----------|-------------|--------------|----------------|------------|
| Hirsch et al., KI      | 694      | 1,299     | 194         | 3,262        | 8.98 [ 7.57, 10.67] | 19.87      |
| Chan et al., preprint  | 638      | 768       | 133         | 1,696        | 10.59 [ 8.63, 13.01] | 19.84      |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 31.39\%$, $H^2 = 1.46$

Test of $\theta_i = \theta$: $Q(1) = 1.46$, $p = 0.23$

ICU/Severe ≥50%

| Study                  | AKI Dead | AKI Alive | No AKI Dead | No AKI Alive | OR with 95% CI | Weight (%) |
|------------------------|----------|-----------|-------------|--------------|----------------|------------|
| Pei et al., JASN       | 19       | 3         | 10          | 301          | 190.63 [ 48.39, 750.94] | 16.93      |
| Zhou et al., Lancet    | 27       | 1         | 27          | 136          | 136.00 [ 17.72, 1044.04] | 14.33      |
| Zhang et al., Clin Micr Inf | 5     | 63        | 20          | 575          | 2.28 [ 0.83, 6.29] | 18.17      |
| Rubin et al., preprint | 4        | 53        | 0           | 14           | 2.44 [ 0.12, 47.97] | 10.86      |

Heterogeneity: $\tau^2 = 5.20$, $I^2 = 88.52\%$, $H^2 = 8.71$

Test of $\theta_i = \theta$: $Q(3) = 32.33$, $p = 0.00$

Overall

Heterogeneity: $\tau^2 = 2.77$, $I^2 = 98.49\%$, $H^2 = 66.27$

Test of $\theta_i = \theta$: $Q(5) = 34.70$, $p = 0.00$

Test of group differences: $Q_a(1) = 0.38$, $p = 0.54$

Random-effects REML model
| Study                        | AKI    | No AKI   | OR with 95% CI | Weight (%) |
|------------------------------|--------|----------|----------------|------------|
|                              | Dead   | Alive    | Dead | Alive |               |              |
| **Peer-Reviewed**            |        |          |      |       |               |              |
| Pei et al., JASN             | 19     | 3        | 10   | 301   | 190.63 [48.39, 750.94] | 11.37        |
| Wang et al., Crit Care       | 14     | 0        | 5    | 88    | 466.64 [24.48, 8896.20] | 7.19         |
| Zhou et al., Lancet         | 27     | 1        | 27   | 136   | 136.00 [17.72, 1044.04] | 9.52         |
| Zhang et al., Clin MicroInf  | 5      | 63       | 20   | 575   | 2.28 [0.83, 6.29] | 12.26        |
| Hirsch et al., Kl           | 694    | 1,299    | 194  | 3,262 | 8.98 [7.57, 10.67] | 13.51        |
| Heterogeneity: $\tau^2 = 4.38$, $I^2 = 93.78\%$, $H^2 = 16.09$ |        |          |      |       | 38.32 [5.30, 276.88] |              |
| Test of $\theta_1 = \theta_2$: $Q(4) = 39.61$, $p = 0.00$ |        |          |      |       |               |              |
| **Preprint**                 |        |          |      |       |               |              |
| Chan et al., preprint        | 638    | 768      | 133  | 1,696 | 10.59 [8.63, 13.01] | 13.49        |
| Brill et al., preprint       | 54     | 31       | 119  | 246   | 3.60 [2.20, 5.90] | 13.22        |
| Rubin et al., preprint       | 4      | 53       | 0    | 14    | 2.44 [0.12, 47.97] | 7.12         |
| Xiao et al., preprint        | 12     | 43       | 7    | 225   | 8.97 [3.34, 24.08] | 12.32        |
| Heterogeneity: $\tau^2 = 0.30$, $I^2 = 77.43\%$, $H^2 = 4.43$ |        |          |      |       | 6.62 [3.33, 13.15] |              |
| Test of $\theta_1 = \theta_2$: $Q(3) = 16.43$, $p = 0.00$ |        |          |      |       |               |              |
| **Overall**                  |        |          |      |       | 15.27 [4.82, 48.36] |              |
| Heterogeneity: $\tau^2 = 2.55$, $I^2 = 97.90\%$, $H^2 = 47.61$ |        |          |      |       |               |              |
| Test of $\theta_1 = \theta_2$: $Q(8) = 56.13$, $p = 0.00$ |        |          |      |       |               |              |
| Test of group differences: $Q_m(1) = 2.70$, $p = 0.10$ |        |          |      |       |               |              |

Random-effects REML model
