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SYSTEMATIC REVIEWS

COVID–19 and chronic kidney disease: an updated overview of reviews

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Abstract

Background Coronavirus disease (COVID–19) has resulted in the death of more than 3.5 million people worldwide. While COVID–19 mostly affects the lungs, different comorbidities can have an impact on its outcomes. We performed an overview of reviews to assess the effect of Chronic Kidney Disease (CKD) on contracting COVID–19, hospitalization, mortality, and disease severity.

Methods We searched published and preprint databases. We updated the reviews by searching for primary studies published after August 2020, and prioritized reviews that are most updated and of higher quality using the AMSTAR tool.

Results We included 69 systematic reviews and 66 primary studies. Twenty-eight reviews reported on the prevalence of CKD among patients with COVID–19, which ranged from 0.4 to 49.0%. One systematic review showed an increased risk of hospitalization in patients with CKD and COVID–19 (RR = 1.63, 95% CI 1.03–2.58) (Moderate certainty). Primary studies also showed a statistically significant increase of hospitalization in such patients. Thirty-seven systematic reviews assessed mortality risk in patients with CKD and COVID–19. The pooled estimates from primary studies for mortality in patients with CKD and COVID–19 showed a HR of 1.48 (95% CI 1.33–1.65) (Moderate certainty), an OR of 1.77 (95% CI 1.54–2.02) (Moderate certainty) and a RR of 1.6 (95% CI 0.88–2.92) (Low certainty).

Conclusions Our review highlights the impact of CKD on the poor outcomes of COVID–19, underscoring the importance of identifying strategies to prevent COVID–19 infection among patients with CKD.

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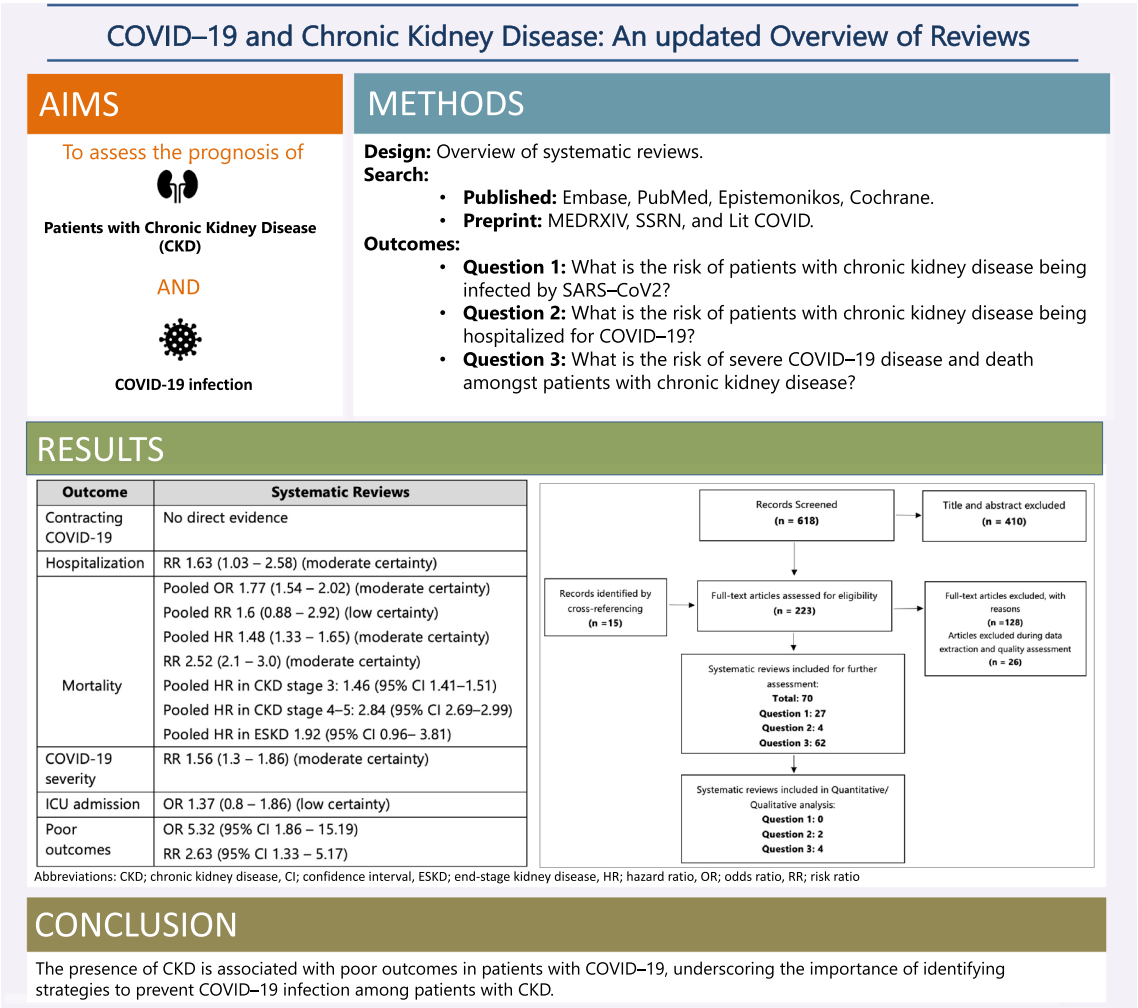
Graphical abstract



Keywords COVID–19 · SARS–CoV–2 · Chronic kidney disease (CKD) · Mortality · Hospitalization

Introduction

Since its emergence in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2) has caused over 240 million confirmed cases and more than 5 million deaths worldwide at the time of writing [1]. The World Health organization (WHO) declared it to be a global pandemic in March 2020. Multiple studies have assessed the association between different comorbidities and coronavirus disease 2019 (COVID–19) outcomes [2, 3]. COVID–19 preferentially affects the lungs with a potential to involve multiple organ systems, including the kidneys.

The global prevalence of chronic kidney disease (CKD) is estimated to be between 9 and 12% [4]. The incidence of CKD increases with age, and about 38% of the estimated CKD population is > 65 years of age [5]. The definition and classification of CKD was established and endorsed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative and the international Kidney Disease Improving Global Outcomes (KDIGO) guideline group which categorizes CKD into five stages based on the estimated glomerular filtration rate (eGFR) (level) with further sub–classification of stage 5 into dialysis-dependent and dialysis-independent [6]. Advanced CKD is associated with a marked increase in the risk of all–cause mortality and morbidity [7]. Cardiovascular causes are estimated to account for 50% of the mortality in patients with CKD, while infections are recognized as a leading cause of non–cardiovascular morbidity and mortality in patients with advanced CKD [8–11].

In this updated overview of reviews, we aim to summarize the effect of CKD on different outcomes among patients

with COVID–19. We reviewed available systematic reviews and large primary studies to assess COVID–19 incidence, severity, risk of hospitalization, and mortality among patients with CKD.

Materials and methods

The protocol for this overview was published online and is available on PROSPERO (International Prospective Register of Systematic Reviews). The registration number is CRD42021227974. There were no amendments from the pre-specified criteria reported in the protocol throughout the review process. The results are reported according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [12].

Inclusion and exclusion criteria

We started by conducting an overview of systematic reviews that reported COVID–19 outcomes in patients with CKD from January 1, 2020 to January 5, 2021. After searching systematic reviews, we updated the search by identifying primary studies published after August 2020, which was the date of last search in the reviews. We included all published and unpublished studies of any design including retrospective, prospective, and cross-sectional observational studies. The review included studies of adult patients with suspected or confirmed COVID–19 who had CKD. The update focused on primary studies with more than 1000 patients with COVID–19. We excluded systematic reviews and primary studies focusing on children, pregnant women, kidney transplant recipients, and those with acute kidney injury. We prioritized the following PICO questions, which we addressed in the review:

PICO 1: What is the risk of patients with chronic kidney disease being infected by SARS–CoV2?

PICO 2: What is the risk of patients with chronic kidney disease being hospitalized for COVID–19?

PICO 3: What is the risk of severe COVID–19 disease and death amongst patients with chronic kidney disease?

Search strategy

The methods team searched the following electronic databases: Embase, PubMed, Epistemonikos, and Cochrane from January 1st, 2020 to January 5th, 2021. Additionally, the investigators searched MEDRXIV, SSRN, and LiTCOVID databases for preprints of unpublished reviews. The detailed search strategy is available in Appendix-1 (See Online Supplementary material). In addition, reviewers manually checked the reference lists of included studies to identify additional relevant publications. The investigators further extended the search to include primary studies that were not incorporated in the systematic reviews from September 1st, 2020 to January 10th, 2021. The investigators also included results from four registries in this review: Hilbrands 2020 [13], Holman 2020 [14], Jager 2020 [15], and Williamson 2020 [16]. Similarly, reviewers assessed the references of included primary studies to identify additional publications that were not captured in the original search.

Data collection

Four investigators (AA, RM, AG, SJ) independently performed title and abstract screening in pairs to identify eligible literature. When present, disagreements were resolved by a third investigator (RAM). After full-text screening, four reviewers extracted data from the included systematic reviews independently (AA, RM, AG, SJ).

We collected the following information from each review: study characteristics (author name, region/country, study design, inclusion and exclusion criteria), patient characteristics (number of patients with CKD, age, gender, comorbidities, and clinical setting), and CKD specifications (CKD stage and whether they included patients with end stage kidney disease (ESKD) or not). We extracted the adjusted effect estimates when available with 95% confidence interval (CI) including odds ratio (OR), relative risk (RR), and hazard ratio (HR) for the following outcomes: incidence of COVID–19 infection, hospitalization, severe illness, ICU admission, mechanical ventilation, mortality, and poor outcomes among patients with CKD and COVID–19 infection from both systematic reviews and primary studies.

Quality and risk of bias assessment

We evaluated the quality of included systematic reviews using the modified Assessment of the methodological quality of systematic reviews (AMSTAR) tool checklist [17], and applying the following criteria: availability of a study protocol, comprehensive search strategy, list of excluded studies and their reason for exclusion, risk of bias (RoB) assessment and evaluation of its impact, appropriate methods for statistical combination of results, and assessment of publication bias.

When more than one review addressed the same question, we prioritized reviews that fulfilled most of the following criteria: higher AMSTAR rating, peer reviewed, recent date of literature search, use of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) assessment. We also prioritized reviews that addressed the outcomes of interest in the most direct way. Appendix 2A (See Online Supplementary material) provides details about the AMSTAR evaluation of all included systematic reviews.

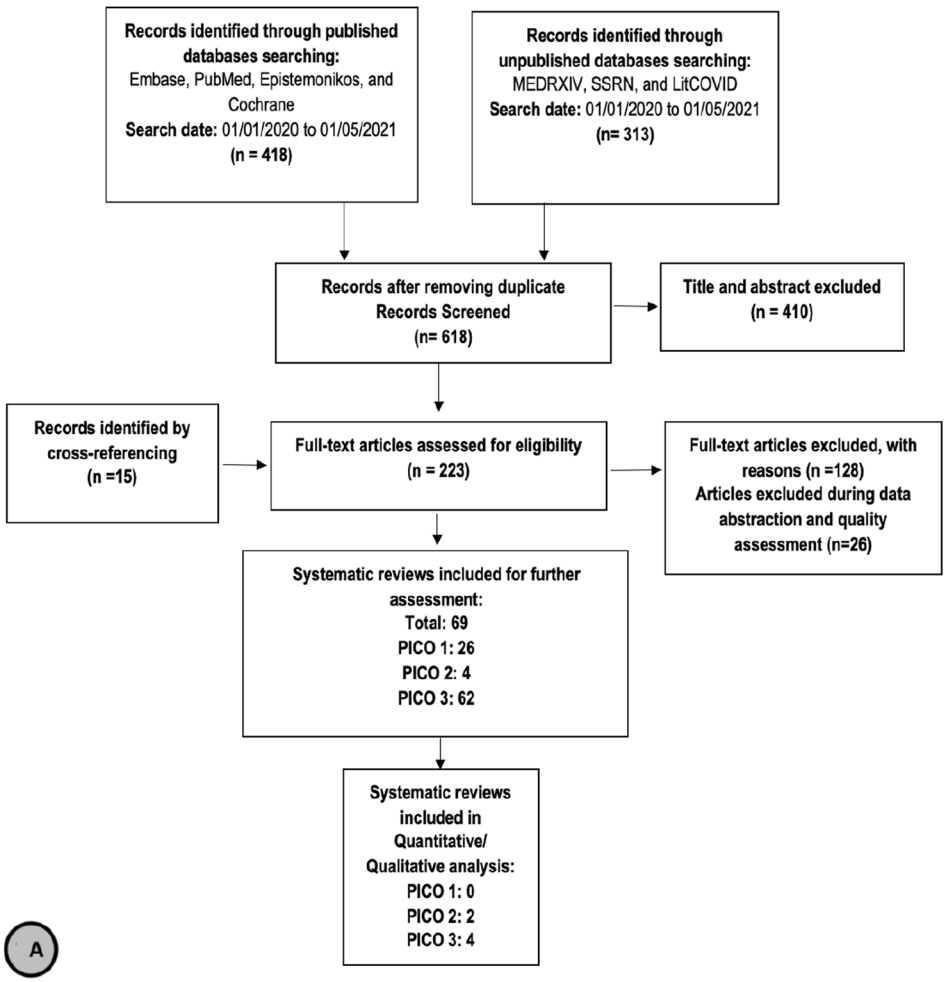


Fig. 1 Flow Chart of **a** systematic reviews and **b** primary studies included in the review

We evaluated the risk of bias of the primary studies using the Quality in Prognostic Studies (QUIPS) tool [18]. The QUIPS tool covers six domains: selection bias, attrition bias, prognostic factor and outcome measurement, confounding, and bias related to statistical analysis or presentation of results. The quality of each study was categorized as low risk, moderate risk, and high risk for each of the six domains. Appendix 2B (See Online Supplementary material) provides details about the QUIPS RoB evaluation for the included primary studies.

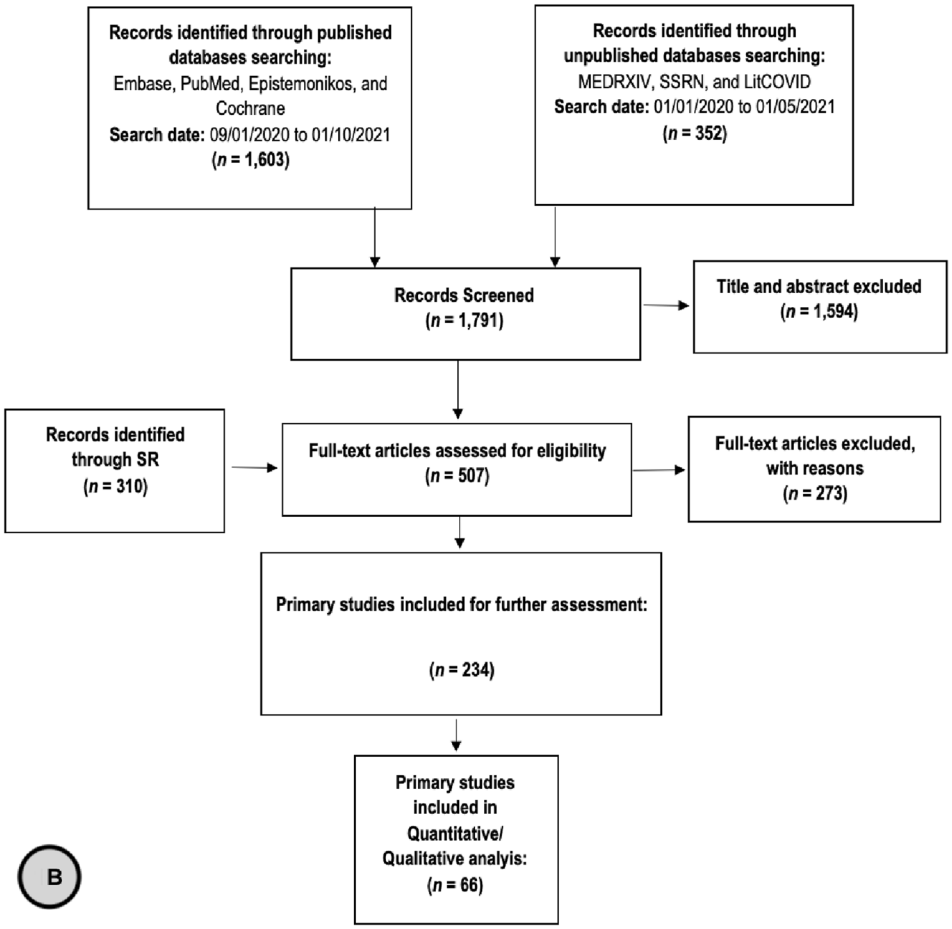
Certainty of the evidence

We assessed the certainty in the evidence using the GRADE approach [19]. This approach has four levels of certainty; very low, low, moderate and high. Observational studies start at low certainty and can be downgraded for concerns of risk of bias, indirectness (applicability of the results to the question), inconsistency (heterogeneity between study results), imprecision, and publication bias, while it can be upgraded if there is a large effect, residual confounding effect, or dose-response gradient.

Statistical analysis

Quantitative and descriptive analyses were conducted. We summarized the characteristics of the included systematic reviews and primary studies. Moreover, overall ORs, HRs, and RRs, along with their respective 95% CIs of the mortality outcome in patients diagnosed with CKD versus without CKD diagnosis and COVID–19 were calculated from the additional primary studies and the studies included in the reviews using a random effect model when more than five studies were available. Study data was considered worthy of exploration of heterogeneity when the I^2 statistic was more than 50%. Attempts were also made to explain heterogeneity based on the patients' clinical characteristics. We explored potential publication bias for the mortality outcome in studies through funnel plots. Reviewers eyeballed the plots to assess their symmetry. Subgroup analyses were conducted according to CKD classification status (stage 3, 4, or 5). All analyses were performed using Review Manager (RevMan) software version 5.4.

Fig. 1 (continued)



Results

We Identified 731 records through published and unpublished databases. After removing duplicates, we screened a total of 618 reviews for title and abstract screening. Two hundred and twenty-three reviews were included for full text screening, during which a total of 69 systematic reviews were included for prioritization: twenty–six reviews reported indirect evidence that informed PICO–1, four reviews addressed the risk of hospitalization in patients with CKD and COVID–19 (PICO–2), and 62 reviews addressed the risk of mortality in patients with CKD and COVID–19 (PICO–3). After prioritization of the 69 reviews, we included six reviews in our final report (Figure 1A). We also identified and screened 1,791 primary studies for eligibility, of which 234 studies were used for further assessment and meta-analysis. We included 66 primary studies in our final report. Table 1 summarizes the effect estimates for the different outcomes in the included systematic reviews and primary studies. The characteristics as well as outcome measurements reported in the systematic reviews and primary studies are detailed in appendix 3 (Tables 3 A–D) (See Online Supplementary material).

CKD and contracting COVID–19

We did not identify any systematic reviews that directly inform on CKD and the risk of contracting Covid–19. We identified 28 systematic reviews [2, 20–46] that reported on the prevalence of CKD among patients with COVID–19, which ranged from 0.4 to 49.0% among different settings. Two [27, 32] reviews reported on the prevalence of ESKD in patients with COVID–19 infection which ranged from 2.3 to 30.9%. One review [33] reported an 8% incidence of COVID–19 infection in patients on chronic hemodialysis (95% CI 4.7–12.0%).

With regard to additional primary studies that were not included in the reviews, there was no convincing difference on the risk of acquiring COVID–19 infection in patients with and without CKD, with inconsistent results being present among different studies. While Rentsch et al. showed no difference in the OR for testing positive for COVID–19 infection in patients with and without CKD, OR 1.00 (95% CI 0.76–1.33) [47], Ji et al. reported an OR of 0.50 (95% CI 0.39–0.65) [48] when examining the relationship between CKD and the presence of COVID–19, and Corbett et al. [49] reported on the rate of COVID–19 infection over a six–week

Table 1 Summary of the effect estimates for the different outcomes in the included systematic reviews and primary studies

Outcome	Systematic Reviews	Primary studies
Contracting COVID-19	No direct evidence	No direct evidence
Hospitalization	RR 1.63 (95% CI 1.03–2.58) ⨁⨁⨁◯	RR 4.0 (95% CI 3.0–5.2) OR from 1.38 (95% CI 1.19–1.60) to 3.9 (95% CI 2.4– 6.3) HR 1.21 (95% CI 1.11–1.32), and 1.9 (95% CI 1.3– 2.9)
Mortality	Pooled OR 1.77 (95% CI 1.54–2.02) ⨁⨁⨁◯ Pooled RR 1.6 (95% CI 0.88–2.92) ⨁⨁◯◯ Pooled HR 1.48 (95% CI 1.33–1.65) ⨁⨁⨁◯ RR 2.52 (95% CI 2.1–3.0) ⨁⨁⨁◯	Pooled OR 1.77 (95% CI 1.54–2.02) ⨁⨁⨁◯ Pooled RR 1.6 (95% CI 0.88–2.92) ⨁⨁◯◯ Pooled HR ESKD vs no ESKD 1.92 (95% CI 0.96–3.81) Pooled HR CKD III vs no CKD 1.46 (95% CI 1.41–1.51)
COVID-19 severity	RR 1.56 (95% CI 1.3–1.86) ⨁⨁⨁◯	OR from 2.1 (95% CI 1.2–3.8) to 3.6 (95% CI 2.2–5.8)
ICU admission	OR 1.37 (95% CI 0.8–1.86) ⨁⨁◯◯	Inconsistent evidence
Poor outcomes	OR 5.32 (95% CI 1.86–15.19) RR 2.63 (95% CI 1.33–5.17)	Pneumonia OR 1.66 (95% CI 1.38–2.00) Acute kidney injury OR 2.86 (95% CI 1.73–4.73) Longer hospital stay OR 1.62 (95% CI 1.27–2.06)

period in a large urban dialysis center in the United Kingdom with 1530 patients. During this period, 19.6% of the dialysis patients developed COVID–19 infection, with the majority of cases (96%) being in patients on in–center dialysis compared to home dialysis patients.

CKD and the risk of hospitalization among patients with COVID–19

We prioritized two of the four systematic reviews addressing this question [50, 51]. Fernandez Villalobos [50] provided the needed information to assess certainty in evidence. The risk of hospitalization appears to be increased in patients with COVID–19 infection and CKD compared to those without CKD, RR = 1.63 (95% CI 1.03–2.58) (Moderate certainty) [50] (Table 2).

Concerning additional primary studies that were not included in the reviews, most of the studies that reported on hospitalization in patients with COVID–19 infection and CKD showed a statistically significant increase in the risk of hospitalization. The majority of these studies calculated the OR for hospitalization, which ranged from 1.38 (95% CI 1.19–1.60) to 3.9 (95% CI 2.4–6.3) [47, 52–58]. One primary study reported a RR of 4.0 (95% CI 3.0–5.2) for hospitalization in patients with COVID–19 infection and CKD [59]. Two studies reported a HR of 1.21 (95% CI 1.11–1.32), and 1.9 (95% CI 1.3– 2.9) [60, 61].

Oetjens et al. analyzed the risk of hospitalization stratified by the advancement of CKD, showing an incremental increase in the odds of hospitalization in patients with COVID–19 infection with advancing CKD stage [54]. The OR for hospitalization in patients with CKD stage 5 and on dialysis was 11.07 (95% CI 4.54–26.97) in the Geisinger health care system, and 8.83 (95% CI 2.76–28.27) in United States Renal Data System (USRDS) data [54].

CKD and mortality among patients with COVID–19

We identified 62 systematic reviews assessing mortality risk in patients with CKD who contracted COVID–19 [2, 20, 24, 40, 43, 44, 46, 50, 51, 62–88]. Dorjee et al. [46] was the most updated systematic review with good AMSTAR quality which showed higher RR of mortality in patients with CKD and COVID–19 infection, RR = 2.52, (95% CI 2.11–3.00) (Moderate certainty) (Table 2).

We identified 20 primary studies assessing the HR of mortality in patients with CKD and COVID–19 [14, 16, 57, 60, 90–104], with a pooled HR of 1.48 (95% CI 1.33–1.65) (Moderate certainty) compared to patients without CKD (Fig. 2A). Holman et al. showed that there is an increase in the HR of mortality with advanced CKD among patients with type 1 diabetes, with a HR of 2.07 (95% CI 1.48–2.89), 2.46 (95% CI 1.72–3.52), 3.71 (95% CI 2.47–5.58), and

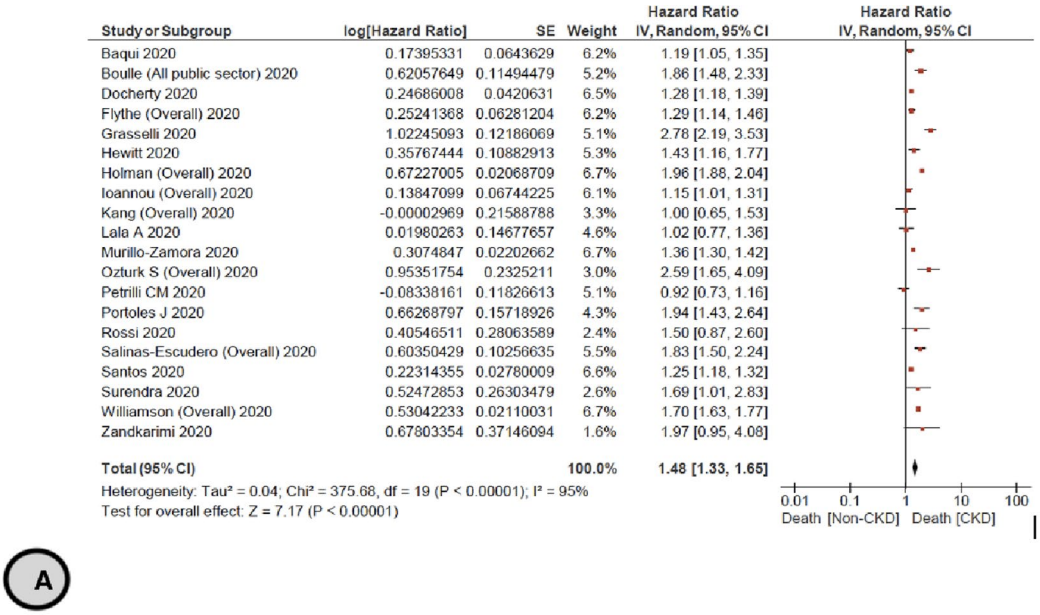


Fig. 2 **A** The pooled hazard ratio for mortality for patients with and without CKD. **B** The pooled odds ratio for mortality for patients with and without CKD. **C** The pooled risk ratio for mortality for patients with and without CKD. **D** The pooled Hazard ratio for mortality for patients with CKD stage 3, 4–5 and without CKD. **E** The pooled Hazard ratio for mortality for patients with and without ESKD

8.35 (95% CI 5.50–12.70) in CKD stages 3A, 3B, 4, and 5, respectively [14]. Patients with type 2 diabetes had a similar increase in mortality risk with advanced CKD, with a HR of 1.39 (95% CI 1.30–1.49), 1.76 (95% CI 1.63–1.89), 2.31 (95% CI 2.10–2.54), and 4.91 (95% CI 4.34–5.56) in CKD stages 3A, 3B, 4, and 5, respectively [14]. This incremental increase in mortality was consistent with findings in Williamson et al. which showed higher HR 3.69 (95% CI 3.09–4.39) for mortality in patients with ESKD compared to those without ESKD [16].

We also identified 24 additional primary studies that were not included in the reviews [52, 53, 55, 56, 58, 106–123] that examined the OR of mortality in patients with CKD and COVID–19 infection with a pooled OR of 1.77 (95% CI 1.54–2.02) (Moderate certainty) compared to patients without CKD (Fig. 2B). Ng et al. [123] reported specifically on patients with ESKD, showing a higher RR of mortality in this population, OR 1.37 (95% CI 1.09–1.73). Additionally, three primary studies [125–126] reported on the RR of mortality in patients with CKD and COVID–19 infection

Table 2 Evidence profile for different outcomes

No of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of events	No of individuals	Relative (95% CI)		
Hospitalization (Fernandez Villalobos 2020) [50]											
8	Observational studies	Serious[a]	Not serious[b]	Not serious	Not serious	None	176	362	RR 1.63 (1.03–2.58)	⨁⨁⨁◯ Moderate	Important
Mortality in hospitalized patients (Dorjee 2020) [46]											
23	Observational studies	Serious[c]	Not serious[d]	Not serious	Not serious	None			RR 2.52 (2.1–3.0)	⨁⨁⨁◯ Moderate	Critical
Pooled Hazard ratio for mortality (Sept 2020 till Jan 2021)											
20	Observational studies	Serious[e]	Not serious[b]	Not serious	Not serious	None	17,163	1,718,678	HR 1.48 (1.33–1.65)	⨁⨁⨁◯ Moderate	Critical
Pooled Odds ratio for mortality (Sept 2020 till Jan 2021)											
24	Observational studies	Serious[f]	Not serious	Not serious	Not serious	None	8929	26,267	OR 1.77 (1.54–2.02)	⨁⨁⨁◯ Moderate	Critical
Pooled Risk ratio for mortality (Sept 2020 till Jan 2021)											
3	Observational studies	Serious [g]	Not serious	Not serious	serious[h]	None	9493	50,411	RR 1.6 (0.88–2.92)	⨁⨁◯◯ Low	Critical
Severe disease (Dorjee 2020) [46][i]											
27	Observational studies	Serious[j]	Not serious[b]	Not serious	Not serious	None			RR 1.56 (1.3–1.86)	⨁⨁⨁◯ Moderate	Important
ICU admission (Degarege, 2020) [62]											
2	Observational studies	Serious[k]	Not serious	Not serious	Serious[l]	None			OR 1.37 (0.8–1.86)	⨁⨁◯◯ Low	Important

[a]The included studies were judged to be at high risk of bias in the domains of bias due to missing data and at moderate risk of bias in the domains of bias due to confounding and bias due to selection of participants and follow–up

[b]Despite the presence of high statistical heterogeneity as reflected by the I^2 of > 80%, most of the effect estimates suggest the same direction of effect

[c]Some of the included studies were judged to be at high risk of bias in the domains of selection, comparability and outcome bias using Newcastle Ottawa tool

[d]Even though I^2 is 72%, the effect estimates point toward increase mortality in patients with CKD

[e]Different included studies were judged to be at high risk of bias in the domains of study participation, prognostic factor measurement, outcome measurement and study confounding

[f]Some of the included studies were judged to be at high risk of bias in the domains of prognostic factor measurement and study confounding

[g]Dominguez–Ramirez, which contributes to 33% of the weight, was judged to be at high risk of bias in the domain of prognostic factor measurement

[h]The effect estimates cross the value of no effect suggesting both possible high and low risk

[i]Severe disease for any of 1) the study classified COVID–19 disease as severe or critical, 2) intensive care unit (ICU) admission, 3) acute respiratory distress syndrome, or 4) mechanical ventilation. Severe disease was defined by studies as respiratory rate > 30 per minute, oxygen saturation < 93%, and PaO2/FiO2 < 300 and/or lung infiltrates > 50% within 24–48 h

[j]Some of the included studies were judged to be at high risk of bias in the domains of selection, comparability and outcome bias using Newcastle Ottawa tool

[k]The included studies with highest weight (98% weight) were judged to be at high risk of bias in the domains of selection bias and data collection

[l]The effect estimates cross the value of no effect suggesting both possible high and low risk

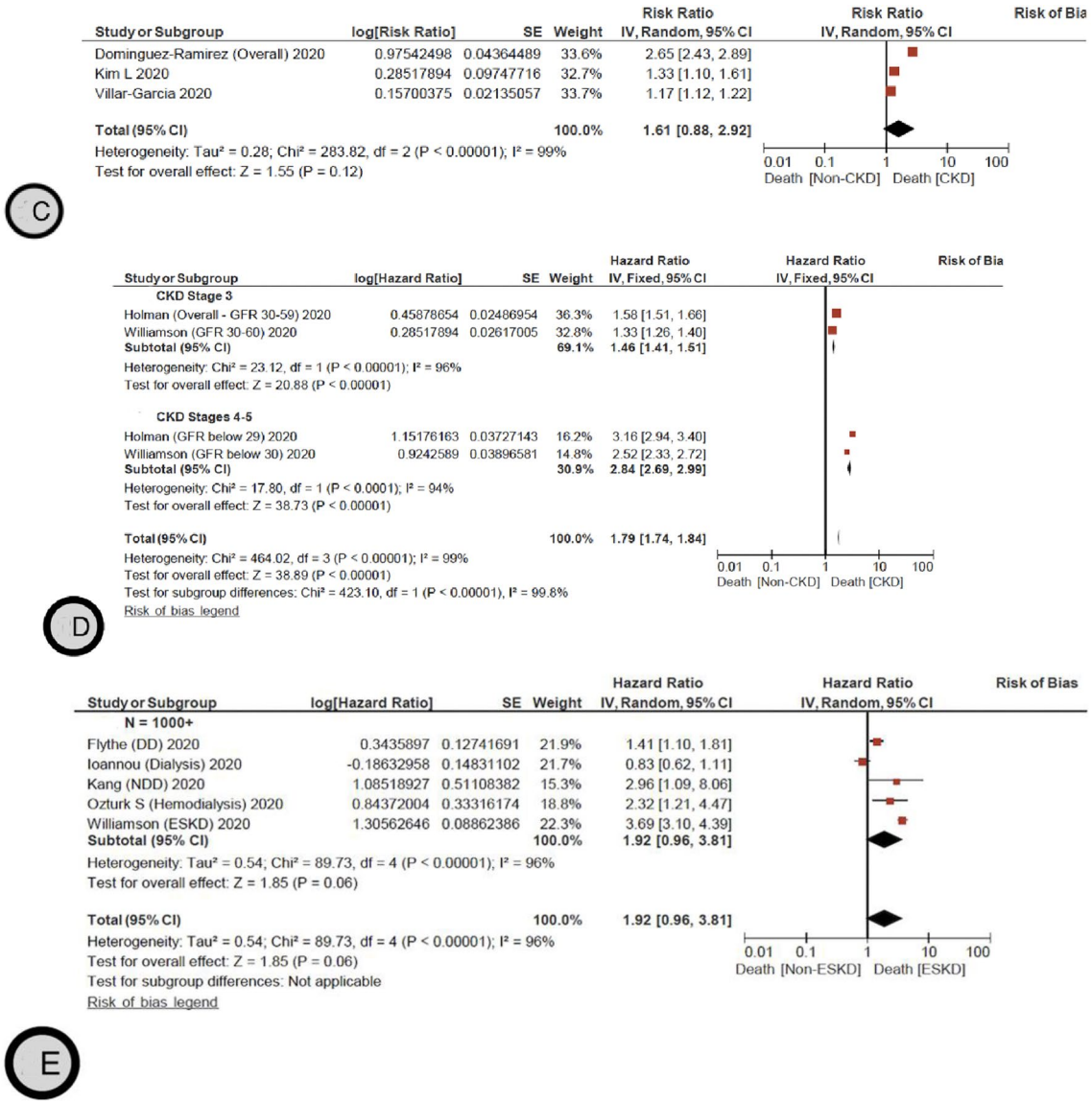


Fig. 2 (continued)

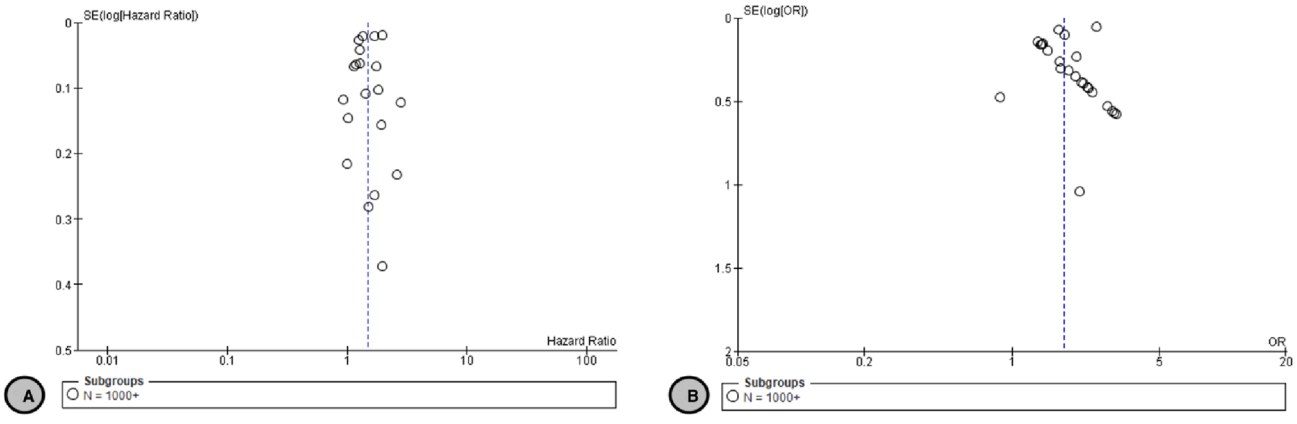


Fig. 3 **A** Funnel plot of comparison: 1 Covid-19 and CKD Mortality Outcomes, outcome: 1.1 HR CKD vs Non-CKD Mortality. **B** Funnel plot of comparison: 1 Covid-19 and CKD Mortality Outcomes, outcome: 1.2 OR CKD vs Non-CKD Mortality

with a pooled RR of 1.6 (95% CI 0.88–2.92) (Low certainty) (Fig. 2C). Jager et al. [15] reported that the attributable mortality was 20% and the mortality risk was 21.1 (95% CI 18.6–23.9) times higher in dialysis patients diagnosed with COVID-19 compared with the 1.2% mortality in the matched control group of dialysis patients without COVID-19. There was no suspected publication bias in the studies reporting mortality (Fig. 3).

In a subgroup analysis, the pooled HR for mortality in patients with CKD stage 3 is 1.46 (95% CI 1.41–1.51) compared to patients without CKD [14, 16] (Fig. 2D). Interestingly, the pooled HR for mortality significantly increased in patients with CKD 4–5, HR 2.84 (95% CI 2.69–2.99) [14, 16] (Fig. 2D). This increased mortality risk was also persistent in patients with ESKD with a pooled HR of 1.92 (95% CI 0.96–3.81) compared to patients without ESKD [16, 60, 93, 101, 103] (Fig. 2E).

CKD and COVID–19 severity

We identified 32 systematic reviews [2, 20, 23, 24, 28, 30, 35, 36, 43, 46, 50, 51, 62, 82, 128–144] reporting on COVID–19 severity in patients with CKD. Dorjee et al. [46] was the most updated systematic review with good AMSTAR quality answering this question and it showed an increased risk of severe COVID–19 infection among patients with CKD with a RR of 1.6 (95% CI 1.3–1.9) (Moderate certainty) (Table 2).

Five additional primary studies that were not included in the reviews [48, 52, 107, 145, 146] examined the effect of CKD on the severity of COVID–19 infection, showing a higher OR for severe COVID–19 infection ranging from 2.1 (95% CI 1.2–3.8) to 3.6 (95% CI 2.2–5.8). However, the definition of severe COVID–19 infection was not consistent among different studies.

CKD and ICU admission among patients with COVID–19

We identified nine systematic reviews [2, 29, 40, 50, 62, 79, 137, 142, 143] reporting on ICU admission in patients with CKD and COVID–19 infection. Among them, Degarege A [62] was the most updated systematic review with the highest AMSTAR quality. Degarege reported a trend towards higher need for ICU admission in patients with CKD and COVID–19 infection with an OR of 1.37 (95% CI 0.88–1.86) (Low certainty) (Table 2).

The effect estimate for the need of ICU admission was inconsistent among additional primary studies that were not included in the reviews. While three studies [52, 108, 147] showed a statistically significant increase in the risk of ICU admission with an OR ranging from 1.7 to 3.6, the other five studies [47, 53, 55, 119, 126] did not provide convincing evidence for higher ICU admission need in patients with CKD and COVID–19 infection (Table 1).

CKD and mechanical ventilation among patients with COVID–19

We identified one relevant systematic review [79] that reported on the risk of mechanical ventilation need in patients with CKD and COVID–19 infection. The meta-analysis included one primary study which did not show convincing evidence that CKD increases the need for mechanical ventilation in this population based on 18 events only.

There was also no convincing evidence that CKD increases the risk of needing mechanical ventilation among patients with COVID–19 infection in five additional primary studies that were not included in the reviews [53, 60, 93, 123, 148]. The ORs for mechanical ventilation ranged from 0.97 to 1.32, and the HRs ranged from 0.87 to 1.16.

CKD and poor outcomes among patients with COVID–19

We identified four systematic reviews [22, 79, 83, 149] reporting on overall poor outcomes in patients with CKD and COVID–19 infection. Nandy, K. et al. [22] defined adverse events such as ICU admission, acute respiratory distress syndrome (ARDS), mechanical ventilation, pneumonia, and death. The OR for adverse events was higher in CKD patients compared to non-CKD OR 5.32 (95% CI 1.86–15.19). Pranata R [79] defined poor outcomes as mortality, severe COVID–19, ARDS, ICU care, and mechanical ventilation, and showed a RR of 2.63 (95% CI 1.33– 5.17) for the CKD population compared to non–CKD. Xiao, W et al. defined adverse outcomes as severe illness, critical illness or death and reported a pooled effect estimate of 1.64 (95% CI 1.28–2.09) [83]. Kunutsor et al. also reported a higher incidence of AKI in patients with baseline CKD [27].

Additional primary studies that were not included in the reviews showed that patients with CKD and COVID–19 infection are at higher risk of pneumonia, OR 1.66 (95% CI 1.38–2.00) [53] and acute kidney injury in the first 48 h, OR 2.86 (95% CI 1.73–4.73) [150]. One study reported longer hospital stay in patients with ESKD compared to non-dialysis CKD, OR 1.62 (95% CI 1.27–2.06) [123].

Discussion

COVID–19 has affected millions of people worldwide. Many chronic medical diseases were reported as risk factors for increased mortality and severity of COVID–19, such as diabetes [56], hypertension, chronic obstructive

pulmonary disease, malignancies, and CKD [127]. In 2019, CKD affected approximately 15.0% of patients aged 65 years or older of the US Medicare population [151]. Some of the major causes of morbidity and mortality in patients with CKD are infections, sepsis, and bacteremia [152]. Infections in patients with CKD can cause longer duration of hospitalization, [153] and the mortality rate from pneumonia in patients with CKD is higher than that of patients without CKD [154]. In our review, we gathered evidence from all systematic reviews and primary studies to report the impact of CKD on COVID–19 mortality, hospitalization, incidence, ICU admission, disease severity, and adverse outcomes. We found that patients with CKD were more likely to have worse outcomes from COVID–19 compared to patients without CKD. This could be attributed to the attenuated immune system activation of both the innate and adaptive immunity systems which lead to an increased susceptibility to infections in patients with CKD [155].

We are reporting moderate certainty evidence that CKD increases the risk of COVID–19-related mortality and of disease severity. Importantly, this mortality risk is higher in patients with advanced CKD stage (Figs. 2 D, E).

In comparison with the impact of other comorbidities on COVID–19 mortality, a meta-analysis showed that cardiovascular disease, hypertension and diabetes were associated with increased mortality and severity of COVID–19: diabetes OR 2.50 (95% CI 1.74–3.59), and OR 2.35 (95% CI 1.80–3.06), hypertension OR 2.88 (95% CI 2.22–3.74), and OR 2.98 (95% CI 2.37–3.75), and cardiovascular disease OR 6.34 (95% CI 3.71–10.84), and OR 4.02 (95% CI 2.76–5.86), respectively for mortality and severity [156]. Another meta-analysis reported that patients with diabetes mellitus RR 1.48 (95% CI 1.02–2.15), cardiovascular diseases RR 2.25 (95% CI 1.60–3.17), malignancy RR 1.47 (95% CI 1.01–2.14), and hypertension RR 1.82 (95% CI 1.43–2.32) suffer a greater mortality risk compared to patients without these comorbidities [81].

Our findings show moderate certainty evidence that risk of hospitalization is increased in patients with COVID–19 infection and CKD compared to those without CKD. Similar to mortality, there is an incremental increase in the risk of hospitalization with advanced CKD stage [54]. In a case-control study that assessed risk factors associated with increased hospitalization in patients with CKD, the presence of comorbid ischemic heart disease was associated with a 3.5fold increase in admission rate (95% CI 2.14–5.9), while other factors included the presence of anemia, hypoalbuminemia, and late referral to a nephrologist [157].

The significance of CKD as an underlying condition for severe COVID–19 remains less well understood. In our review, we found one high quality systematic review [46] and five primary studies [48, 52, 107, 145, 146] that reported an increased risk of severe COVID–19 disease in patients with CKD, with an OR ranging from 2.1 (95% CI 1.2–3.8) to 3.6 (95% CI 2.2–5.8). However, the definition of severe COVID–19 infection was not clear and likely inconsistent in all studies. In one meta-analysis, no primary study reported CKD as a risk factor for COVID–19 severity, but a significant association was found, OR 3.03 (95% CI, 1.09–8.47) when pooling of data took place [128].

It is worthy to note that the results informing some of the outcomes were inconsistent among studies. For example, the effect estimates for the need of ICU admission and poor outcomes in patients with CKD and COVID–19 were inconsistent among the identified primary studies. Moreover, some inconsistencies in the inclusion of primary studies among the published reviews were noted. These discrepancies can be attributed to several possible factors, like the use of different definitions of CKD and disease severity, the use of different inclusion criteria in the systematic reviews, the difference in sample sizes and the timing of the studies, and different management and care that is provided to patients in each study. In addition, some studies did not adjust for all appropriate confounders, which may have played a role in the inconsistencies among results.

The findings in this review and in other studies have shed some light on the importance of implementing clear guidelines for the prevention and management of COVID–19 that are specific to patients with CKD. Because studies on these patients have shown an increased risk of mortality, hospitalization, and adverse outcomes of COVID–19, physicians should maintain a low threshold for hospital admission and close monitoring of patients with CKD who are not hospitalized, as well as early aggressive management to prevent complications. The findings should also guide us to prioritize patients with CKD during vaccine administration, regardless of their age and the advancement of their disease. Recent literature on vaccinated patients on maintenance hemodialysis showed that those patients have mounted an immune response to the vaccine, however, their antibody titers were lower than their controls [158, 159]. Studies examining the protective effect of the COVID–19 vaccine in CKD patients are underway.

Limitations

Some limitations to our overview of reviews could be noted. First, we relied on existing systematic reviews to identify studies published before September 2020. Given the inconsistency in studies included among the published reviews that is unexplained by the reviews' inclusion and exclusion criteria, it is possible that some primary studies may have been missed. However, due to the extensive effort in identifying large and well–done studies, it is unlikely that

any major study that would have a considerable impact on the conclusions has been missed. Some of the systematic reviews and primary studies were preprints, which lack the vigilant peer–review process. Another limitation is the high risk of bias in multiple domains in the included primary studies, and some primary studies did not consistently adjust for important confounders. In addition, the methods of diagnosing chronic kidney disease and measuring different confounders were not explicitly detailed in most of the included primary studies. In the mortality outcome, study data were considered worthy of exploration of heterogeneity when the I^2 statistic was more than 50%. Attempts were also made to explain heterogeneity based on the patients' clinical characteristics. However, due to lack of reporting of factors that may explain heterogeneity in the included studies, we were unable to explore them for all the outcomes in our analysis.

Conclusions

This overview of reviews addressed systematic reviews and primary studies that evaluated different outcomes in patients with CKD who contracted COVID–19. Our overview also evaluated the quality of both systematic reviews and individual studies. Evidence consistently demonstrated an increased risk of mortality and hospitalization in patients with CKD and COVID–19. The extent to which CKD increases the likelihood of the rate of infection, and other poor outcomes is not currently well understood, and the results are inconsistent among studies. The results shed some light on the significance of prioritizing patients with CKD for COVID–19 vaccination and critical care management. Further research studying the pathophysiology behind the effect of CKD on COVID–19 outcomes would provide deeper insight for the management of such patients.

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Declarations

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