Original Article

Diabetes and Mortality among Patients with Chronic Kidney Disease and COVID-19: A Systematic Review, Meta-analysis, and Meta-regression

Abstract

Introduction: Patients with kidney disease and COVID-19, whether on hemodialysis (HD) or not, have a higher risk of contracting COVID-19 accompanied by a higher mortality rate due to suppressed immune functions. Diabetes, one of the ubiquitous etiology of kidney disease, is also associated with a composite of poor outcomes. **Methods:** Meta-analysis and meta-regression of 13 articles on COVID-19 patients with chronic kidney disease, with information on diabetes and mortality were performed using Review Manager 5.4 and OpenMetaAnalyst. **Results:** The meta-analysis of a pooled subject of 18,822 patients showed that the presence of diabetes in CKD patients with COVID-19 was associated with an increased risk of mortality (RR 1.41 (1.15, 1.72); $P < 0.001$; I2 70%, $P < 0.001$). Subgroup analysis showed that diabetes was not associated with mortality in the HD group (RR 1.27 (1.06, 1.54); $P = 0.01$; I2 0%, $P = 0.70$) but showed a significant association in the non-HD group (RR 1.66 (1.59, 1.73); $P < 0.001$; I2 85%, $P < 0.001$). Male gender ($P = 0.070$) contributed to the effect size differences (age: $P < 0.001$; hypertension: $P = 0.007$; CVD: $P < 0.001$; lung disease: $P < 0.001$). **Conclusions:** Diabetes was associated with higher mortality risk among CKD patients, primarily those who did not need RRT.

Keywords: *Chronic kidney disease, COVID-19, diabetes, hemodialysis*

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has persisted as a major worldwide public health challenge since its emergence in December 2019 in Wuhan, China.[1] As of May 21, 2020, more than 160 million people infected with more than three million died due to coronavirus disease of 2019 (COVID-19).[2] Although vaccination rollouts are still being held worldwide, COVID-19's mortality rate still keeps increasing, mainly attributed to underserved communities, more common in low and middle-income countries (LMICs).

It is well known that patients with comorbidities are disproportionately affected by COVID-19 and associated with a grim prognosis.[3] It is well-established that advanced age and various comorbidities, such as hypertension, diabetes mellitus, chronic kidney disease (CKD), stroke, dementia, and older age, are independently associated with a higher mortality rate when infected with COVID-19.[4–8] Charlson comorbidity index (CCI), an easy-to-use clinical prediction tool to predict the mortality risk in patients with comorbidities, showed that a per-point increase in the CCI score in COVID-19 patients was associated with a 16% increase in mortality risk.[9]

There is no exception for patients with CKD and COVID-19. Whether on hemodialysis (HD) or not, CKD patients have a higher risk of contracting COVID-19 accompanied by a higher mortality rate due to suppressed immune functions.[10] Moreover, diabetes, one of the ubiquitous etiology of CKD, is also associated with a poor composite outcomes.[11]

Interestingly, several studies showed that diabetes did not significantly increase the risk of mortality among HD patients.[12–14] A study by Aoun *et al*.[12] showed that multimorbidities, including heart failure, coronary artery disease (CAD) stroke, dementia, and older age, increased the risk of mortality in HD patients with COVID-19, but not diabetes. The European Renal Association COVID-19 Database (ERACODA) study consistently showed that diabetes was not a risk factor

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for mortality among dialysis and kidney transplant patients with COVID-19.[13] Goicoechea also declared that diabetes was not associated with higher mortality in maintenance hemodialysis patients infected by COVID-19 ($P = 0.475$).[14]

Therefore, contrasting evidence on the impact of DM in CKD patients, especially those who were on HD, needs to be investigated. To fill the evidence gap, we performed a systematic review and meta-analysis to delineate better the association between diabetes and mortality among patients with CKD and COVID-19.

Methods

Eligibility criteria

We included articles enrolling COVID-19 patients with CKD with information on the presence of diabetes and mortality. We excluded case reports or case series with less than ten patients, review articles, commentaries, non-research letters, non-English language articles, and preprint articles to prevent the inclusion of fraudulent research.

Search strategy and study selection

We systematically searched literature from PubMed, EMBASE, and Europe PMC databases. Keywords used were "2019-nCoV" OR "COVD-19" OR "SARS-CoV-2" AND "Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "T2DM" OR "Diabetes" OR "Diabetic Nephropathy" OR "Diabetic Kidney Disease" OR "DKD" AND "Chronic Kidney Disease" OR "CKD" OR "End Stage Kidney Disease" OR "ESKD" OR "Chronic Renal Failure" OR "CRF" AND "Mortality" OR "Outcomes" up until March 31, 2021. After removal of duplicates, two authors independently screened the title and abstract of the records. The full-texts of remaining articles were evaluated by applying the inclusion and exclusion criteria. Any discrepancies were resolved through discussion and adjudicated by a third person. This study was carried out under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[15]

Data extraction

We used a standardized form to collect all the information, including author, year, country, study design, sample size, age, gender, diabetes, hypertension, cardiovascular disease, and lung disease. The outcome of interest of this meta-analysis was mortality.

Risk of bias evaluation

We evaluated the risk of bias of included studies by using Joanna Briggs Institute Critical Appraisal Checklist [Table 1]. We assessed each study for its risk of bias according to its type of study. Each tool for cross-sectional study and case series consisted of eight and ten questions, respectively. Subsequently, we interpreted the overall evaluation of the bias assessment risk with low risk of bias, high risk of bias, or unclear. Studies with a suspected high risk of bias were excluded. We used the funnel plot graphic to assess the potency of publication bias.

Table 1: Risk of bias assessment using Joanna Briggs Institute Critical Appraisal Checklist

Author	1	2	3	4	5	6	7	8	9	10	Description
Leon Abarca 2020[11]	Y	Y	Y	Y	Y	NA	Y	Y			Included
Aoun et al. 2020[12]	Y	Y	Y	Y	N	U	Y	Y			Included
Hilbrands[13]	Y	Y	Y	Y	N	Y	Y	Y			Included
Goicoechea 2020[14]	Y	Y	Y	Y	NA	NA	Y	Y			Included
Akchurin 2020[16]	Y	T	T	Y	NA	NA	Y	Y			Included
Xu 2021[17]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Included
Sipahi; 2020[18]	Y	Y	Y	Y	N	U	Y	Y			Included
Stefan 2020[19]	Y	Y	Y	Y	Y	Y	Y	Y			Included
Fisher 2020[20]	Y	Y	Y	Y	NA	NA	Y	Y			Included
Valeri 2020[21]	Y	Y	Y	Y	Y	NA	Y	Y			Included
Zou 2020[22]	Y	Y	Y	Y	Y	NA	Y	Y			Included
Parra Bracamonte 2020[23]	Y	Y	Y	Y	Y	Y	Y	Y			Included
Gok 2020[24]	Y	Y	Y	Y	Y	Y	Y	Y			Included

Statistical analysis

Review Manager 5.4 (Cochrane Collaboration) and OpenMetaAnalyst (Brown University, RI, USA) were utilized to perform the meta-analysis and meta-regression, respectively.

We calculated the pooled estimates and its 95% confidence interval in the form of risk ratios (RRs) by using the Mantel–Haenszel formula to determine the association between dichotomous variables (DM and mortality). We used a random-effects model regardless of the heterogeneity to account for interstudy variability. We also used two-tailed P values with a significance set at ≤ 0.05. We did sensitivity analysis by a leave-one-out method to determine the source of heterogeneity and test the statistical robustness. We divided all studies into two subgroups (HD and non-HD) to analyze the association between DM and mortality from each group. Meta-regression was utilized to assess the covariates' influence on the effect size differences, including age, gender, hypertension, cardiovascular disease (CVD), and lung disease. Finally, we performed a funnel-plot analysis to assess the risk of publication bias qualitatively.

Results

We collected 13 studies: six observational studies, five retrospective studies, one case series, and one case report [Table 2].[11–14,16–24] A total of 18,822 patients were included in the quantitative synthesis. Figure 1 shows the study profile [Figure 1].

Diabetes and mortality

The meta-analysis with a pooled subject of 18,822 patients showed that the presence of diabetes in CKD patients

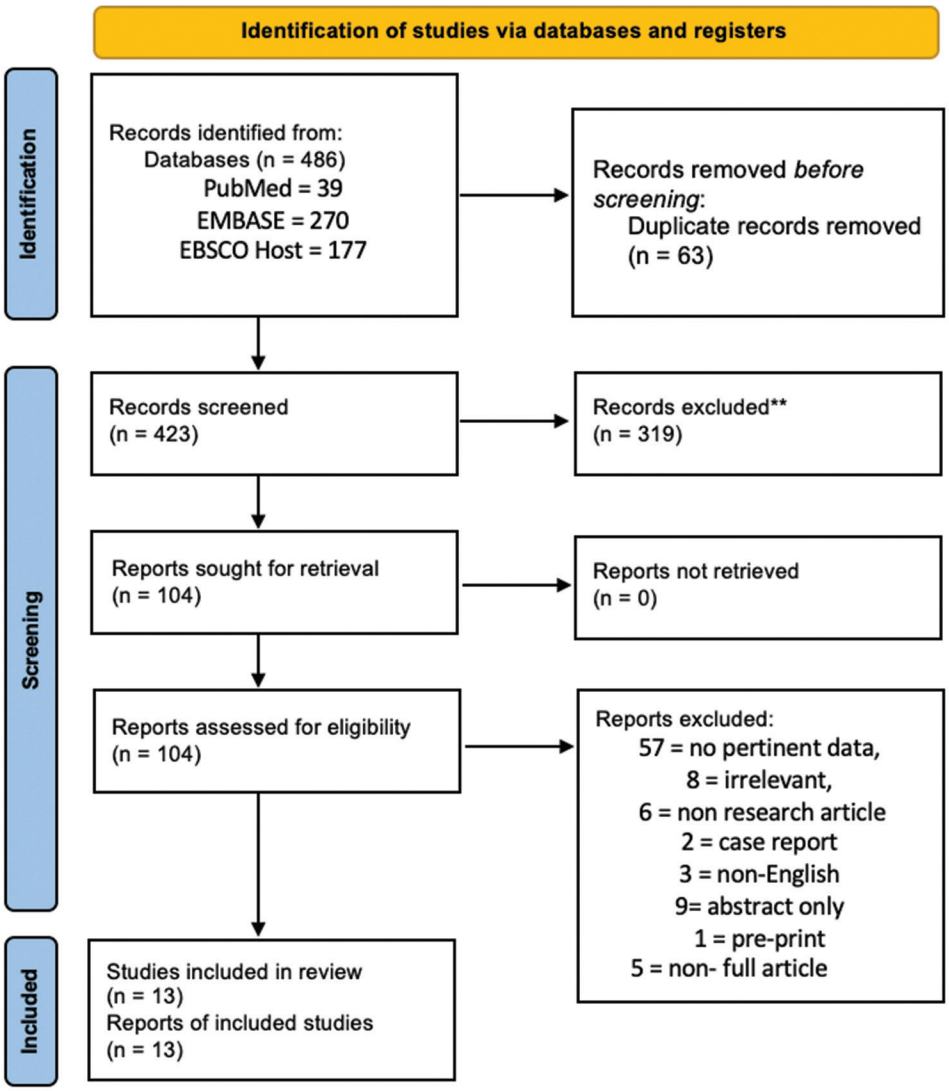

Figure 1: PRISMA flow diagram

with COVID-19 was associated with an increased risk of mortality (RR 1.41 (1.15, 1.72); $P < 0.001$; I2 70%, $P < 0.001$). Strikingly, subgroup analysis showed that diabetes was not associated with mortality in the HD group (RR 1.27 (1.06, 1.54); $P = 0.01$; I2 0%, $P = 0.70$) but showed a significant association in the non-HD group (RR 1.66 (1.59, 1.73); $P < 0.001$; I2 85%, $P < 0.001$) [Figures 2 and 3].

Meta-regression

The meta-regression showed that all covariates, but male gender ($P = 0.070$) contributed to the effect size differences (age: $P < 0.001$; hypertension: $P = 0.007$; CVD: $P < 0.001$; lung disease: $P < 0.001$). Furthermore, a multivariate meta-regression performed by including these significant covariates in a single analysis showed that none are significant, suggesting dependent nature between the covariates (age: $P = 0.105$; hypertension: $P = 0.690$; CVD: P: 0.366; lung disease: $P = 0.731$) [Figure 4].

Publication bias

Funnel-plot diagram analysis showed a qualitatively asymmetrical funnel plot for the association between diabetes and mortality in CKD patients, indicating the presence of a publication bias [Figure 5].

Discussion

This meta-analysis supports previous studies regarding the risk factors of mortality in COVID-19 and showed that patients with COVID-19 were significantly higher in patients with diabetes and CKD than those in CKD without diabetes.

Patients with CKD are more susceptible to bacterial and viral infections due to the alterations of the immune system caused by excessive levels of pro-inflammatory cytokines and oxidative stress.[25] Further, diabetic patients are also at risk of pneumonia due to the lung defense system dysfunction caused by a higher concentration of glucose

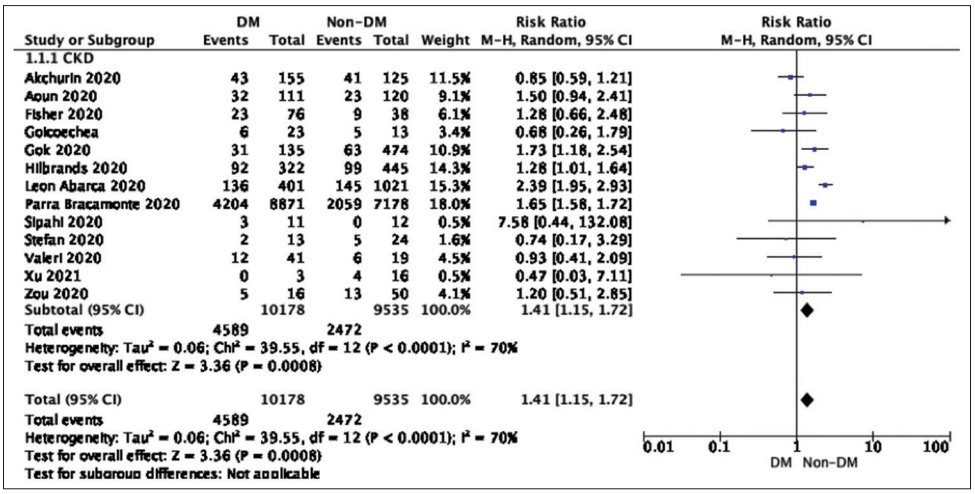

Figure 2: Diabetes in chronic kidney disease (CKD) and mortality. The meta-analysis showed a significant association between diabetes in CKD and mortality

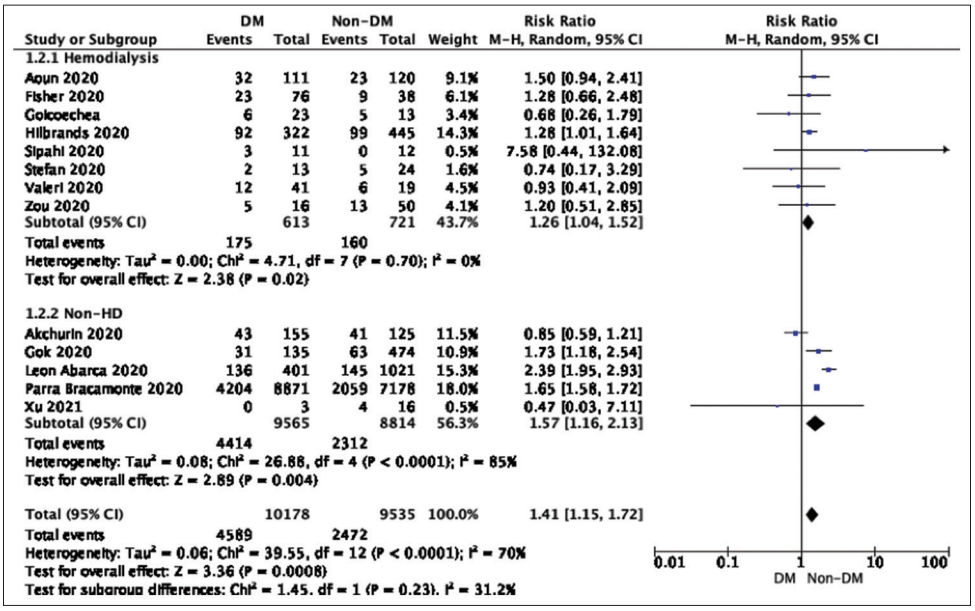

Figure 3: Subgroup analysis among HD and non-HD patients. The meta-analysis showed a significant association in the non-HD group

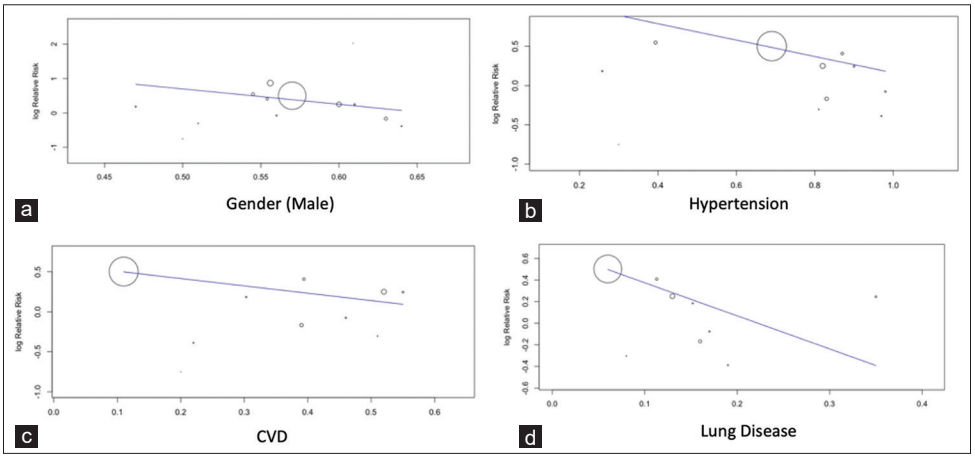

Figure 4: Meta-regression analysis showed that the association between diabetes and mortality in CKD was influenced by (a) gender, (b) hypertension, (CVD), and (d) lung disease

Table 2: Characteristic of the included studies

Authors	Country	Study design	Samples	Male (%)	Mean overall age (SD) (years)	Diabetes	HT	CVD	Lung disease	Mortality (DM vs. Non-DM)
Leon Abarca 2020[11]	Pakistan	retrospective study	530	1576 (55.6)	58.2 (13.7)	225 (42.4)	NA	NA	NA	136/401 vs. 145/1021
Aoun et al. 2020[12]	Lebanon	observational study	231	128 (55.4)	61.46 (13.99)	111 (48.1)	201 (87)	91 (39.4)	26 (11.3)	32/111 vs. 23/120
Hilbrands[13]	Netherland	observational study	768	460 (60)	67 (14)	322 (42)	629 (82)	230 (52)	99 (13)	92/322 vs. 99/445
Goicoechea 2020[14]	Spain	observational study	36	23 (64)	71 (12)	23 (64)	35 (97)	8 (22)	7 (19) [COPD]	6/23 vs. 5/13
Akchurin 2020[16]	US	retrospective study	280	176 (63)	75 (3)	155 (55)	232 (83)	109 (39) [CHF]	44 (16) [COPD]	43/155 vs. 41/125
Xu 2021[17]	China	case series	20	10 (50)	67 (11)	3 {15}	13 (65)	4 {20}	NA	0/4 vs. 4/16
Sipahi; 2020[18]	Turkey	cross sectional study	23	14 (60.9%)	66 (10)	11 (55)	NA	NA	NA	3/11 vs. 0/12
Stefan 2020[19]	Romania	observational study	37	19 (51)	64 (4)	13 (35)	30 (81)	19 (51)	3 (8) [COPD]	2/13 vs. 5/24
Fisher 2020[20]	US	retrospective study	114	70 (61)	64.5 (3.5)	76 (67)	102 (90)	63 (55)	40 (35)	23/76 vs. 9/38
Valeri 2020[21]	US	observational study	59	33 (56)	63.5 (4.7)	41 (69)	58 (98)	27 (46)	10 (17)	12/41 vs. 6/19
Zou 2020[22]	China	retrospective study	66	31/66 (47.0)	64.5 (3)	16 (24.2)	17 (25.8)	20 (30.3)	10 (15.2)	5/16 vs. 13/50
Parra Bracamonte 2020[23]	Mexico	retrospective study	16049	9084 (57%)	0-20: 196 (1%) 21-40: 2914 (18%) 41-60: 6145 (38%) 61-80: 5899 (33%) >80: 895 (6%)	8871 (55%)	10995 (69%)	1808 (11%)	951 (6%) [COPD]	4204/8871 vs. 2059/7178
Gok 2020 [24]	Turkey	observational study	609	332 (54.52)	59.23 (15.5)	135 (22.17)	240 (39.41)	NA	NA	31/135 vs. 63/474

Figure 5: Publication bias analysis. The funnel plot showed a qualitatively asymmetrical funnel plot for the association between diabetes and mortality in CKD patients

in the alveolar surface liquid (ASL), imbalance of reactive oxygen species (ROS), and inflammatory chemokine production.[26] Diabetic patients are also more susceptible to infections and are at excess risk for complications, morbidity, and mortality associated with these infections.[27] Therefore, diabetes in combination with CKD may confer a greater chance of hypoxemia and severe hyperinflammation. Consequently, these vulnerabilities translate to poor outcomes.

Leon-Abarca *et al*.[11] showed that diabetic kidney disease patients were more susceptible to be infected by SARS-CoV-2, had higher rates of getting pneumonia, mechanical intubation, ICU admission, and greater case-fatality rate. Gilbert *et al*.[28] did a kidney biopsy among patients with diabetic kidney disease and COVID-19 and found a twofold higher angiotensin-converting enzyme (ACE) 2 messenger RNA level. This may increase the possibility of kidney infection, risk of AKI, and death. The accumulating body of evidence showed that renin-angiotensin-aldosterone-system (RAAS) blockers did not increase the risk of poor outcomes in COVID-19 patients and were even protective for HD patients.[29]

In this meta-analysis, the subgroup analysis showed that diabetes in the HD group infected with COVID-19 was not associated with the increased risk of mortality. Consistently, this result was in line with other studies among HD patients with COVID-19.[12,13] In contrast to non-COVID-19 patients, the presence of diabetes in HD patients increased the risk of death 1.9 fold compared to those without diabetes (95% CI: 1.25–2.89; $P = 0.003$), along with age, serum albumin, CAD, and vascular access as the independent predictors of mortality. A possible explanation for this phenomenon is an excess mortality risk in COVID-19 patients with CKD and DM. Still, it is equalized when the CKD stage progresses to ESKD, which mandates renal replacement therapy (RRT). This finding aligns with the multinational dialysis cohort analysis showing that diabetes was not a

significant predictor of COVID-19 mortality.[30] Therefore, a kidney protective strategy is needed to mitigate the elevated mortality risk faced by the DKD patients with COVID-19 who did not need RRT.

Importantly, in the form of HbA1C levels, long-term glucose monitoring in this group was shown to be important in a non-COVID-19 setting. A U-shaped curve of HbA1C levels was demonstrated in CKD patients with DM, with levels of <6.5% and >8.0% associated with higher mortality[27] This finding can be explained by malnutrition-inflammation syndrome and cachexia for HbA1C levels of <6.5%, which are rampant in these patients, and HbA1C levels of >8.0% were associated with microvascular and macrovascular complications of diabetes. On the contrary, the prognostic role of the HbA1C group is somewhat controversial in COVID-19 patients with diabetes in general.[31]

Finally, we underscore the importance of comorbidities' impact on DKD patients, whether on hemodialysis or not. In line with other studies of CKD patients, primarily those on routine hemodialysis, our meta-analysis showed that the overall effect size of CKD patients' mortality was influenced by comorbidities and more severe in older patients.[12,29,32] Understandably, our findings reflect on a frailer population, in which primary prevention through vaccination will play a crucial role.[33]

There were some limitations in this study. First, most of the studies included in this meta-analysis were retrospective in nature, which precluded us from establishing a cause and effect relationship. Second, the overall effect size was driven mainly by the Parra–Bracamonte *et al*. study, with the most study subjects.[23] Third, we did not divide the CKD groups into categories based on the glomerular filtration rate or CKD stages. Fourth, we did not analyze the effect of blood glucose controls and alterations and their influence on COVID-19 mortality in DKD patients as these data were not available in the included studies. Finally, we only included English language studies, which may have affected the number of studies included in this research. Finally, our meta-analysis findings need to be carefully interpreted because of the presence of publication bias.

Conclusion

This meta-analysis showed that diabetes was associated with higher mortality risk among CKD patients, primarily those who did not need RRT. Renal protective strategies are needed for these patients because intervention beyond this opportunity window may render them useless. Nevertheless, future studies with enrolling large subjects and prospective in nature are needed to confirm our findings in the future. Finally, as DKD patients with or without the need for RRT are frailer, vaccination should be the priority for this population.

Data availability

The data used to support the findings of this study are included in the article.

Availability of data and materials

All data generated or analyzed during this study are included in this published article. The corresponding author (MRI) can be contacted for more information.

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Conflicts of interest

There are no conflicts of interest.

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