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Effect of Antidiabetic Therapy on Clinical Outcomes of COVID-19 Patients With Type 2 Diabetes: A Systematic Review and Meta-Analysis

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Abstract

Background: No study has yet systematically evaluated the effect of antidiabetic therapy on clinical outcomes of COVID-19 patients with type 2 diabetes (T2D). **Objective:** We aimed to evaluate the effect of different antidiabetic therapy on clinical outcomes of COVID-19 patients with T2D. **Methods:** We comprehensively retrieved the published research which examined the effect of antidiabetic therapy on clinical outcomes of COVID-19 patients with T2D. The odds ratio (OR) and its 95% confidence interval (95% CI) for clinical outcomes were calculated using the random-effects model, and meta-regression was adopted to evaluate the potential sources of heterogeneity between studies. **Results:** A total of 54 studies were included in this study. We found that the use of metformin (OR = 0.66, 95% CI: 0.58-0.75), SGLT-2i (OR = 0.80, 95% CI: 0.73-0.88), and GLP-1ra (OR = 0.83, 95% CI: 0.70-0.98) were significantly associated with lower mortality risk in COVID-19 patients with T2D, while insulin use might unexpectedly increase the ICU admission rate (OR = 2.32, 95% CI: 1.34-4.01) and risk of death (OR = 1.52, 95% CI: 1.32-1.75). No statistically significant associations were identified for DPP-4i, SUs, AGIs, and TZDs. **Conclusion and Relevance:** We demonstrated that the usage of metformin, SGLT-2i, and GLP-1ra could significantly decrease mortality in COVID-19 patients with T2D. The heterogeneity across the studies, baseline characteristics of the included patients, shortage of dosage and the duration of antidiabetic drugs and autonomy of drug selection might limit the objectivity and accuracy of results. Further adequately powered and high-quality randomized controlled trials are warranted for conclusive findings.

Keywords

COVID-19, SARS-CoV-2, meta-analysis, diabetes, antidiabetic therapy

Introduction

To date, the coronavirus disease-2019 (COVID-19) pandemic has resulted in more than 614 million confirmed infections, including 6.5 million deaths, up to September 30, 2022, as reported by the World Health Organization (WHO).[1] Amongst these rapidly increasing cases of confirmed COVID-19 infection, type 2 diabetes (T2D) has been found to be the second comorbidity.[2-6] COVID-19 patients with T2D are more prone to requiring hospital care, developing severe respiratory symptoms, and COVID-19-related death.[7-9] A large population-based cohort study from England showed that patients with T2D have twice the risk of COVID-19 mortality than those without.[10] Some studies have also noted that hyperglycemia is significantly associated with death and poor clinical prognosis in patients with T2D and COVID-19.[11,12] Interest in the potential effect of antidiabetic therapy on clinical outcomes of COVID-19 patients with T2D has increased.[11,13,14]

There are a wide variety of antidiabetic drugs with different mechanisms, however, no study has yet systematically evaluated the effect of antidiabetic therapy on clinical outcomes of COVID-19 patients with T2D. At present, these antidiabetic drugs, including metformin, insulin, thiazolidinediones (TZDs), dipeptidyl-peptidase 4 inhibitors (DPP-4i), sulfonylureas (SUs), sodium-glucose cotransporter-2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1ra), and α-glycosidase inhibitors (AGIs), are being used to control blood glucose level and improve clinical outcomes of COVID-19 patients with T2D.[15-18] However, so far the results of these trials were inconsistent due to the limited sample size and heterogeneous methodological quality.[15,19-23]

Some studies found that metformin could improve the clinical outcomes of COVID-19 patients with T2D,[24-27] while some reported no difference.[18,28-30] For other antidiabetic drugs, the results are variable and contradictory. For example, a multinational retrospective cohort study reported the use of GLP-1RA, DPP-4i, or pioglitazone could improve outcomes for COVID-19 patients with T2D,[15] while another study found that DPP-4i was not associated with improved clinical outcomes in Dutch patients.[23] Thus, up-to-date and comprehensive summaries of available evidence are crucial.

A systematic review and meta-analysis could summarize and evaluate a comprehensive and up-to-date view of the evidence, as well as reveal more robust estimates, or even form clinical practice guidelines. In this study, we comprehensively retrieved the published research which examined the effect of antidiabetic therapy on clinical outcomes of COVID-19 patients with T2D to update the pre-existing evidence which may contribute to the selection of appropriate antidiabetic drugs for these COVID-19 patients.

Methods

Selection Criteria

This study was conducted and reported according to the guidelines proposed by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[31,32] Selection criteria for studies were based on the Patient-Intervention-Comparison-Outcome-Study (PICOS) framework is as follows: (1) P: COVID-19 patients with T2D; (2) I: taking one of the anti-diabetes drugs; (3) C: the control group that didn't take the candidate anti-diabetes drugs; (4) O: COVID-19 related deaths and other poor clinical outcomes including ICU admission and invasive mechanical ventilation; (5) S: cohort, case-control, cross-sectional design in human beings. Excluded studies, on the other hand, fall into one of the following categories: (1) case report; (2) unrelated article; (3) no complete data available; (4) no full text available; (5) no related outcomes; (6) published in non-English; (7) duplicated cohort.

Search Strategy

We searched PubMed, EMBASE, and the Cochrane Library for eligible studies from December 1, 2019 until July 10, 2022. The search strategy used the following terms: "COVID-19," "diabetes," "metformin," "DDP-4i," "Insulin," "SGLT-2i," "SUs," "GLP-1RAs," "TZDs," and "AGIs," as well as their synonyms, full name, and related keywords. Each search item was a combination of one antidiabetic drug, COVID-19, and diabetes. Details of the search strategies were listed in the Supplementary Materials.

Data Extraction and Quality Assessment

All the relevant studies included in this analysis were imported into Endnote X9 software (developed by Clarivate Analytics, Philadelphia, PA, USA), and a team of paired reviewers independently performed further filtering of the retrieved studies. Duplicate records were removed by Endnote X9. The remaining studies were then further screened, first for title, abstract, and then for full text, leaving only those studies that met our criteria.

At least two researchers independently performed the data extraction from the eligible studies, and any disagreements were solved by discussion or, when necessary, by third-party adjudication. We developed a standardized extraction form to collect the following data: first author, publication year, country, study design, sample size, characteristic of the population (age, gender, co-hypertension, and antidiabetic agent use), the definition of control groups, information about the adjustment for confounds, and clinical endpoints. When extracting outcome data, we extracted the reported OR or adjusted OR that had been calculated by the study authors if it was available, and we also extracted the number of events in each group whenever possible. All of the medications documented in the patients were taken before admission. The studies' quality was evaluated with the New-castle–Ottawa Scale (NOS) by assessing the selection, comparability, and outcome of each study, assigning each study a total score from zero to nine.

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Outcomes

The primary study outcome was COVID-19-related death (defined by the total number of COVID-19 patients with T2D who died during the follow-up period). The secondary outcomes for our study were other clinical outcomes including (1) intensive care unit (ICU) admission; (2) invasive mechanical ventilation.

Statistical Analysis

Meta-analysis was performed with statistical packages "meta" and "metafor" in *R* (version 4.0.5). All tests were two-sided, and a *P* value of less than .05 for any test or model was considered statistically significant unless otherwise stated. The odds ratio (OR) and its 95% confidence interval (95% CI) for clinical outcomes were calculated using the random-effects model to promote the universality of the results. I^2 statistics were used to assess the degree of heterogeneity, and we deemed I^2 values at around 25% as low heterogeneity, I^2 values at around 50% as moderate heterogeneity, and I^2 values at around 75% high heterogeneity. Furthermore, we performed meta-regression analysis to evaluate the potential sources of heterogeneity between studies. The funnel plot was used to evaluate the qualitative risk of publication bias, while Egger's regression method was used to assess the quantitative risk of publication bias.

Results

Description of Included Studies

The flow chart of the selection process of this study is shown in Figure 1. By electronic searching up to July 10, 2022, a total of 1746 records were identified. After eliminating 686 duplicates, 1060 records remained. A total of 929 articles were excluded for the titles and abstracts, 131 articles were further evaluated by full text, and 77 records were excluded for following reasons: (1) case report (n = 13); (2) unrelated article (n = 12); (3) no complete data available (n = 9); (4) no full text available (n = 8); (5) no related outcomes (n = 6); (6) the objects did not meet the inclusion criteria (n = 12); (7) published in non-English (n = 2); (8) duplicate study cohorts (n = 7). Finally, the remaining 54 studies were included in this meta-analysis (Details were presented in Supplementary Table 2). Of the 54 studies included in this analysis, 34 studies were related to metformin, 28 to insulin, 24 to DPP-4i, 13 to SUs, 11 to GLP-1RA, 10 to SGLT-2i, 5 to AGIs, and 3 to TZDs. The basic characteristics of the studies are presented in Supplementary Table 1. The NOS scores of all studies were no less than 6, indicating high quality.

Metformin

Totally 34 studies related to metformin were included in the quantitative analysis. Among them, 29 reported mortality, 5 reported ICU admission rate, and 2 reported incidence of mechanical ventilation. Metformin use could reduce mortality significantly in COVID-19 patients with T2D (OR = 0.66, 95% CI: 0.58-0.75, I^2 = 70%; Figure 2). However, as opposed to our expectation, no statistically significant reduction in ICU admission or mechanical ventilation was observed (ICU admission: OR = 0.99, 95% CI: 0.82-1.19, I^2 = 78%; mechanical ventilation: OR = 0.35, 95% CI: 0.01-10.41, I^2 = 97%).

Insulin

Of the 28 insulin-related studies, 23 reported mortality from COVID-19, 3 reported ICU admissions, and 2 reported the incidence of mechanical ventilation. We noted that insulin use could increase the risk of death in COVID-19 patients with T2D (OR = 1.52, 95% CI: 1.32-1.75, I^2 = 77%) (Figure 3). Insulin was also associated with a higher ICU admission rate (OR = 2.32, 95% CI: 1.34-4.01, I^2 = 98%).

DPP-4i

Totally 24 studies related to DPP-4i were included in the quantitative analysis. Among them, 20 reported mortality, 8 reported ICU admission rate, and 6 reported incidence of mechanical ventilation. No statistically significant association was identified between DPP-4i use and mortality (OR = 0.92, 95% CI: 0.80-1.06, I^2 = 67%) (Figure 4), ICU admission (OR = 1.07, 95% CI: 0.88-1.31, I^2 = 50%), or mechanical ventilation (OR = 0.82, 95% CI: 0.42-1.60, I^2 = 90%).

Other Antidiabetic Drugs

There were 13 studies related to SUs, 11 studies related to GLP-1RA, 10 studies related to SGLT-2i, 5 studies related to AGIs, and 3 studies related to TZDs included in our meta-analysis. Both SGLT-2i use (OR = 0.80, 95% CI: 0.73-0.88, I^2 = 12%) and GLP-1ra use (OR = 0.83, 95% CI: 0.70-0.98, I^2 = 47%) were associated with lower mortality risk in COVID-19 patients with T2D. However, studies related to SUs (OR = 0.97, 95% CI: 0.85-1.09, I^2 = 50%), AGIs (OR = 0.30, 95% CI: 0.05-1.85, I^2 = 88%) and TZDs (OR = 0.88, 95% CI: 0.61-1.27, I^2 = 55%) did not reveal a significant effect. The relevant results are shown in Supplementary Figures 1 to 5.

Sensitivity Analysis

Furthermore, we considered that insulin use might be associated with a patient's initial poorer physiological status and might be more likely to be admitted to the hospital. Thus, we re-examined both metformin and insulin in patients who received in-hospital treatment and obtained similar results to the main analysis, and it is reasonable to assume that

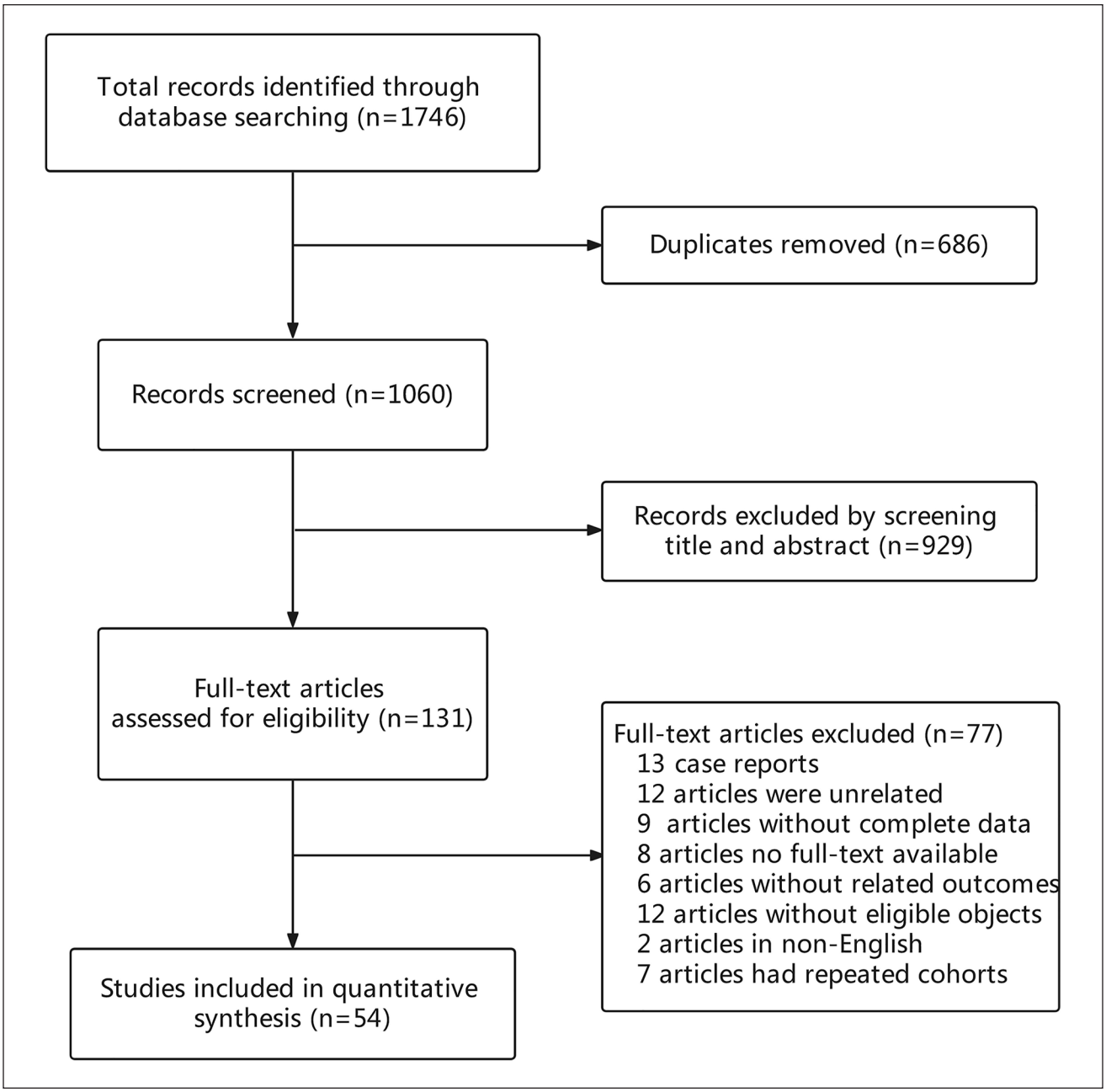

Figure 1. Flow chart of the study.

hospitalization did not play a confounding role in our study (Supplementary Figures 6–7).

Meta-Regression

The full results of the meta-regression are shown in Supplementary Figures 8 to 13 with bubble plots. Among metformin users, age ($P = .04$) had a significant effect on the association between metformin use and mortality. Among GLP-1ra users, hypertension ($P = .01$) was associated with a higher risk of death.

Publication Bias

Funnel plot and Egger's test were used to evaluate the publication bias of the included studies on the candidate antidiabetic drugs (Supplementary Figures 14–21). Asymmetry was noted in funnel plot examining the studies related to

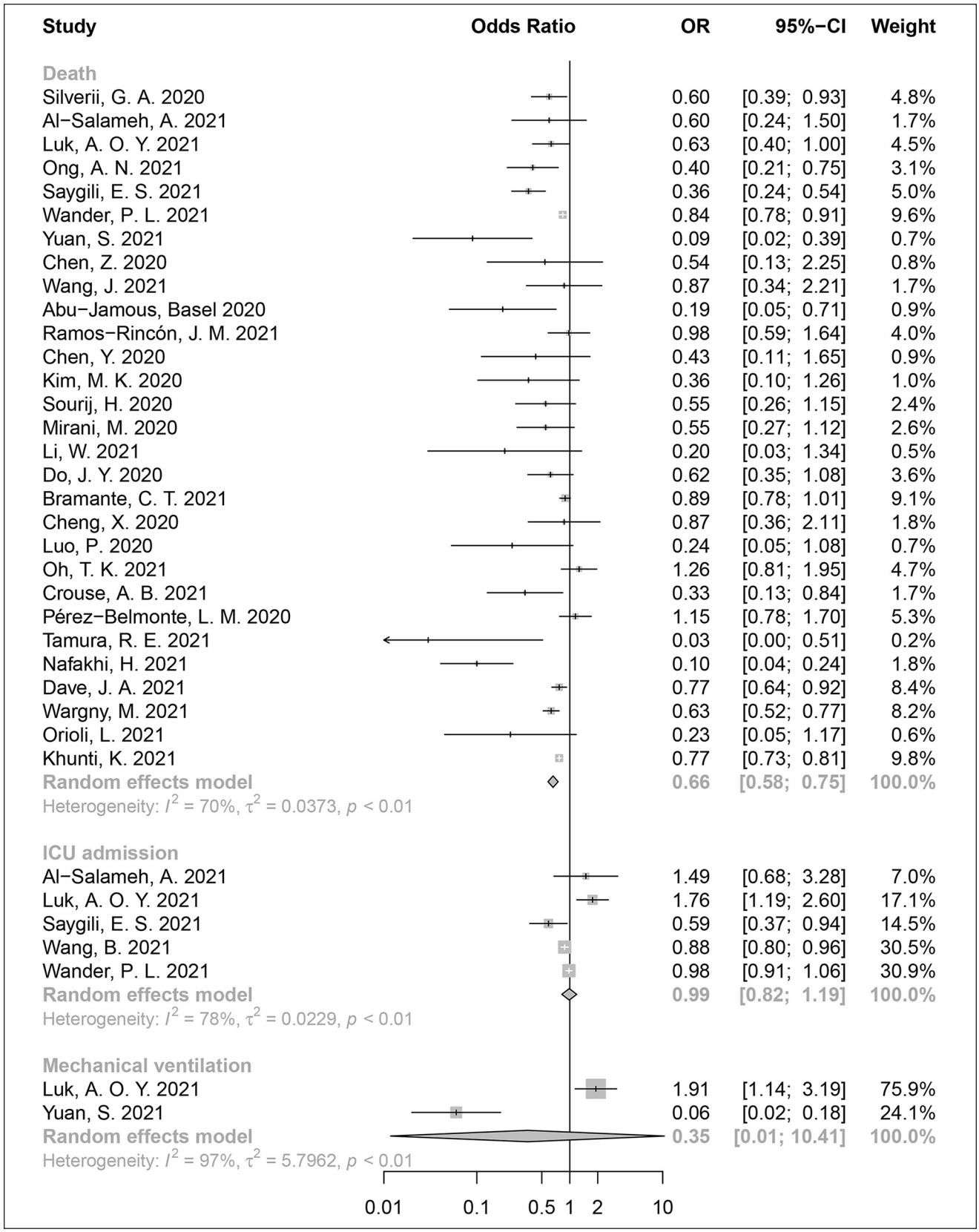

Figure 2. Forest plot for the association between metformin use and poor clinical outcomes in COVID-19 patients with T2D.

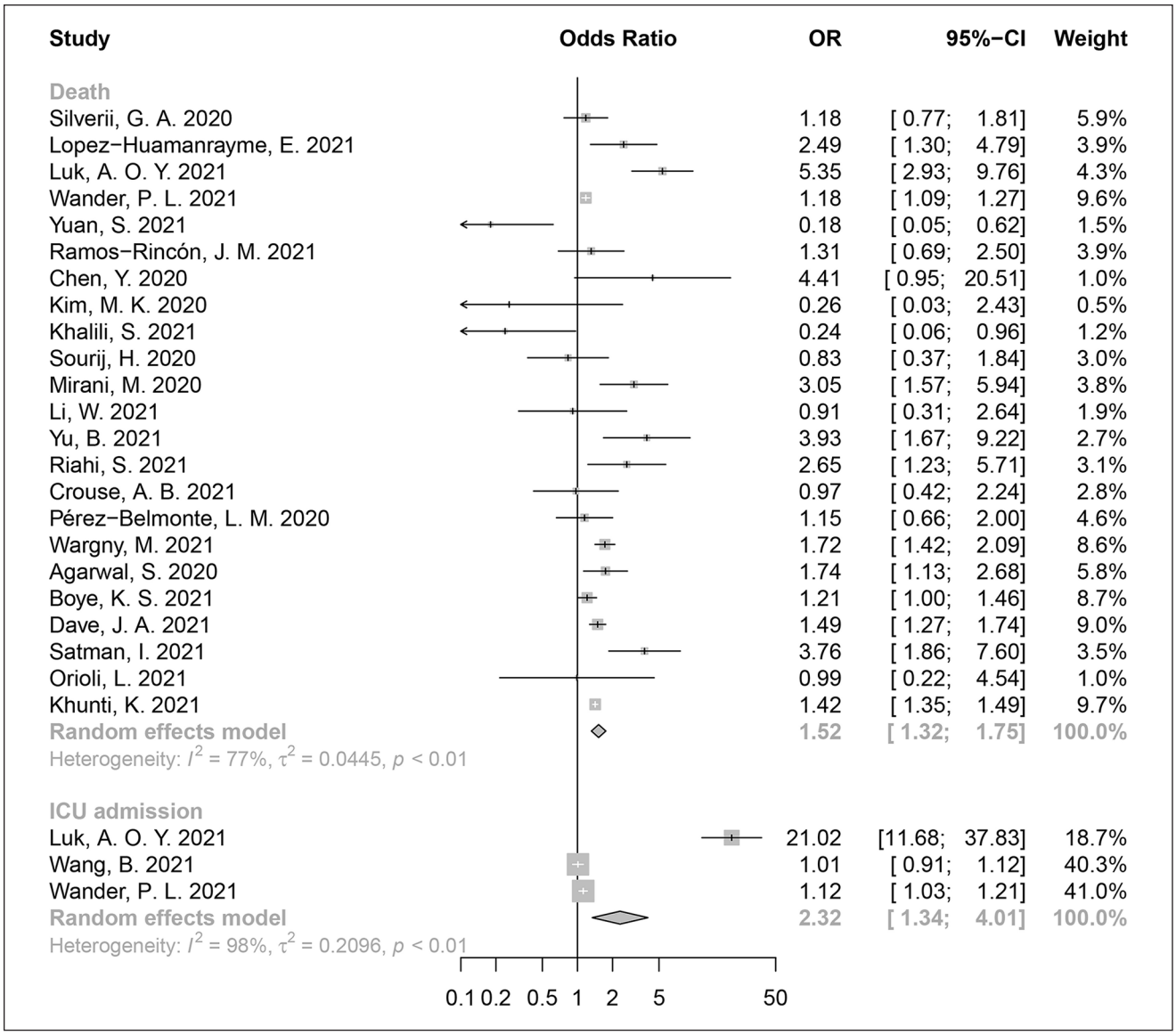

Figure 3. Forest plot for the association between insulin use and poor clinical outcomes in COVID-19 patients with T2D.

metformin use, and validated by Egger's test ($P < .01$), indicating a potential threat of publication bias.

Discussion

Based on this systematic review and meta-analysis of the available evidence, we found that usage of metformin, SGLT-2i, and GLP-1ra use were associated with a lower risk of mortality in COVID-19 patients with T2D, while insulin use could unexpectedly increase the ICU admission rate and risk of death. Meta-regression analysis demonstrated that age had a direct impact on the association between metformin use and reduced mortality. Older age was associated with a higher risk of death in metformin users. Among GLP-1ra users, hypertension was associated with a higher risk of death. However, no statistically significant associations were identified for DPP-4i, SUs, AGIs, and TZDs. To our knowledge, this study provides the most comprehensive and up-to-date overview of the evidence for the effect of antidiabetic therapy on clinical outcomes of COVID-19 patients with T2D to date.

Metformin is one of the most widely used antidiabetic drugs. In this study, metformin was identified to be associated with a lower risk of mortality in COVID-19 patients with T2D. Interestingly, a large retrospective cohort study[33] (n = 6256) demonstrated that metformin use was significantly associated with decreased mortality in female COVID-19 patients with T2D, but not in males. Another

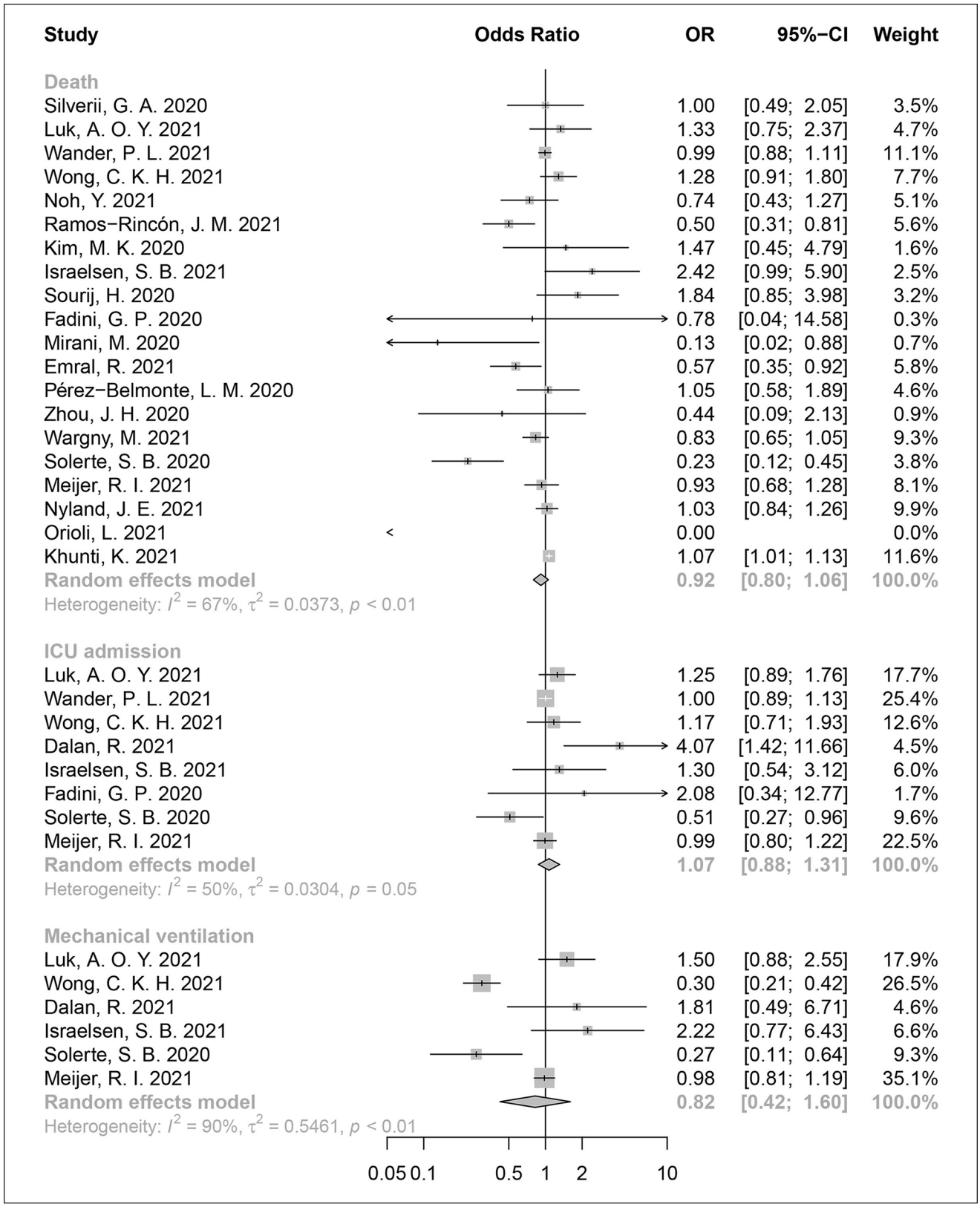

Figure 4. Forest plot for the association between DPP-4i use and poor clinical outcomes in COVID-19 patients with T2D.

retrospective study (n = 1213) by Cheng et al[28] showed a 41% reduction of heart failure risk in metformin users compared to the nonusers in COVID-19 patients with T2D. Research by Crouse et al[34] revealed that metformin use before the diagnosis of COVID-19 has more potential benefits compared to in-hospital use. Except for glycemic control, metformin also has roles of attenuating endothelial dysfunction, inhibiting viral entry and infection, and modifying inflammatory and immune responses.[35] Considering the multiple protective effects of metformin, further exploration should also expand the usage of metformin in COVID-19 patients without T2D.

Unexpectedly, we found that insulin use may increase the risk of mortality and ICU admission among COVID-19 patients with T2D in our analysis. However, these results should be interpreted with caution because insulin is usually given to patients in a late stage of diabetes.[36] It is difficult to rule out the negative effect of the more advanced diabetes on poor outcomes, especially in severe cases. Riahi et al[37] indicated that the association between insulin use and poor outcomes did not necessarily mean causation, as the severity of diabetes might play a bigger role in determining clinical outcomes among patients with COVID-19.[16,38] At present, the basal-bolus insulin regimen is still encouraged to be adopted in COVID-19 patients with T2D, especially in patients with acute hyperglycemia.[39,40] It is worth noting that diabetic patients on insulin have a higher risk of developing hypoglycemia during treatment,[41,42] and the real-time blood glucose of patients should be monitored in clinical practice to adjust their insulin dose in a timely manner.

We considered that the use of glucocorticoids during the treatment of COVID-19 patients might have a potential effect on our results. Glucocorticoids are potent anti-inflammatory and immunosuppressive drugs, and are now widely used in COVID-19 patients with respiratory failure.[43,44] However, glucocorticoids could exacerbate hyperglycemia in patients with diabetes, even cause hyperglycemia in nondiabetics,[45] and the adverse effects of hyperglycemia on patients' clinical prognosis are obvious.[46,47] There is no clear evidence that the choice of antidiabetic drugs is significantly beneficial for glucocorticoid-induced hyperglycemia. Insulin is often recommended in clinical practice as the drug of choice for inpatients with COVID-19 on glucocorticoids with hyperglycemia,[43,48] and it is clearly unreasonable to convert all patients to insulin without clear evidence.

In our pooled analysis, we did not find a significant association between DPP-4i use and risk of mortality or other clinical outcomes in COVID-19 patients with T2D. Initially, DPP-4i was considered to affect the progression of COVID-19 via their anti-inflammatory actions, which may be beneficial for patients exposed to cytokine storms due to COVID-19.[49,50] However, several large cohort studies have reported no association between DPP-4i use and mortality of COVID-19 among COVID-19 patients with T2D.[15,51,52] Interestingly, Nyland et al[15] reported that use of DPP-4i was associated with a reduction in respiratory complications (24.0% vs 29.2%; RR 0.82; 95% CI 0.74-0.90), and continued use of DPP-4i after hospitalization was associated with a decrease in mortality compared with those who discontinued use (9% vs 19%, OR 0.45, 95% CI 0.28-0.72) in a multicenter multinational retrospective cohort study.

There was also a significant association between GLP-1RA use and reduced risk of mortality in COVID-19 patients with T2D. GLP-1 exerts significant anti-inflammatory and antiatherogenic properties, supporting that GLP-1RA might attenuate acute lung disease.[53-55] Due to the cardiovascular protective action of GLP-1RA, it was used as a first-line drug to glycemic control in diabetic patients at high risk for cardiovascular diseases.[56] We also found that SGLT-2i use was associated with lower odds of mortality in COVID-19 patients with T2D. In addition, two meta-analyses reported that SGLT-2i was associated with reduced risk of cardiovascular events and chronic kidney disease progression in diabetic patients.[57,58] SGLT-2i was mainly adopted in nonsevere patients with COVID-19.[59]

This study has several limitations. First, the heterogeneity across the included studies cannot be ignored, although we have used meta-regression to explore the potential causes of heterogeneity. Second, clinical characteristics, particularly complications during hospitalization, are critical factors contributing to adverse clinical endpoints in COVID-19 patients, which may confound our results. We assessed as many patients as possible for co-existing hypertension, but not for other comorbidities or factors such as the length of diabetes. Third, most of the included studies do not include information regarding the dosage and the duration of antidiabetic drug use which might be an independent source of potential bias. Fourth, the choice of antidiabetic drugs was affected by the different status of the patients, and this could further affect the conclusion on the association between antidiabetic drugs and the prognosis of COVID-19 patients with T2D.

Conclusion and Relevance

In summary, this systematic review and meta-analysis provides the most up-to-date and comprehensive evidence for a range of antidiabetic drugs in the management of COVID-19 patients with T2D. We established that usage of metformin, SGLT-2i, and GLP-1ra could significantly decrease the mortality in COVID-19 patients with T2D. The heterogeneity across the studies, baseline characteristics of the included patients, shortage of dosage and the duration of antidiabetic drugs and autonomy of drug selection might limit the objectivity and accuracy of results. Further adequately powered and high-quality randomized controlled

trials are warranted to provide a more solid evidence-based basis for developing treatment guidelines.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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