Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Archives of Medical Research 53 (2022) 186–195

ORIGINAL ARTICLE

Association Between Anti-diabetic Agents and Clinical Outcomes of COVID-19 in Patients with Diabetes: A Systematic Review and Meta-Analysis

Tiantian Han,[a,*] Shaodi Ma,[a,*] Chenyu Sun,[b] Huimei Zhang,[a] Guangbo Qu,[a] Yue Chen,[c] Ce Cheng,[d] Eric L. Chen,[b] Mubashir Ayaz Ahmed,[b] Keun Young Kim,[b] Raveena Manem,[b] Mengshi Chen,[e] Zhichun Guo,[f] Hongru Yang,[f] Yue Yan,[f] and Qin Zhou[g]

[a] *Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Anhui Province, China*
[b] *Internal Medicine, AMITA Health Saint Joseph Hospital Chicago, Chicago, Illinois, USA*
[c] *Department of Clinical Medicine, School of the First Clinical Medicine, Anhui Medical University, Hefei, Anhui Province, China*
[d] *The University of Arizona College of Medicine at South Campus, Tucson, AZ, USA*
[e] *Hunan Provincial Key Laboratory of Clinical Epidemiology, Xiangya School of Public Health, Central South University, Changsha, Hunan Province, China*
[f] *Massachusetts college of Pharmacy and Health sciences, Boston, MA, USA*
[g] *Department of Radiation Oncology, Mayo Clinic, Rochester, MN, USA*

Received for publication June 9, 2021; accepted August 3, 2021 (ARCMED-D-21-00789).

Background and Aims. During the current Coronavirus Disease 2019 (COVID-19) pandemic, patients with diabetes face disproportionately more. This study was performed to clarify anti-inflammatory effects of anti-diabetic agents on COVID-19 in patients with diabetes.

Methods and Results. Relevant literature was searched on 15 databases up to November 14, 2020 and was updated on April 13, 2021. The pooled ORs along with 95% CIs were calculated to evaluate combined effects. 31 studies with 66,914 patients were included in qualitative and quantitative synthesis. Meta-analysis showed that metformin was associated with a statistically significant lower mortality (pooled OR = 0.62, 95% CI, 0.50–0.76, $p = 0.000$) and poor composite outcomes (pooled OR = 0.83, 95% CI, 0.71–0.97, $p = 0.022$) in diabetic patients with COVID-19. Significance of slight lower mortality remained in sulfonylurea/glinides (pooled OR = 0.93, 95% CI, 0.89–0.98, $p = 0.004$), but of poor composite outcomes was not (pooled OR = 1.48, 95% CI, 0.61–3.60, $p = 0.384$). Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) were associated with statistically non-significant lower mortality (pooled OR = 0.95, 95% CI, 0.72–1.26, $p = 0.739$) or poor composite outcomes (pooled OR = 1.27, 95% CI, 0.91–1.77, $p = 0.162$) of COVID-19 in diabetic patients.

Conclusion. Metformin might be beneficial in decreasing mortality and poor composite outcomes in diabetic patients infected with SARS-CoV-2. DPP-4 inhibitors, sulfonylurea/glinides, SGLT-2 inhibitors, and GLP-1RA would not seem to be adverse. There was insufficient evidence to conclude effects of other anti-diabetic agents. Limited by retrospective characteristics, with relative weak capability to verify causality, more prospective studies, especially RCTs are needed. Registration number: PROSPERO-CRD42020221951.

Keywords: Diabetes, Anti-diabetic agents, Metformin, DPP-4 inhibitors COVID-19, Meta-analysis.

* These authors contributed equally to this work.

Address reprint requests to: Chenyu Sun, MD, MSc, Internal Medicine, AMITA Health Saint Joseph Hospital Chicago, 2900 N. Lake Shore Drive, Chicago 60657, Illinois, USA; Phone: (+773) 665-3000. FAX: (+828) 372-4658; E-mail: drsunchenyu@yeah.net

0188-4409/$ - see front matter.
https://doi.org/10.1016/j.arcmed.2021.08.002

Introduction

During the current Coronavirus Disease 2019 (COVID-19) pandemic, there are a limited number of medications evidenced to be effective in treating COVID-19 patients (1). The global number of test-positive cases and deaths caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to increase. Accumulating evidence suggests that the release of a large amount of pro-inflammatory cytokines known as "cytokine storm" triggered by host immune response to the SARS-CoV-2 correlates directly with poor prognosis of COVID-19 (2). Diabetes mellitus was reported as a major comorbidity, ranking after hypertension and cardiovascular disease (3). The prospective Dutch COVID-PREDICT cohort showed that the presence of hypertension, dyslipidemia and diabetes led to a stepwise increased risk for short-term mortality in hospitalized COVID-19 patients independent of age and sex (4), and similar results were reported by China CDC Weekly (5) and American CDC (6). A meta-analysis containing a total of 6,452 patients from 30 studies showed that diabetes was associated with increased mortality, severe illness, Acute Respiratory Distress Syndrome (ARDS), and disease progression in patients with COVID-19, and this association might be connected by inflammatory response (7).

Anti-diabetic agents including metformin, dipeptidyl-peptidase 4 inhibitors (DPP-4i), sulfonylurea, glinides, sodium-glucose co-transporter 2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1RA), α-glycosidase inhibitors, and thiazolidinediones (TZDs) have been approved, effective, generally safe, and widely used in treating diabetes (8,9). Beyond their antidiabetic role, anti-inflammatory and antiviral effects of anti-diabetic agents have been noticed. Metformin, the most prescribed and first-line drug for diabetes, was evaluated as adjuvant therapy for patients with COVID-19 (10). Five clinical trials have been registered thus far, and previous reports of effects of metformin on clinical prognosis of COVID-19 remain controversial (11,12). DPP-4i, another commonly used antidiabetic drug, might not protect people from infection as reported in a large case-control study in which DPP-4i was more prevalent in diabetic patients with confirmed COVID-19 than those without COVID-19, but might still play an important role in protecting COVID-19 patients from organ failure and evolving pneumonia to pulmonary fibrosis (13). A clinical trial is ongoing in France to assess the efficacy of several repurposed drugs against COVID-19 including repaglinide (14). A propensity-score-matched cohort study also noted the influence of SGLT-2i on susceptibility to COVID-19 in diabetic patients (15). Unsolved queries remain about the effects of GLP-1RA, α-glycosidase inhibitors, and TZDs in patients with COVID-19. Thus, we conducted this systemic review and meta-analysis to further explore queries about effects of anti-diabetic agents on mortality and poor composite outcomes of COVID-19 in diabetic patients.

Methods

A systematic review and meta-analysis were conducted under guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements. The PROSPERO registration number is CRD42020221951.

Search Strategy and Selection Criteria

Included studies needed to meet the following criteria: a) Observational study including cohort and retrospective cohort study; b) Patients were older than 18 years of age and diagnosed with both diabetes and COVID-19; c) Home use or in-hospital use of specific anti-diabetic agents (including metformin, DPP-4i, sulfonylurea, glinides, SGLT-2i, GLP-1RA, α-glycosidase inhibitors, and TZDs) vs. drugs or therapy except specific anti-diabetic agents; d) Clinically validated definition of death, poor composite outcomes including intubation ventilation, Acute Respiratory Distress Syndrome (ARDS), Disseminated intravascular coagulation (DIC), intensive care unit (ICU) admission, disease progression, or other adverse outcomes. The following articles were excluded: a) Repeated research; b) Effective data was not applicable; c) Could not obtain full text.

A systematic literature search was performed by two reviewers on China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform, Chinese periodical service platform VIP Database, China Biology Medicine (CBM, Sinomed), MedRxiv, PubMed, ScienceDirect, Web of Science, Ovid Databases (LWW), Springer Link, Wiley Online Library, Oxford Academic, Nature Press Group, Cochrane Library, and BMJ Evidence-Based Medicine up to November 14, 2020. Literature search was updated on April 13, 2021. Search terms included anti-diabetic agents, metformin, DPP-4i, sulfonylurea, glinides, SGLT-2i, GLP-1RA, α-glycosidase inhibitors, TZDs, and COVID-19. Each search strategy was combination of one hypoglycemic agent and COVID-19. Exact search terms were shown in Supplementary Table 3. Studies in non-English were translated to English. Appendices and supplements of relevant studies were also reviewed.

Data Extraction and Analysis

Duplicate results were removed automatically and manually. We screened the remaining articles by reading the title and abstract according to the inclusion and exclusion criteria. Any disagreements were solved by discussion. Residual articles were assessed by full text. Before collecting data, quality assessment was performed by using Newcastle-Ottawa Quality Assessment Scale (16). We

developed a standardized extraction form to collect the following data: first author's name, publication year, date of study conduction, study geographical region, study design, sample size, male (percentage), age (mean and standard deviation), death, poor composite outcomes, home/in-hospital use drugs, and NOS stars. Data was extracted and checked. Disagreements were resolved by discussion. Hazard ratios (HRs) were broadly equivalent to risk ratios (RRs) when the risk is not constant with respect to time and RRs were transformed to ORs before merging (17,18).

The outcomes of interest were clinically validated definition of death, poor composite outcomes comprised of intubation ventilation, Acute Respiratory Distress Syndrome (ARDS), Disseminated intravascular coagulation (DIC), intensive care unit (ICU) admission, disease progression, or other adverse outcomes. We contacted one author for further information that was not presented in detail in one of the published studies.

Stata 14.0 (Stata, version 14; Stata Corp, College Station, TX, USA) were used for meta-analysis. The effect estimate was reported as pooled odd ratios (ORs) along with its 95% confidence intervals (95% CIs) by generic inverse variance. Pooled ORs and 95% CIs of mortality, and poor composite outcomes were calculated. Two-tailed $p \leq 0.05$ was considered statistically significant. Random effects model was chosen to promote the universality of the results. Q test and I^2 statistic was performed to judge heterogeneity. Funnel plot and Egger's test was done to investigate publication bias. Sensitivity analysis was performed to explore the source of heterogeneity and determine subsequent analysis. If applicable, subgroup analysis was performed between adjusted or unadjusted ORs, home or in-hospital use of anti-diabetic agents, different regions and in patients with only type 2 diabetes, respectively.

Results

A total of 925 records were identified through database searching up to November 14, 2020, and *18* records were added on April 13, 2021. 699 records remained after duplicates were removed. After screening the titles and abstracts, 65 records remained and were evaluated by full text. Afterwards, 34 records were excluded for the following reasons: 7 articles were unrelated; 12 articles related to mechanism; 8 articles had no clear comparable groups; 4 articles had no related outcomes; 3 articles were repetitive. Finally, the remaining 31 studies with 66914 patients were included for qualitative and quantitative synthesis (meta-analysis). The flow chart is shown in Figure 1.

Among the 31 studies included, these, 23 studies related to metformin (11,12,19–37), 13 studies related to DPP-4i (23,28,29,32,36,38–45), 5 studies related to sulfonylurea or glinides (23,29,36,41,46), 5 studies related to SGLT-2i (23,29,36,41,42) and 4 study related to GLP-1RA (23,29,42,46). Some of these studies included multiple outcomes to different medications. All included studies were assessed with ≥6 stars by NOS. All studies included in quantitative synthesis were cohort and retrospective cohort studies, and most were electronic medical records collected by clinicians with high authenticity and credibility. Details are shown in Supplementary Table 1. Meta-analysis of 20 studies investigating mortality risk of COVID-19 for diabetic patients taking metformin showed that metformin was associated with a statistically significant reduced mortality risk (pooled OR = 0.62, 95% CI, 0.50–0.76, $p = 0.000$, $I^2 = 77.6\%$) (Figure 2A).

Subgroup analysis was performed between adjusted and unadjusted data, home use and in-hospital use of medication, different geographical regions, and only patients with type 2 diabetes to explore potential confounders and expose biases. After adjustment by age, gender, comorbidities, etc., metformin use was still associated with a statistically significant reduced mortality risk in diabetic patients with COVID-19 (pooled adjusted OR = 0.73, 95% CI, 0.60–0.88, $p = 0.001$, $I^2 = 70.8\%$) (Figure 3A).Home use of metformin was associated with a statistically significant reduced death risk (pooled OR = 0.58, 95% CI, 0.47–0.71, $p = 0.000$, $I^2 = 79.5\%$), but in-hospital use of metformin did not show such an association (pooled OR = 1.14, 95% CI, 0.42–3.10, $p = 0.804$, $I^2 = 66.8\%$) (Figure 3B).The subgroup analysis based on the study locations showed a statistically significant reduced mortality risk of COVID-19 among diabetic patients using metformin in Europe (pooled OR = 0.67, 95% CI, 0.50–0.89, $p = 0.006$, $I^2 = 71.3\%$) and North America (pooled OR = 0.51, 95% CI, 0.28–0.93, $p = 0.027$, $I^2 = 78.1\%$), but not in Asia (pooled OR = 0.60, 95% CI, 0.31–1.15, $p = 0.124$, $I^2 = 83.1\%$) (Figure 3C).A subgroup analysis of study whether reported patients with only type 2 diabetes and COVID-19 showed that metformin was not associated with a statistically significant reduced mortality risk in patients with only type 2 diabetes (pooled OR = 0.95, 95% CI, 0.82–1.11, $p = 0.527$, $I^2 = 12.2\%$) while was statistically significant in patients with not only type 2 diabetes (Figure 3D).

Considering different studies reported different outcomes, we defined poor composite outcomes to include intubation ventilation, ARDS, DIC, ICU admission, disease progression, and other adverse outcomes (34,35). Studies reporting any of these outcomes were included in combined analysis. Statistically significant association was found between metformin and poor composite outcomes (pooled OR = 0.83, 95% CI, 0.71–0.97, $p = 0.022$, $I^2 = 32.1\%$) (Supplementary Figure 1).

DPP-4i were associated with statistically non-significant reduced risk of mortality (pooled OR = 0.95, 95% CI, 0.72–1.26, $p = 0.739$, $I^2 = 72.1\%$) (Supplementary Figure 2) and poor composite outcomes of COVID-19 in pa-

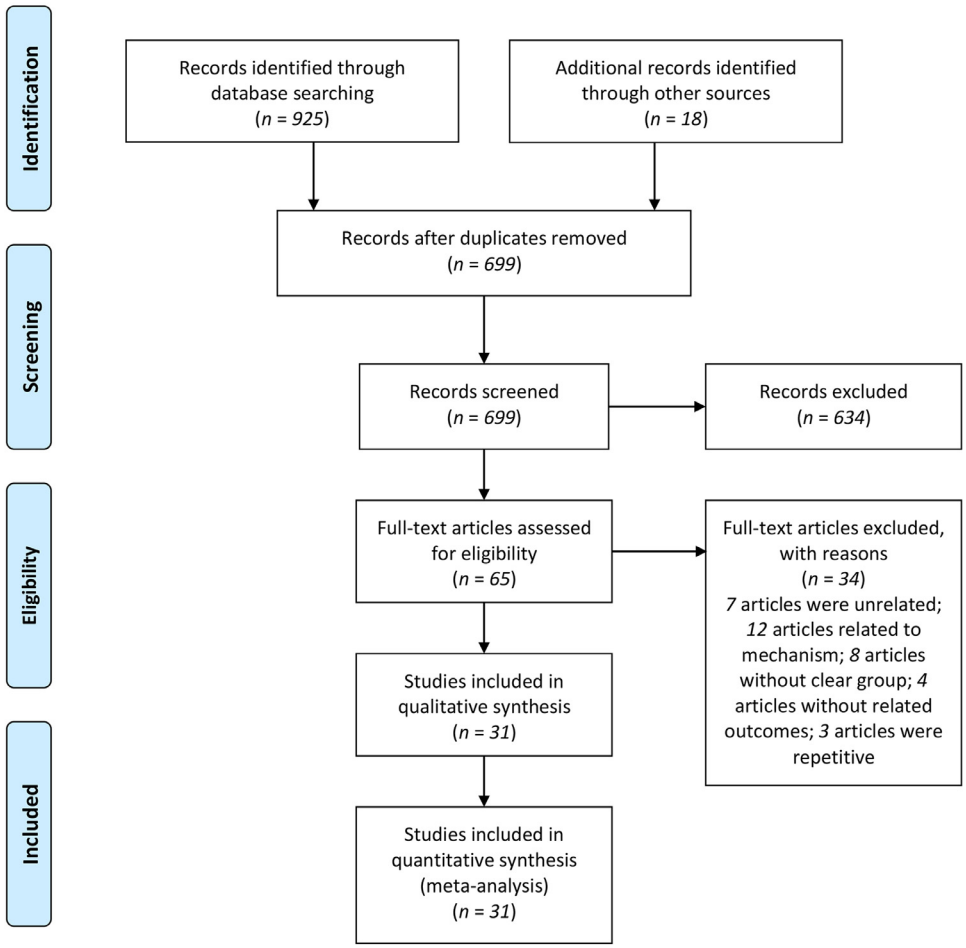

Figure 1. Flow diagram of study selection processes.

tients with diabetes (pooled OR = 1.27, 95% CI, 0.91–1.77, $p = 0.162$, $I^2 = 51.4\%$) (Supplementary Figure 3).

Quantitative analysis was conducted to effects of sulfonylurea/glinides, SGLT-2i and GLP-1RA on mortality risk and poor composite outcomes of COVID-19 in patients with diabetes. Statistical significance only existed in sulfonylurea and glinides with slightly lower mortality risk (pooled OR = 0.93, 95% CI, 0.89–0.98, $p = 0.004$, $I^2 = 0\%$). Results were showed in Table 1 and Supplementary Figure 4–9.

A funnel plot was drawn to judge the publication bias of the association between metformin and mortality risk of COVID-19 for patients with diabetes (Figure 2C). Egger's test was performed to quantitatively assess the publication bias ($p = 0.123 > 0.05$) and results showed no publication bias (Figure 2D).

We detected significant heterogeneity in analysis of the association between metformin and mortality risk of COVID-19 for diabetic patients ($I^2 = 77.6\%$). To identify the influence of individual studies on combined effects, sensitivity analysis was performed by excluding each original study. The fluctuation of the pooled ORs was found to be between 0.43 and 0.81, with lower limit and upper limit of 95% CI constantly less than 1, and p-value constantly less than 0.05, suggesting the stability of this meta-analysis. (Figure 2B).

Qualitative analysis was conducted to evaluate other anti-diabetic agents including α-glycosidase inhibitors and TZDs. Quantitative analysis was not performed due to insufficient data. Two studies investigated TZDs' effects on mortality risk of COVID-19 in patients with diabetes (23,29). One study investigated the use of α-glycosidase inhibitors (23). No statistically significant effect on mortality risk or poor composite outcomes was found (47). The results may have been limited by the study design.

Discussion

As reported in a retrospective cohort of hospitalized patients in the UK, long-term antidiabetic medications reduced COVID-19 mortality in diabetic patients (30), especially as diabetic patients are particularly susceptible to cumulative organ injury by SARS-CoV-2 because of already compromised pulmonary, cardiac and renal

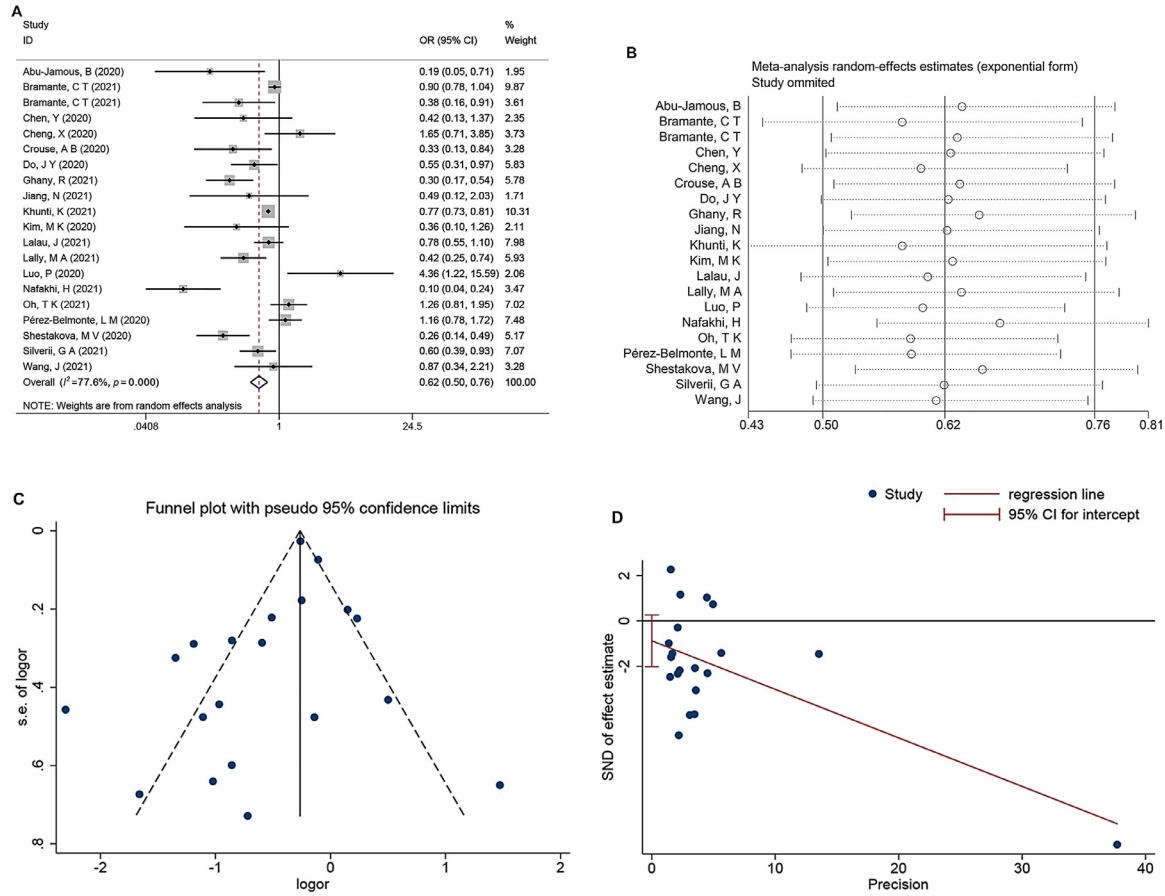

Figure 2. Metformin and mortality risk of COVID-19 in patients with diabetes (A. forest plot; B. sensitivity analysis; C. funnel plot; D. Egger regression).

Table 1. The main results of the meta-analysis

Results	*df*	Pooled OR (95% CI)	*p*	I^2	*p* for Egger regression
Metformin death	*19*	0.62 (0.50, 0.76)	$p = 0.000$	77.60%	0.123
Death adjusted	*15*	0.73 (0.60, 0.88)	$p = 0.001$	70.80%	/
Death unadjusted	*3*	0.29 (0.13, 0.65)	$p = 0.002$	78.80%	/
Death home use of drugs	*15*	0.58 (0.47, 0.71)	$p = 0.000$	79.50%	/
Death in-hospital use of drugs	*3*	1.14 (0.42, 3.10)	$p = 0.804$	66.80%	/
Death Europe	*6*	0.67 (0.50, 0.89)	$p = 0.006$	71.30%	/
Death North America	*3*	0.51 (0.28, 0.93)	$p = 0.027$	78.10%	/
Death Asia	*8*	0.60 (0.31, 1.15)	$p = 0.124$	83.10%	/
Death not only T2D	*12*	0.42 (0.29, 0.62)	$p = 0.000$	81.80%	/
death only T2D	*6*	0.95 (0.82, 1.11)	$p = 0.527$	12.20%	/
Metformin poor composite outcomes	*16*	0.83 (0.71, 0.97)	$p = 0.022$	32.10%	0.981
DPP-4i death	*10*	0.95 (0.72, 1.26)	$p = 0.739$	72.10%	0.562
DPP-4i poor composite outcomes	*11*	1.27 (0.91, 1.77)	$p = 0.162$	51.40%	0.089
Sulfonylurea/glinides death	*3*	0.93 (0.89, 0.98)	$p = 0.004$	0.00%	0.761
Sulfonylurea/glinides poor composite outcomes	*2*	1.48 (0.61, 3.60)	$p = 0.384$	37.10%	0.17
SGLT-2i death	*2*	1.04 (0.56, 1.92)	$p = 0.904$	38.00%	0.114
SGLT-2i poor composite outcomes	*3*	0.81 (0.47, 1.40)	$p = 0.458$	0.00%	0.296
GLP-1RA death	*2*	0.92 (0.80, 1.04)	$p = 0.190$	2.30%	0.044
GLP-1RA poor composite outcomes	*1*	0.86 (0.51, 1.44)	$p = 0.558$	0.00%	/

functions. Therefore, furthering our understanding of antidiabetic medications can yield a practical and effective approach in dramatically improving outcomes in this vulnerable population disproportionately affected by COVID-19.

The result of our meta-analysis showed that metformin was associated with a statistically significant reduced mortality risk of COVID-19 in patients with diabetes, both before and after adjusting for other factors. This was consistent with several previous small-scale meta-analyses

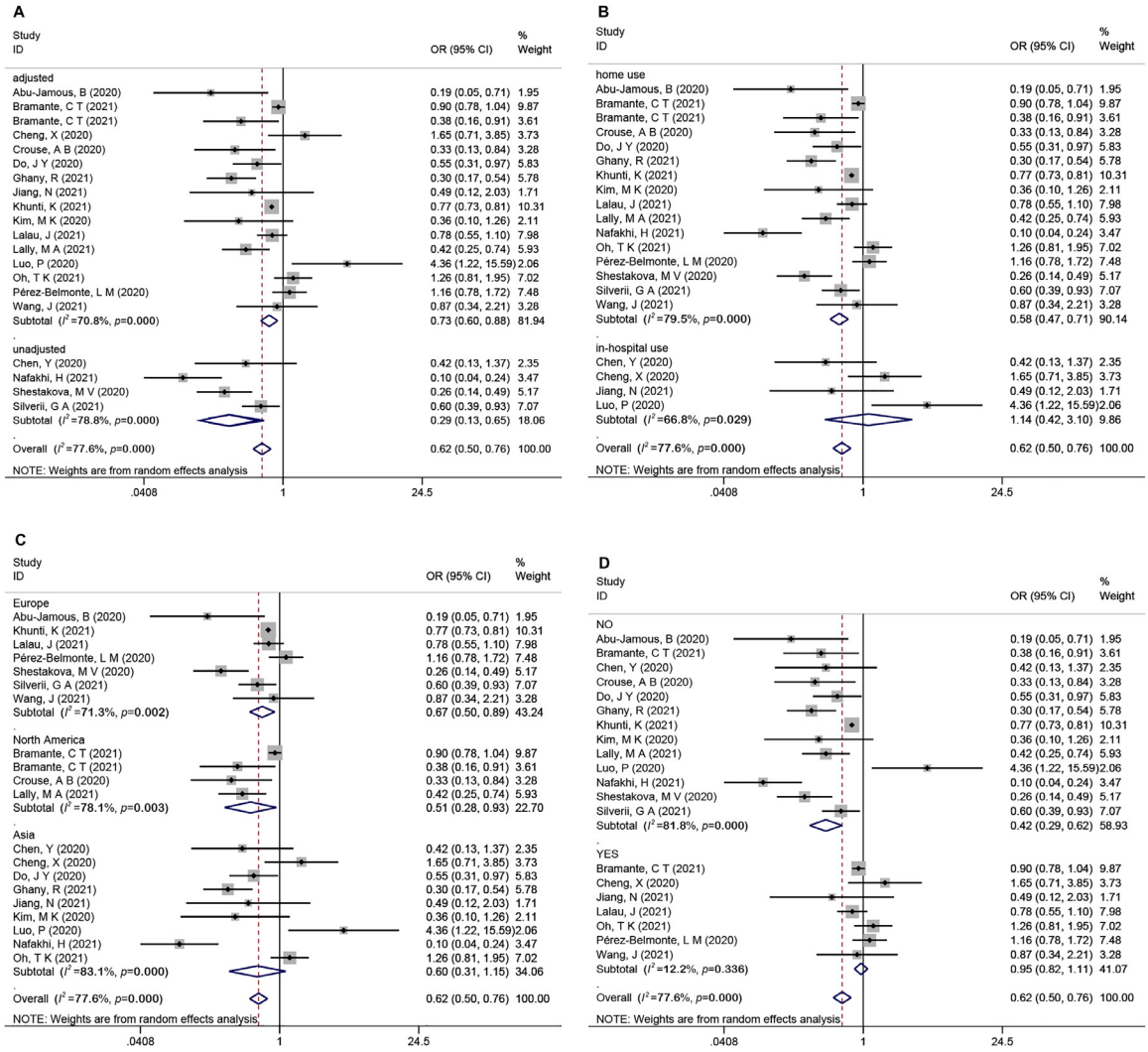

Figure 3. Metformin and mortality of COVID-19 in patients with diabetes: subgroup analysis (A. adjusted vs. unadjusted; B. home use vs. in-hospital use of drugs; C. different continents; D. not only type 2 diabetes vs. only type 2 diabetes).

(48–50). Comparison between this meta-analysis with previous analyses was shown in Supplementary Table 2. Home use of metformin was more effective compared to in-hospital use, which was shown in previous analyses (51). This might be explained by side effects, e.g., an increased risk for metabolic acidosis (11), induced by metformin (52) in hospitalized patients. In patients with organ function compromised by COVID-19, the benefits of metformin were likely to be overshadowed by its side effects (11,53). As a result, metformin was discontinued and switched to insulin for inpatients in many countries. However, choice of anti-diabetic medications was affected by different status of patients, and this could further affect the conclusion of association between anti-diabetic agents and prognosis of COVID-19. Benefits of metformin on mortality were more obvious in Europe and North America compared to Asia according to our analysis, although the benefits of metformin were still evident in the United States. For example, a large retrospective review from UnitedHealth Group's Clinical Discovery Database in the USA reported that home use of metformin was significantly associated with reduced mortality in female inpatients with COVID-19, and reduction of TNF-α might underly the mechanistic pathway (31). In addition, confounders such as race, gender, and disease severity require further study. Metformin had beneficial effects on poor composite outcomes including tracheal intubation, ARDS, DIC, ICU admission, and disease progression, indicating anti-inflammatory effects of metformin. Current discussions on metformin's role in reducing COVID-19 mortality involves several different mechanisms. One possible mechanism is that metformin inhibits cytokine storm by suppressing interleukin-6 (IL-6) signaling, preventing the process of lung fibrosis, and suppressing endocytosis, thereby elevating angiotensin converting enzyme 2 (ACE2) expression (54). Increased ACE2 offers cardiopulmonary benefits

in patients with COVID-19 by activating AMP-activated protein kinase (AMPK), which is involved in phosphorylating key molecules regulating metabolism and cardiovascular health (55). Activated AMPK phosphorylates ACE2, thereby changing conformation and function of ACE2 and resulting in decreased integration with the SARS-CoV-2 receptor and binding domain due to steric hindrance (56). The mortality benefits may also be explained by metformin's effect on cellular pH, which needs to be acidic for optimal viral membrane fusion of SARS-CoV-2. By increasing cellular pH, metformin subsequently interferes with the endocytic cycle to inhibit viral infection by acting on the eNHEs and/or the V-ATPase (10). Reducing production of pro-inflammatory cytokines by macrophages and formation of neutrophil extracellular traps (NETs) might play a role as well (53). Although current evidence supports metformin use, further studies are needed to understand its mechanistic link to mortality benefits.

Use of DPP-4i for diabetic patients is associated with statistically non-significant reduced mortality risk or poor composite outcomes of COVID-19 according to our analysis. This was consistent with previous meta-analyses (57) but was conflicting with the other research (58,59). Previous studies comparing the prevalence of DPP-4i use between diabetic patients with or without COVID-19 showed that DPP-4i use was more prevalent in COVID-19 patients (60), implying that DPP-4i might not prevent people from contracting SARS-CoV-2 (61). However, some opinions indicated that diabetic patients with COVID-19 could benefit from DPP-4i not only by controlling blood glucose, but also improving long-term prognosis of COVID-19 caused by pulmonary fibrosis, heart, and kidney injury via blocking the tissue remodeling function of activating myofibroblasts and migrating fibroblasts, suppressing inflammatory sign, and proliferating vascular smooth muscle cells to avoid adverse outcomes (13). As DPP-4 is hypothesized to be a binding partner for corona-like viruses to enter host immune cells, DPP-4i also exerts influence on prohibiting invasion of SARS-CoV-2 into cells (62). However, concentration of circulating soluble DPP-4 serum in patients suffering from severe COVID-19 was significantly lower compared to that in healthy human subjects (63), which contradicts the protective effects of DPP-4i. In addition, it is not recommended DPP-4i for patients with COVID-19 and diabetes with a hypercoagulability state as DPP-4 inhibitors have the potential to induce a prothrombic state, especially sitagliptin (64). Sitagliptin, a DPP-4i drug, was thought to have anti-inflammatory effects on diabetic patients via the NF-κ-β signaling pathway (65). This hypothesis needs to be verified by more studies.

Significance of slight lower mortality was found in sulfonylurea/glinides users. A nationwide observational cohort study from England evaluated effects of sulfonylurea (23) weighted more in pooled estimates. Results suggest that continuous treatment of sulfonylurea or glinidesis might be safe for patients with COVID-19 and diabetes without additional risks and burdens according to existing reports. So, the SGLT-2i and GLP-1RA were. Existing studies of other anti-diabetic agents, including α-glycosidase inhibitors, and TZDs, were insufficient for quantitative analysis. Apart from existing clinical studies, an *in vitro* experiment found that E protein, a potential ion channel on SARS-CoV-2, could be inhibited by Gliclazide (a type of sulfonylurea) (66). A propensity-score-matched cohort study showed that SGLT-2i did not decrease susceptibility compared to DPP-4i (15). Dapagliflozin, a type of SGLT-2i, was assumed to reduce the viral load by lowering of cytosolic pH (67). GLP-1RA was considered for treating asymptomatic and non-critically ill COVID-19 patients due to its anti-inflammatory effects (68) and this effect might be related with ACE2 as well. Pioglitazone, a common type of TZDs, was recommended to treat COVID-19 patients for its potential to improve liver injuries (69) and block macrophage activation by uptake of oxidized LDL to reduce the progression of atherosclerosis, which results in less risk of developing into severe illness of COVID-19 (70).

Heterogeneity existed in analysis of effects of metformin and DPP-4i on mortality risk and poor composite outcomes. Even after subgroup analysis of adjusted and unadjusted data, home use and in-hospital use of medication, different geographic regions, heterogeneity was not eliminated or significantly reduced. I^2 was only decreased in analysis of metformin and mortality of COVID-19 in only type 2 diabetes. Sensitivity analysis did not identify any specific original study that led to unstable results, which might be explained by the discrepancy of included studies themselves. Gender ratio and average age accounted for a portion of unstable results as female and young patients (33,37) reportedly have a better prognosis. Elements including duration of medication (from $<$21 d to $>$6 months) (30), dose, common drugs in exposure and control groups (32), long-term blood glucose control (HbA1c) (37,71), BMI (31) and comorbidities (72) varied in different studies and were likely related to heterogeneity. Moreover, the assessment of association between metformin and death risk of COVID-19 included both patients who were constantly on metformin, and those who were previously on metformin but not on them while enrolled in those studies. This could lead to heterogeneity and bias to a certain extent. Additionally, considering patients with diabetes that only require metformin for glucose control might be theoretically less susceptible to SARS-Cov-2 infection (73), this might confound assessment of association between metformin and death risk of COVID-19. Results showed unstable predictive effects and heterogeneity which urges some caution about the findings.

In addition, there are several other potential limitations. Firstly, meta-analyses are inherently subject to design biases and variations of included original studies with discrepancies in methods and patient characteristics; despite

this, statistically significant results were achieved by inclusion of large-sample studies and more original studies, as well as various dimensions and parameters of analysis to expose confounding variables and narrow this discrepancy. Although most studies contained in our analysis were electronic medical records collected by clinicians with high authenticity and credibility, most studies were retrospective cohort studies with relative weak capability to verify causality. As participants of Bramante' study included both diabetic patients and patients with obesity (31), confounding factors such as obesity may have influenced the result. We contacted the author for raw data, but as there was no response, the HR was directly merged with other studies' OR which may marginally affect the pooled OR, but would not change the final conclusion.

Conclusion

Metformin might be beneficial in decreasing mortality and poor composite outcomes (intubation ventilation, ARDS, ICU admission, disease progression, and other adverse outcomes) in diabetic patients infected with SARS-CoV-2. Long-term home use of metformin is strongly supported because of its anti-inflammatory and antiviral effects. DPP-4 inhibitors, sulfonylurea/glinides, SGLT-2 inhibitors, and GLP-1RA would not increase risk of death or poor composite outcomes of COVID-19 in patients with diabetes. Current evidence is insufficient to draw a solid conclusion regarding the effects of α-glycosidase inhibitors or TZD on clinical outcomes of COVID-19 in diabetic patients. More prospective research studies, especially RCTs, are needed to verify and explore the effects of anti-diabetic agents on COVID-19 in diabetic patients.

Conflic of Interest

This study is financially supported by Hunan Provincial Key Laboratory of Clinical Epidemiology (grant number: 2020ZNDXLCL002). We declare no competing interest.

Acknowledgements

Tiantian Han and Dr. Chenyu Sun designed research; Tiantian Han, Shaodi Ma, Huimei Zhang and Guangbo Qu conducted literature search and data extraction; Tiantian Han, Shaodi Ma, Huimei Zhang, Guangbo Qu and Dr. Chenyu Sun analyzed data; Tiantian Han and Dr. Chenyu Sun wrote the manuscript. Dr. Chenyu Sun, Yue Chen, Dr. Ce Cheng, Dr. Eric L. Chen, Dr. Mubashir Ayaz Ahmed, Dr. Keun Young Kim, Dr. Raveena Manem, Mengshi Chen, Zhichun Guo, Hongru Yang, Yue Yan; Dr. Qin Zhou revised the paper. All authors contributed critically for content, commented on previous versions of the manuscript, and approved the final manuscript. We appreciate all authors for their contributions, and support from AMITA Health Saint Joseph Hospital Chicago and Anhui Medical University.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2021.08.002.

References

1. Jean S, Lee P, Hsueh P. Treatment options for COVID-19: The reality and challenges. J Microbiol Immunol Infect 2020;53:436–443.
2. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol 2021;93:250–256.
3. Emami A, Javanmardi F, Pirbonyeh N, et al. Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. Arch Acad Emerg Med 2020;8:e35.
4 Collard D, Nurmohamed NS, Kaiser Y, et al. Cardiovascular risk factors and COVID-19 outcomes in hospitalised patients: a prospective cohort study. BMJ open 2021;11(2):e045482. doi:10.1136/bmjopen-2020-045482.
5. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (Team TNCP). The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19)- China. China CDC Wkly 2020 2020;2:113–122. doi:10.46234/ccdcw2020.032.
6. National Center for Immunization and Respiratory Diseases (NCIRD)Division of Viral Diseases (DOVD). Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19 November 2, 2020. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html Accessed.
7. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia-A systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr 2020;14:395–403.
8. Chinese Diabetes SocietyGuidelines for the prevention and control of type 2 diabetes in China. Chinese Journal of Practical Internal Medicine 2018;38:292–344. doi:10.19538/j.nk2018040108.
9 9 American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44(S1):S111–S124. doi:10.2337/dc21-S009.
10. Esam Z. A proposed mechanism for the possible therapeutic potential of Metformin in COVID-19. Diabetes Res Clin Pract 2020;167:108282.
11. Cheng X, Liu Y, Li H, et al. Metformin Is Associated with Higher Incidence of Acidosis, but Not Mortality, in Individuals with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab 2020;32:537–547 e3.
12. Luo P, Qiu L, Liu Y, et al. Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis. Am J Trop Med Hyg 2020;103:69–72.
13. Smelcerovic A, Kocic G, Gajic M, et al. DPP-4 Inhibitors in the Prevention/Treatment of Pulmonary Fibrosis, Heart and Kidney Injury Caused by COVID-19-A Therapeutic Approach of Choice in Type 2 Diabetic Patients? Front Pharmacol 2020;11:1185.
14. Duvignaud A, Lhomme E, Pistone T, et al. Home Treatment of Older People with Symptomatic SARS-CoV-2 Infection (COVID-19): A structured Summary of a Study Protocol for a Multi-Arm Multi-Stage (MAMS) Randomized Trial to Evaluate the Efficacy and Tolerability of Several Experimental Treatments to Reduce the Risk of Hospitalisation or Death in outpatients aged 65 years or older (COVERAGE trial). Trials 2020;21:846.

15. Sainsbury C, Wang J, Gokhale K, et al. Sodium-glucose co–transporter-2 inhibitors and susceptibility to COVID-19: A population-based retrospective cohort study. Diabetes Obes Metab 2021;23:263–269.
16. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute 2000. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Accessed November 2, 2020.
17. Ronksley PE, Brien SE, Turner BJ, et al. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ 2011;342:d671.
18. Stare J, Maucort-Boulch D. Odds Ratio, Hazard Ratio and Relative Risk. Metodoloski Zvezki 2016;13:59–67.
19. Bramante CT, Buse J, Tamaritz L, et al. Outpatient metformin use is associated with reduced severity of COVID-19 disease in adults with overweight or obesity. J Med Virol 2021;93:4273–4279.
20. Cheng X, Xin S, Chen Y, et al. Effects of metformin, insulin on COVID-19 patients with pre-existed type 2 diabetes: A multicentral retrospective study. Life Sci 2021;275:119371.
21. Ghany R, Palacio A, Dawkins E, et al. Metformin is associated with lower hospitalizations, mortality and severe coronavirus infection among elderly medicare minority patients in 8 states in USA. Diabetes Metab Syndr 2021;15:513–518.
22. Jiang N, Chen Z, Liu L, et al. Association of metformin with mortality or ARDS in patients with COVID-19 and type 2 diabetes: A retrospective cohort study. Diabetes Res Clin Pract 2021;173:108619.
23. Khunti K, Knighton P, Zaccardi F, et al. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. Lancet Diabetes Endocrinol 2021;9:293–303.
24. Lalau JD, Al-Salameh A, Hadjadj S, et al. Metformin use is associated with a reduced risk of mortality in patients with diabetes hospitalised for COVID-19. Diabetes Metab 2021;47:101216.
25. Lally MA, Tsoukas P, Halladay CW, et al. Metformin is Associated with Decreased 30-Day Mortality Among Nursing Home Residents Infected with SARS-CoV2. J Am Med Dir Assoc 2021;22:193–198.
26. Nafakhi H, Alareedh M, Al-Buthabhak K, et al. Predictors of adverse in-hospital outcome and recovery in patients with diabetes mellitus and COVID-19 pneumonia in Iraq. Diabetes Metab Syndr 2021;15:33–38.
27. Oh TK, Song IA. Metformin use and risk of COVID-19 among patients with type II diabetes mellitus: an NHIS-COVID-19 database cohort study. Acta Diabetol 2021;58:771–778.
28. Pérez-Belmonte LM, Torres-Peña JD, López-Carmona MD, et al. Mortality and other adverse outcomes in patients with type 2 diabetes mellitus admitted for COVID-19 in association with glucose-lowering drugs: a nationwide cohort study. BMC Med 2020;18:359.
29. Silverii GA, Monami M, Cernigliaro A, et al. Are diabetes and its medications risk factors for the development of COVID-19? Data from a population-based study in Sicily. Nutr Metab Cardiovasc Dis 2021;31:396–398.
30. Abu-Jamous B, Anisimovich A, Baxter J, et al. Associations of comorbidities and medications with COVID-19 outcome: A retrospective analysis of real-world evidence data. medRxiv 2020.08.20:.20174169. doi:10.1101/2020.08.20.20174169.
31. Bramante CT, Ingraham NE, Murray TA, et al. Metformin and risk of mortality in patients hospitalised with COVID-19: a retrospective cohort analysis. Lancet Healthy Longev 2021;2:e34–e41.
32. Chen Y, Yang D, Cheng B, et al. Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication. Diabetes Care 2020;43:1399–1407.
33 Crouse AB, Grimes T, Li P, et al. Metformin Use Is Associated With Reduced Mortality in a Diverse Population With COVID-19 and Diabetes. Front Endocrinol (Lausanne) 2021;11:600439. doi:10.3389/fendo.2020.600439.
34. Do JY, Kim SW, Park JW, et al. Is there an association between metformin use and clinical outcomes in diabetes patients with COVID-19? Diabetes Metab 2020;101208. doi:10.1016/j.diabet.2020.10.006.
35. Gao Y, Liu T, Zhong W, et al. Risk of Metformin in Patients With Type 2 Diabetes With COVID-19: A Preliminary Retrospective Report. Clin Transl Sci 2020;13:1055–1059.
36. Kim MK, Jeon JH, Kim SW, et al. The Clinical Characteristics and Outcomes of Patients with Moderate-to-Severe Coronavirus Disease 2019 Infection and Diabetes in Daegu, South Korea. Diabetes Metab J 2020;44:602–613.
37. Shestakova MV, Vikulova OK, Isakov MA, et al. Diabetes and COVID-19: analysis of the clinical outcomes according to the data of the Russian diabetes registry. Probl Endokrinol (Mosk) 2020;66:35–46.
38. Fadini GP, Morieri ML, Longato E, et al. Exposure to dipeptidyl-peptidase-4 inhibitors and COVID-19 among people with type 2 diabetes: A case-control study. Diabetes Obes Metab 2020;22:1946–1950.
39. Rhee SY, Lee J, Nam H, et al. Effects of a DPP-4 Inhibitor and RAS Blockade on Clinical Outcomes of Patients with Diabetes and COVID-19. Diabetes Metab J 2021;45:251–259.
40. Solerte SB, D'Addio F, Trevisan R, et al. Sitagliptin Treatment at the Time of Hospitalization Was Associated With Reduced Mortality in Patients With Type 2 Diabetes and COVID-19: A Multicenter, Case-Control, Retrospective, Observational Study. Diabetes Care 2020;43:2999–3006.
41. Dalan R, Ang LW, Tan WYT, et al. The association of hypertension and diabetes pharmacotherapy with COVID-19 severity and immune signatures: an observational study. Eur Heart J Cardiovasc Pharmacother 2021;7:e48–e51.
42. Israelsen SB, Pottegård A, Sandholdt H, et al. Comparable COVID-19 outcomes with current use of GLP-1 receptor agonists, DPP-4 inhibitors, or SGLT-2 inhibitors among patients with diabetes who tested positive for SARS-CoV-2. Diabetes Obes Metab 2021;23:1397–1401.
43. Noh Y, Oh IS, Jeong HE, et al. Association Between DPP-4 Inhibitors and COVID-19-Related Outcomes Among Patients With Type 2 Diabetes. Diabetes Care 2021;44:e64–e66.
44. Roussel R, Darmon P, Pichelin M, et al. Use of dipeptidyl peptidase-4 inhibitors and prognosis of COVID-19 in hospitalized patients with type 2 diabetes: A propensity score analysis from the CORONADO study. Diabetes Obes Metab 2021;23:1162–1172.
45. Zhou JH, Wu B, Wang WX, et al. No significant association between dipeptidyl peptidase-4 inhibitors and adverse outcomes of COVID-19. World J Clin Cases 2020;8:5576–5588.
46. Wargny M, Potier L, Gourdy P, et al. Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study. Diabetologia 2021;64:778–794.
47. Cariou B, Hadjadj S, Wargny M, et al. Correction to: Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020;63:1953–1957.
48. Hariyanto TI, Kurniawan A. Metformin use is associated with reduced mortality rate from coronavirus disease 2019 (COVID-19) infection. Obes Med 2020;19:100290. doi:10.1016/j.obmed.2020.100290.
49. Lukito AA, Pranata R, Henrina J, et al. The Effect of Metformin Consumption on Mortality in Hospitalized COVID-19 patients: a systematic review and meta-analysis. Diabetes Metab Syndr 2020;14:2177–2183.
50. Zangiabadian M, Nejadghaderi SA, Zahmatkesh MM, et al. The Efficacy and Potential Mechanisms of Metformin in the Treatment of COVID-19 in the Diabetics: A Systematic Review. Front Endocrinol (Lausanne) 2021;12:645194. doi:10.3389/fendo.2021.645194.

51. Kow CS, Hasan SS. Mortality risk with preadmission metformin use in patients with COVID-19 and diabetes: A meta-analysis. J Med Virol 2021;93:695–697.
52. Wang GS, Hoyte C. Review of Biguanide (Metformin) Toxicity. J Intensive Care Med 2019;34:863–876.
53. Chen X, Guo H, Qiu L, et al. Immunomodulatory and Antiviral Activity of Metformin and Its Potential Implications in Treating Coronavirus Disease 2019 and Lung Injury. Front Immunol 2020;11:2056.
54. Pan Y, Han R, He Y. Metformin: one of the possible options to reduce the mortality of severe coronavirus disease 2019? Zhonghua wei zhong bing ji jiu yi xue 2020;32:1131–1134 [Article in Chinese].
55 Malhotra A, Hepokoski M, McCowen KC, et al. ACE2, Metformin, and COVID-19. iScience 2020;23(9):101425. doi:10.1016/j.isci.2020.101425.
56. Sharma S, Ray A, Sadasivam B. Metformin in COVID-19: A possible role beyond diabetes. Diabetes Res Clin Pract 2020;164:108183. doi:10.1016/j.diabres.2020.108183.
57. Bonora BM, Avogaro A, Fadini GP. Disentangling conflicting evidence on DPP-4 inhibitors and outcomes of COVID-19: narrative review and meta-analysis. J Endocrinol Invest 2021;44:1379–1386.
58. Rakhmat II, Kusmala YY, Handayani DR, et al. Dipeptidyl peptidase-4 (DPP-4) inhibitor and mortality in coronavirus disease 2019 (COVID-19)-A systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr 2021;15:777–782.
59. Pal R, Banerjee M, Mukherjee S, et al. Dipeptidyl peptidase-4 inhibitor use and mortality in COVID-19 patients with diabetes mellitus: an updated systematic review and meta-analysis. Ther Adv Endocrinol Metab 2021;12:2042018821996482. doi:10.1177/2042018821996482.
60. Yan H, Valdes AM, Vijay A, et al. Role of Drugs Used for Chronic Disease Management on Susceptibility and Severity of COVID-19: A Large Case-Control Study. Clin Pharmacol Ther 2020;108:1185–1194.
61. Scheen AJ, Marre M, Thivolet C. Prognostic factors in patients with diabetes hospitalized for COVID-19: Findings from the CORONADO study and other recent reports. Diabetes Metab 2020;46:265–271.
62. Bardaweel SK, Hajjo R, Sabbah DA. Sitagliptin: a potential drug for the treatment of COVID-19? Acta Pharm 2021;71:175–184.
63. Schlicht K, Rohmann N, Geisler C, et al. Circulating levels of soluble Dipeptidylpeptidase-4 are reduced in human subjects hospitalized for severe COVID-19 infections. Int J Obes (Lond) 2020;44:2335–2338.
64. Kow CS, Hasan SS. Use of DPP-4 inhibitors in patients with COVID-19. Acta Diabetol 2021;58:245–246.
65. Mozafari N, Azadi S, Mehdi-Alamdarlou S, et al. Inflammation: A bridge between diabetes and COVID-19, and possible management with sitagliptin. Med Hypotheses 2020;143:110111. doi:10.1016/j.mehy.2020.110111.
66. Singh Tomar PP, Arkin IT. SARS-CoV-2 E protein is a potential ion channel that can be inhibited by Gliclazide and Memantine. Biochem Biophys Res Commun 2020;530:10–14.
67. Cure E, Cumhur Cure M. Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis. Diabetes Metab Syndr 2020;14:405–406.
68. Longo M, Caruso P, Maiorino MI, et al. Treating type 2 diabetes in COVID-19 patients: the potential benefits of injective therapies. Cardiovasc Diabetol 2020;19:115.
69. Penlioglou T, Papachristou S, Papanas N. COVID-19 and Diabetes Mellitus: May Old Anti-diabetic Agents Become the New Philosopher's Stone? Diabetes Ther 2020;11:1–3.
70. Erol A. Role of oxidized LDL-induced "trained macrophages" in the pathogenesis of COVID-19 and benefits of pioglitazone: A hypothesis. Diabetes Metab Syndr 2020;14:713–714.
71. Zhu L, She ZG, Cheng X, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab 2020;31:1068–1077.
72. Iaccarino G, Grassi G, Borghi C, et al. Age and Multimorbidity Predict Death Among COVID-19 Patients. Hypertension 2020;76:366–372.
73. Wang J, Cooper JM, Gokhale K, et al. Association of Metformin with Susceptibility to COVID-19 in People with Type 2 Diabetes. J Clin Endocrinol Metab 2021;106:1255–1268.