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Preadmission use of antidiabetic medications and mortality among patients with COVID-19 having type 2 diabetes: A meta-analysis

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ABSTRACT

Background: Diabetes is an independent predictor of poor outcomes in patients with COVID-19. We compared the effects of the preadmission use of antidiabetic medications on the in-hospital mortality of patients with COVID-19 having type 2 diabetes.

Methods: A systematic search of PubMed, EMBASE, Scopus and Web of Science databases was performed to include studies (except case reports and review articles) published until November 30, 2021. We excluded papers regarding in-hospital use of antidiabetic medications. We used a random-effects meta-analysis to calculate the pooled OR (95% CI) and performed a sensitivity analysis to confirm the robustness of the meta-analyses.

Main findings: We included 61 studies (3,061,584 individuals), which were rated as having low risk of bias. The OR (95% CI) indicated some medications protective against COVID-related death, including metformin [0.54 (0.47–0.62), \textit{I}^2 86\%], glucagon-like peptide-1 receptor agonist (GLP-1RA) [0.51 (0.37–0.69), \textit{I}^2 85\%], and sodium–glucose transporter-2 inhibitor (SGLT-2i) [0.60 (0.40–0.88), \textit{I}^2 91\%]. Dipeptidyl peptidase-4 inhibitor (DPP-4i) [1.23 (1.07–1.42), \textit{I}^2 82\%] and insulin [1.70 (1.33–2.19), \textit{I}^2 97\%] users were more likely to die during hospitalization. Sulfonylurea, thiazolidinedione, and alpha-glucosidase inhibitor were mortality neutral [0.92 (95\% CI 0.83–1.01, \textit{I}^2 44\%), 0.90 (95\% CI 0.71–1.14, \textit{I}^2 46\%), and 0.61 (95\% CI 0.26–1.45, \textit{I}^2 77\%), respectively]. The sensitivity analysis indicated that our findings were robust.

Conclusions: Metformin, GLP-1RA, and SGLT-2i were associated with lower mortality rate in patients with COVID-19 having type 2 diabetes. DPP-4i and insulin were linked to increased mortality. Sulfonylurea, thiazolidinedione, and alpha-glucosidase inhibitors were mortality neutral. These findings can have a large impact on the clinicians’ decisions amid the COVID-19 pandemic.

1. Introduction

Since late 2019, SARS-CoV-2 has emerged as a novel pathogenic microbe, resulting in the COVID-19 pandemic. By the end of November 2021, more than 257 million people had been infected with SARS-CoV-2 globally, approximately 5.1 million of whom died [1]. Several risk factors have been linked with the progression and deterioration of COVID-19, such as advanced age, diabetes, hypertension, cardiovascular diseases, and obesity [2]. Diabetes, with its increasing worldwide prevalence, has become major comorbidity in patients with COVID-19 and predisposes them to poor outcomes. Many potential pathways for this have been proposed, including increased inflammatory cascade,
immunocompromised status, glucose homeostasis dysfunction, hypercoagulability, alveolar hyperpermeability, and vascular endothelial damage. These pathophysiological changes might lead to acute respiratory distress syndrome, thromboembolism events, and cytokine storms, thereby contributing to increased COVID-19-related deaths [3].

In the past two decades, many drugs have been approved for diabetic patients, leading to a noticeable change in the trend of medication use. Glucose-lowering therapies have also received much critical attention recently as potential host-directed therapies due to their mechanisms of action that may influence the natural course of SARS-CoV-2 infection. Many studies have evaluated whether the premadmission use of certain antidiabetic medications might improve outcomes in those participants. The results have remained controversial, partly because different classes of drugs may differ in their effectiveness and safety against SARS-CoV-2. The gap between preclinical research and real-world data must be bridged. For example, dipeptidyl peptidase-4 inhibitor (DPP-4i) has recently gained much attention due to its safety, cardiovascular neutrality, and potential mechanistic pathways that could alleviate the course of SARS-CoV-2 infection. Although the exact mechanisms underly the effect of this class on the prognosis of COVID-19 remain unclear, several hypotheses may provide some insights. In addition to glucose homeostasis, DPP-4i inhibits the enzyme DPP-4, which is involved in many events of COVID-19 pathophysiology, including T-cell proliferation, nuclear factor kappa-light-chain-enhancer of activated B (NF-κB) activation, CD86 expression, and inflammatory cytokines production [4]. However, many studies and meta-analyses have indicated no significant benefit of DPP-4i against COVID-19 [5,6]. Moreover, even for the same drug class, previous small meta-analyses have indicated inconsistent effects regarding the severity or mortality of patients with COVID-19, as in the case of the glucagon-like peptide-1 receptor agonist (GLP-1RA) [5,7]. Therefore, little is known about their true efficacy in the prognosis of that disease.

In this systematic review and meta-analysis, we (1) summarized the effects of every single antidiabetic medication on the mortality of patients with COVID-19 having diabetes and (2) evaluated the dose-responsiveness of the impacts of medications on mortality. By incorporating much more original papers, our findings would strengthen or reject the evidence for effects of each antidiabetic medication on COVID-19 mortality from inconsistent meta-analyses, and provided novel results regarding the effect of TZD and AGI, and the relationship between dosages and effects, which have not been previously reported.

2. Material and methods

2.1. Population, intervention, comparison, outcomes, and study design (PICOS)

Participants included patients with confirmed COVID-19 who had diabetes and were on prehospital medications extending to the pandemic. A confirmed case of COVID-19 was defined using a positive result on reverse transcription-polymerase chain reaction (RT-PCR) according to the diagnostic procedures of each center. Preexisting diabetes was ascertained through a diabetes diagnosis in medical records. The diagnostic procedures of each center. Preexisting diabetes and were on prehospital medications extending to the pandemic. Although the exact mechanisms underlying the effect of this class on the prognosis of COVID-19 remain unclear, several hypotheses may provide some insights. In addition to glucose homeostasis, DPP-4i inhibits the enzyme DPP-4, which is involved in many events of COVID-19 pathophysiology, including T-cell proliferation, nuclear factor kappa-light-chain-enhancer of activated B (NF-κB) activation, CD86 expression, and inflammatory cytokines production [4]. However, many studies and meta-analyses have indicated no significant benefit of DPP-4i against COVID-19 [5,6]. Moreover, even for the same drug class, previous small meta-analyses have indicated inconsistent effects regarding the severity or mortality of patients with COVID-19, as in the case of the glucagon-like peptide-1 receptor agonist (GLP-1RA) [5,7]. Therefore, little is known about their true efficacy in the prognosis of that disease.

In this systematic review and meta-analysis, we (1) summarized the effects of every single antidiabetic medication on the mortality of patients with COVID-19 having diabetes and (2) evaluated the dose-responsiveness of the impacts of medications on mortality. By incorporating much more original papers, our findings would strengthen or reject the evidence for effects of each antidiabetic medication on COVID-19 mortality from inconsistent meta-analyses, and provided novel results regarding the effect of TZD and AGI, and the relationship between dosages and effects, which have not been previously reported.

2.2. Systematic review protocol

This systematic review and meta-analysis were registered in the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42021293064).

2.3. Search strategy and data sources

We systematically searched PubMed/MEDLINE, EMBASE, Scopus, and Web of Science databases for relevant articles up to November 30, 2021, without limiting the language or publication year. The following main keywords and related terms were used: “COVID-19,” “diabetes,” “antidiabetic medication,” or the names of specific classes. The detailed search strategy is presented in Table A1 (Supplementary appendix). We further identified additional articles through a manual search. We used Endnote (version 20; Clarivate. Philadelphia, PA, USA) to manage studies found.

2.4. Data extraction

The number of events, the number of observations, and other demographic variables, including race/ethnicity, sex, age, HbA1c, diabetes duration, BMI, and percentage of important comorbidities such as hypertension and chronic kidney disease, were documented for each group. OR was also extracted from the papers. The article’s corresponding author was contacted through e-mail if raw data were required.

2.5. Data analysis

The risk of bias was assessed by two independent reviewers by using the Newcastle–Ottawa Scale [8].

Effect sizes were calculated as the natural logarithm of ORs. The logOR and standard error of the logOR were used as input for meta-analysis in statistical software. Forest plots were used to display the OR from each original study and the pooled findings. We used Cochran’s Q test and I² statistics to assess heterogeneity between studies [9,10]. A random-effects model was chosen when the Cochran’s Q test p-value of <0.1 or an I² of >50% was obtained. A fixed-effects model was preferred if there was no evidence of heterogeneity. Publication bias was statistically assessed using Egger’s asymmetry test [11]. A publication bias was suspected if the p-value for Egger’s test was <0.05. Meta-regression and subgroup analysis were predefined to explore the source of heterogeneity further. We performed meta-regression on a set of pre-specified important characteristics, comorbidities, and chronic complications that are commonly found in diabetes patients, including age, gender, race/ethnicity, BMI, hypertension, and chronic kidney disease. We performed sensitivity analysis by outlier removal and trim-and-fill methods and then compared the original results with reanalyzed results to confirm the stability and robustness of our main meta-analyses. A two-sided p-value of <0.05 was considered statistically significant. We analyzed data by using R software (version 4.0.2; R Foundation for Statistical Computing; Vienna, Austria).
2.6. Ethics

Formal ethics approval is not required because we only collect nonconfidential information from which the patients’ identities could not be ascertained.

3. Results

3.1. Literature search and study selection

A total of 6920 articles were identified from the databases through a systematic search (Fig. 1). Next, 5790 articles remained after deduplication to be screened for their titles and abstracts. Of these articles, 5644 were excluded due to full-text inaccessibility (n = 173), duplication (n = 566), and irrelevancy (n = 4905); thus, 146 papers remained for eligibility assessment. The other 85 publications were further excluded because they did not include the outcome of interest; reported composite endpoint of intensive care unit admission, mechanical ventilation, and death; involved the same cohort; investigated inpatient use of antidiabetic drugs; or were irrelevant to our topic. Finally, 61 studies met our inclusion criteria for a systematic review. However, only 59 articles were pooled in the meta-analyses because one publication reported the hazard ratio instead of odds ratio, and one reported longer-term mortality (7 months) [12,13].

3.2. Study and participant characteristics

A total of 3,061,584 participants were recruited from studies [14–72]. Most of them were retrospective, except for two cross-sectional studies [26,52]. The antidiabetic drugs that were investigated included metformin (42 articles), SU (21), TZD (8), AGI (8), GLP-1RA (12), DPP-4i (28), SGLT-2i (13), and insulin (33) (Table 1). Only two papers reported glinide-associated mortality in patients with COVID-19 with few users [34,50]. Therefore, we did not present this drug in our research. The Newcastle–Ottawa assessment results revealed that all studies were rated as having adequate quality (Table A.2). No publication bias was found using Egger’s test (Table A.3).

3.3. Main findings

3.3.1. Mortality between medication users and nonusers

Compared with nonusers, metformin (OR 0.54, 95% CI 0.47–0.62, I² 86%), GLP-1RA (OR 0.51, 95% CI 0.37–0.69, I² 85%), and SGLT-2i (OR 0.60, 95% CI 0.40–0.88, I² 91%) use significantly reduced mortality among patients with COVID-19 with diabetes (Figs. 2–4). By contrast, DPP-4i (OR 1.23, 95% CI 1.07–1.42, I² 82%) and insulin (OR 1.70, 95% CI 1.33–2.19, I² 97%) were associated with an increased risk of in-hospital death (Figs. A.1, A.2). SU (OR 0.92, 95% 0.83–1.01, I² 44%), TZD (0.90, 95% CI 0.71–1.14, I² 46%), and AGI (OR 0.61, 95% 0.26–1.45, I² 77%) were mortality neutral (Figs. A.3–A.5).

3.3.2. Meta-regression of confounding factors

Using meta-regression, we observed some significant variables that were significantly associated with mortality due to COVID-19, including continent, white race, male sex, age, BMI, HbA1C, hypertension, and CKD (Table 2).

3.3.3. Subgroup analysis

We performed subgroup analyses based on confounding factors identified through meta-regression to compare the effects of antidiabetic
Table 1
Characteristics of studies (systematic review).

| Study            | Country | Number of patients | Race/ethnicity (%) | Male sex (%) | Age (years) | HbA1C (%) | Body mass index (kg/m^2) or obesity (%) | Hypertension (%) | CKD (%) | Mortality |
|------------------|---------|--------------------|--------------------|--------------|-------------|-----------|----------------------------------------|------------------|---------|-----------|
| Metformin users/nonusers |
| An et al. [15]  | Korea   | 423/598            |                    |              | 39.9        | 45.0 ± 19.9 | 8.1 ± 23 vs. 8.4 ± 1.8                | 18.2             | 0.8     | NS        |
| Bliden et al. [16] | USA     | 34/41              |                    |              | 51.6        | 73.0       | (66.0–80.0) vs. 76.0                   | Obesity: 4.8% vs. 9.0% | 56.3 vs. 60.4 | NS        |
| Bramante et al. [18] | USA    | 2333/3923         |                    |              |             | 44.6       | (67.0–84.0) | | | 18.6 |
| Cernigliaro et al. [19] | Italy   | 82/90              |                    |              | 43.9        | 64.5       |                        | Decreased         |         |           |
| Chen et al. [20] | China   | 43/77              |                    |              | 51.6        | 72.6       |                        | 32.8 ± 8.9        | 47.7     | 15.5 Decreased |
| Cheng et al. [21] | China   | 18/32              |                    |              | 67.0        | 64.5       |                        | 24.2 vs. 33.8     | 20.4 vs. 37.5 | NS |
| Crouse et al. [22] | USA     | 76/144             | White: 27.6, African American: 64.9 | | | | | | | |
| Dave et al. [23] | Africa   | 4084/1624          |                    |              | 43.9        | 55.0       |                        | 37.78 vs. 40.3     | 29.4 vs. 47.4 | 4.6 |
| Do et al. [25]  | Korea    | 469/1396           |                    |              | 39.0        | 44.8       | (11.4 ± 14) vs. 74.1 ± 12.1 | 74.1             | 55.5  |
| Eliboi et al. [26] | Turkey   | 379/53             |                    |              | 46.0        | 63.3       | (10.3) | | | |
| Ghany et al. [29] | USA      | 243/350            | Black: 71.0 vs. 70.0 | | | | | | | |
| Goodall et al. [31] | England | 210/166            | White: 25.5, Black: 13.9, Asian: 37.8 | | | | | | | |
| Khunti et al. [34] | England | 1,800,005/1,051,460 | White: 64.5, Black: 4.8, Asian: 16.0 | | | | | | | |
| Kim et al. [35]  | Korea    | 113/122            |                    |              | 59.5        | 66.2       | (11.2 ± 12) vs. 72.7 ± 11.7 | 24.2 ± 3.2         | 78.0     |
| Lally et al. [37] | USA      | 127/172            | White: 61.4, Black: 30.7 | | | | | | | |
| Li et al. (1) [39] | China    | 37/94              |                    |              | 50.0        | 68.3 ± 18.0 |                        | 62.6             | 7.7     | NS        |
| Li et al. (2) [38] | China    | 142/245            |                    |              | 45.1        | 72.3 ± 8.3 | 7.5 ± 1.4 vs. 6.5 ± 1.3 | 29.7 ± 6.6 vs. 28.0 ± 7.0 | | |
| Luk et al. [40]  | China    | 737/254            | Asian              |              | 50.0        | 68.9       | (2.6 ± 8.5) vs. (6.3 ± 8.5) | 24.1             | 19.5     | Decreased |
| Luo et al. (1) [41] | China    | 104/179            |                    |              | 50.0        | 63.0       |                        | 63.1 vs. 56.7     | 13.2     | NS        |
| Luo et al. (2) [42] | China    | 54/137             |                    |              | 50.0        | 61.0       | (19.1 ± 8.2) vs. (19.1 ± 1.9) | 55.5             | 2.0      | Decreased |
| Ma et al. [43]   | USA      | 361/995            | White: 72.6, Black: 12.2, Asian: 1.9 | | | | | | | |
| Mirani et al. [46] | Iran     | 69/21              |                    |              | 50.0        | 69.0 ± 13.0 | (21.5 vs. 27.7) vs. (22.2–27.0) | 81.6             | 0.8      | |
| Mirsoleymani et al. [47] | Iraq  | 35/32              |                    |              | 43.0        | 59.8 ± 17.2 |                        | 29.8 ± 5.0        | 66.0  |
| Nafakhi et al. [48] | USA      | 5077/24,439        | White: 47.9, African American: 25.5, Asian: 3.1 | | | | | | | |

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| Study                | Country     | Number of patients | Race/ethnicity (%) | Age (years) | HbA1C (%) | Body mass index (kg/m²) or obesity (%) | Hypertension (%) | CKD (%) | Mortality |
|----------------------|-------------|--------------------|--------------------|-------------|-----------|----------------------------------------|-----------------|---------|-----------|
| Oh et al. [51]       | Korea       | 7204/20,289        |                    | 44.7 ± 11.6 | 7.0 ± 2.4 | Obesity: 62.0% vs. 65.1%              | 73.1 ± 76.3     | 3.4     | NS        |
| Ong et al. [52]      | Philippines | 186/169            |                    | 56.6 ± 11.6 | 7.6 ± 1.9 | Obesity: 55.4% vs. 58.1%              | 48.6 ± 70.1     | 4.1     | Decreased |
| Orio et al. [53]     | Belgium     | 45/23              |                    | 69.0 ± 11.0 | 7.1 ± 6.8 | Obesity: 26.4% vs. 26.1%              | 30.5 ± 5.3       | 80.8    | Decreased |
| Perez-Belmonte et al. [54] | Spain    | 825/663            |                    | 74.8 ± 11.0 | 7.7 ± 6.8 | Obesity: 26.4% vs. 26.1%              | 74.2 ± 79.5      | 4.7     | NS        |
| Philipose et al. [55] | England   | 100/59             | White: 45.5, Afro-Caribbean: 20.2, Asian: 19.1 | 59.0        |          |                                        |                 |         |           |
| Ramos-Rincón et al. [56] | Spain   | 421/369            |                    | 47.1        |           | Obesity: 17.7%                       | 84.3 ± 71.7      | 17.2    | NS        |
| Ravindra et al. [57] | India      | 53/313             |                    | 63.2 ± 17.1 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              | 28.7 ± 70.1      | 0.9     | NS        |
| Saygili et al. [60]  | Turkey      | 432/154            |                    | 65.0 ± 11.2 | 7.7 ± 6.8 | Obesity: 26.4% vs. 26.1%              | 67.1 ± 70.1      | 0.0     | Decreased |
| Shetaskova et al. [61] | Russia   | 196/113            |                    | 54.1 ± 12.7 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Silveri et al. [62]  | Italy       | 76/83              |                    | 63.1 ± 11.0 | 7.7 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Sourir et al. [63]   | Austria     | 77/103             |                    | 63.9 ± 16.0 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Tamura et al. [65]   | Brazil      | 116/72             |                    | 63.5 ± 15.0 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Wander et al. [66]   | USA         | 29,685/64,892      | White: 66.0, Black: 27.0, Hispanic: 9.0 | 64.0 ± 12.5 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Wang et al. (1) [67] | USA         | 9/7                | African American: 23.0, Hispanic: 16.0 | 52.0 ± 12.5 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Wang et al. (2) [68] | England     | 110/54             |                    | 52.0 ± 12.5 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Wargny et al. [69]   | France      | 1553/1241          | White: 58.1, African: 17.4, Asian: 3.6 | 36.3 ± 12.5 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Cheng et al. [12]    | China       | 678/553            |                    | 53.8 ± 12.5 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Yuan et al. [72]     | China       | 73/109             |                    | 52.1 ± 12.5 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Pazoki et al. [13]   | Iran        | 177/216            |                    | 56.2 ± 12.5 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| **SU users/nonusers**|             |                    |                    |             |           |                                        |                 |         |           |
| An et al. [15]       | Korea       | 212/809            |                    | 39.9 ± 19.0 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Cernigliaro et al. [19] | Italy    | 35/137             |                    | 39.9 ± 19.0 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Chen et al. [20]     | China       | 53/67              |                    | 42.9 ± 12.5 | 8.3 ± 7.7 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Dave et al. [23]     | Africa      | 2110/3598          |                    | 39.3 ± 19.0 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Elbibi et al. [26]   | Turkey      | 66/366             |                    | 45.6 ± 12.5 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Khunti et al. [34]   | England     | 561,290/2,290,175  | White: 63.7, Black: 5.0, Asian: 17.2 | 60.5 ± 12.5 | 7.1 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Kim et al. [35]      | Korea       | 60/175             |                    | 45.1 ± 11.9 | 7.9 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Li et al. (1) [39]   | China       | 22/109             |                    | 56.5 ± 11.9 | 7.9 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Li et al. (2) [38]   | China       | 91/296             |                    | 51.1 ± 11.9 | 7.9 ± 7.0 | Obesity: 26.4% vs. 26.1%              |                 |         |           |
| Luk et al. [40]      | China       | 385/679            | Asian              | 57.7 ± 11.9 | 7.7 ± 6.9 | Obesity: 26.4% vs. 26.1%              |                 |         |           |

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Table 1 (continued)

| Study                  | Country   | Number of patients | Race/ethnicity                  | Male sex (%) | Age (years) | HbA1C (%) | Body mass index (kg/m²) or obesity (%) | Hypertension (%) | CKD (%) | Mortality |
|------------------------|-----------|--------------------|---------------------------------|--------------|-------------|-----------|----------------------------------------|------------------|---------|-----------|
| Luo et al. [42]        | China     | 37/154             |                                 | 56.5         | 62.7 ± 11.0 | 7.9 (6.3–9.0) | 23.5 (21.5–27.0) | 55.5           | 0.0     | Decreased |
| Mirani et al. [46]     | Italy     | 10/80              |                                 | 60.0 vs. 73.8 | 70.0 ± 12.0 |           | 55.5 (80.0 vs. 76.3) vs. 21.4 | NS              |         |         |
| Nyland et al. [50]     | USA       | 1889/27,627        | White: 47.9, African American: 25.5, Asian: 3.1 | 48.2         | 60.9 ± 15.0 | 7.7 ± 2.1 | 32.8 ± 8.9 | 47.7           | 15.5    |         |
| Oh et al. [51]         | Korea     | 3680/23,813        |                                 |              |             |           |                                         | NS              |         |         |
| Orioli et al. [53]     | Belgium   | 19/49              |                                 | 48.0         | 69.0 ± 14.0 | 7.1 (6.6–8.3) | 30.5 ± 5.3 | 80.8           | 34.2    |         |
| Svetaskova et al. [61] | Russia    | 129/180            |                                 |              |             |           |                                         | NS              |         |         |
| Silveri et al. [62]    | Italy     | 33/126             |                                 | 54.1         | 73.3 ± 12.7 |           |                                         | NS              |         |         |
| Sourij et al. [63]     | Austria   | 14/166             |                                 | 63.9         | 67.6 ± 14.0 | 6.7 (1.9) | 29.4 ± 5.7 | 77.0           | 23.1    |         |
| Wander et al. [66]     | USA       | 12,298/52,594      | White: 66.0, Black: 27.0, Hispanic: 9.0 | 64.0         | 67.7        |           |                                         | 89.0           | 36.0    | NS         |
| Wargny et al. [69]     | France    | 782/2012           | White: 58.1, African: 17.4, Asian: 3.6 | 36.3         | 69.7 ± 13.2 | 7.7 (6.8–9.0) | 28.4 (25.0–32.4) | 76.8           | NS      |         |
| Yuan et al. [72]       | China     | 43/139             |                                 | 55.8         | 67.0        | 8.5 (7.0–9.5) | 23.7 (22.0–25.4) | 48.8           | 0.0     | Decreased |
| Pazoki et al. [13]     | Iran      | 72/321             |                                 | 56.2         | 65.4 ± 11.6 |           |                                         | 65.4           | 7.9     | NS         |
| **TZD users/nonusers** |           |                    |                                 |              |             |           |                                         | NS              |         |         |
| Cernigliaro et al. [19]| Italy     | 10/162             |                                 |              |             |           |                                         | 74.1           | 4.6     | NS         |
| Elbibi et al. [26]     | Turkey    | 27/405             |                                 | 45.6         | 63.3 ± 10.3 |           |                                         | 80.5           | NS      |         |
| Khunti et al. [34]     | England   | 60,085/2,791,380   | White: 63.5, Black: 3.7, Asian: 18.4 | 63.4         | 67.0        |           |                                         | 87.4           | NS      |         |
| Luo et al. [42]        | China     | 7/184              | White: 52.4, African American: 23.2, Asian: 3.5 | 56.5         | 62.7 ± 11.0 | 7.9 (6.3–9.0) | 34.3 ± 9.0 | 55.5           | 3.0     | NS         |
| Nyland et al. [50]     | USA       | 469/23,714         | White: 58.1, African American: 17.4, Asian: 3.6 | 53.3 vs. 48.8 | 63.1 ± 12.5 | 8.2 ± 2.0 | 32.3 ± 8.7 | 52.1 vs. 14.9 | 17.4    | NS         |
| Oh et al. [51]         | Korea     | 1264/26,229        |                                 |              |             |           |                                         | 89.0           | 36.0    | NS         |
| Silveri et al. [62]    | Italy     | 19/49              |                                 | 54.1         | 73.3 ± 12.7 |           |                                         | NS              |         |         |
| Wander et al. [66]     | USA       | 2075/62,817        | White: 66.0, Black: 27.0, Hispanic: 9.0 | 64.0         | 67.7        |           |                                         | 89.0           | 36.0    | NS         |
| **AGI users/nonusers** |           |                    |                                 |              |             |           |                                         | NS              |         |         |
| An et al. [15]         | Korea     | 7/1014             |                                 | 39.9         | 45.0 ± 19.9 | 66.0      | 8.4 (7.4–10.3) | 61.2           | 10.2    | NS         |
| Chen et al. [20]       | China     | 69/51              |                                 | 42.9         | 66.0 (57.5–73.0) vs. 65.0 (56.0–72.0) |           | 18.2          | 10.2     | NS         |
| Khunti et al. [34]     | England   | 1665/2,849,800     | White: 56.5, Black: 7.5, Asian: 23.4 | 56.8         | 67.0        |           |                                         | 87.4           | NS      |         |
| Li et al. [1] [39]     | China     | 38/93              |                                 | 56.5         | 66.8 ± 11.6 | 7.9 ± 1.9 | 24.2 ± 3.4 | 59.5           | 1.0     | NS         |
| Li et al. [2] [38]     | China     | 140/247            |                                 | 51.1         | 60.0 (49.0–68.0) |           | 48.6          |         | NS         |
| Luo et al. [42]        | China     | 77/114             |                                 | 65.0         | 62.3 ± 9.6 | 7.9 ± 1.8 | 8.3 ± 2.0 | 55.5           | 2.2     | Decreased |
| Nyland et al. [50]     | USA       | 16/29,500          | White: 47.9, African American: 25.5, Asian: 3.1 | 48.2         | 60.9 ± 15.0 | 7.7 ± 2.1 | 32.8 ± 8.9 | 47.7           | 15.5    | NS         |
| Yuan et al. [72]       | China     | 88/94              |                                 | 51.1         | 8.2 (7.0–9.2) | 58.0      | 1.1          |         |         |

(continued on next page)
| Study                  | Country        | Number of patients | Race/ethnicity (%) | Male sex (%) | Age (years) | HbA1C (%) | Body mass index (kg/m²) or obesity (%) | Hypertension (%) | CKD (%) | Mortality |
|-----------------------|----------------|--------------------|--------------------|--------------|-------------|-----------|----------------------------------------|-----------------|----------|------------|
|                       |                |                    |                    |              |             |           |                                        |                 |          |            |
| GLP-1RA users/nonusers|                |                    |                    |              |             |           |                                        |                 |          |            |
| Cernigliaro et al.    | Italy          | 8/164              |                    |              |             |           |                                        |                 |          |            |
| Israelensen et al.    | Denmark        | 370/558            |                    |              |             |           |                                        |                 |          |            |
| Noh et al.            | Korea          | 453/133            |                    |              |             |           |                                        |                 |          |            |
| Meijer et al.         | USA            | 6692/5854          | White: 64.1        |              |             |           |                                        |                 |          |            |
| Luo et al.            | China          | 11/180             |                    |              |             |           |                                        |                 |          |            |
| Khunti et al.         | England        | 100,820/3,750,645  | White: 76.3,       |              |             |           |                                        |                 |          |            |
|                       |                |                    | Black: 3.3,       |              |             |           |                                        |                 |          |            |
|                       |                |                    | Asian: 7.9        |              |             |           |                                        |                 |          |            |
| Nyland et al.         | USA            | 1774/23,714        | White: 52.3,       |              |             |           |                                        |                 |          |            |
|                       |                |                    | Black: 28.7,      |              |             |           |                                        |                 |          |            |
|                       |                |                    | Asian: 0.9        |              |             |           |                                        |                 |          |            |
| Orioli et al.         | Belgium        | 5/63               |                    |              |             |           |                                        |                 |          |            |
|                       |                |                    |                    |              |             |           |                                        |                 |          |            |
| Ramos-Rincon et al.   | Spain          | 37/753             |                    |              |             |           |                                        |                 |          |            |
| Shibaskova et al.     | Russia         | 1/308              |                    |              |             |           |                                        |                 |          |            |
| Silveri et al.        | Italy          | 7/152              |                    |              |             |           |                                        |                 |          |            |
| Sourj et al.          | Austria        | 3/177              |                    |              |             |           |                                        |                 |          |            |
| Wander et al.         | USA            | 4737/60,155        | White: 66.0,       |              |             |           |                                        |                 |          |            |
|                       |                |                    | Black: 27.0,      |              |             |           |                                        |                 |          |            |
|                       |                |                    | Hispanic: 9.0,    |              |             |           |                                        |                 |          |            |
|                       |                |                    | Black: 7.9,       |              |             |           |                                        |                 |          |            |
| Wargny et al.         | France         | 254/2540           | White: 58.1,       |              |             |           |                                        |                 |          |            |
|                       |                |                    | African: 17.4,    |              |             |           |                                        |                 |          |            |
|                       |                |                    | Asian: 3.6        |              |             |           |                                        |                 |          |            |
| DPP-4i users/nonusers |                |                    |                    |              |             |           |                                        |                 |          |            |
| An et al.             | Korea          | 229/792            |                    |              |             |           |                                        |                 |          |            |
| Chen et al.           | Italy          | 13/159             |                    |              |             |           |                                        |                 |          |            |
| Eliboi et al.         | Turkey         | 246/186            |                    |              |             |           |                                        |                 |          |            |
| Emral et al.          | Turkey         | 6846/26,632        |                    |              |             |           |                                        |                 |          |            |
| Fanidi et al.         | Italy          | 9/72               |                    |              |             |           |                                        |                 |          |            |
|                       |                |                    |                    |              |             |           |                                        |                 |          |            |
| Israelensen et al.    | Denmark        | 284/664            |                    |              |             |           |                                        |                 |          |            |
| Kablkoska et al.      | USA            | 3511/8935          | White: 57.4        |              |             |           |                                        |                 |          |            |
| Khunti et al.         | England        | 479,555/2,371,910  | White: 65.5,       |              |             |           |                                        |                 |          |            |
|                       |                |                    | Black: 4.7,       |              |             |           |                                        |                 |          |            |
|                       |                |                    | Asian: 15.7       |              |             |           |                                        |                 |          |            |
| Kim et al.            | Korea          | 85/150             |                    |              |             |           |                                        |                 |          |            |
| Kristian et al.       | USA            | 76/756             |                    |              |             |           |                                        |                 |          |            |
| Luk et al.            | China          | 199/952            |                    |              |             |           |                                        |                 |          |            |
| Luo et al.            | China          | 11/180             |                    |              |             |           |                                        |                 |          |            |
| Meijer et al.         | Netherlands    | 28/537             |                    |              |             |           |                                        |                 |          |            |
| Mirani et al.         | Italy          | 11/79              |                    |              |             |           |                                        |                 |          |            |
| Noh et al.            | Korea          | 453/133            |                    |              |             |           |                                        |                 |          |            |

(continued on next page)
| Study                | Country | Number of patients | Race/ethnicity (%) | Male sex (%) | Age (years) | HbA1C (%) | Body mass index (kg/m²) or obesity (%) | Hypertension (%) | CKD (%) | Mortality |
|---------------------|---------|--------------------|--------------------|--------------|-------------|-----------|----------------------------------------|-----------------|---------|-----------|
|                     |         |                    |                    |              | 49.2        | 64.6 ± 13.5 vs. 60.9 ± 15.3 | 8.0 ± 2.0 vs. 7.5 ± 2.1 | 31.4 ± 8.1 vs. 32.3 ± 8.7 | 55.9 vs. 44.9 | 21.2 vs. 18.0 | Increased |
| N. N. Nguyen et al. | USA     | 2264/23,714        | White: 49.2, African American: 36.6, Asian: 5.1 | 49.1 vs. 48.8 | 64.6 ± 13.5 vs. 60.9 ± 15.3 | 8.0 ± 2.0 vs. 7.5 ± 2.1 | 31.4 ± 8.1 vs. 32.3 ± 8.7 | 55.9 vs. 44.9 | 21.2 vs. 18.0 | Increased |
|                     | Korea   | 4132/23,361        |                    |              | 48.0        | 69.0 ± 14.0 | 7.1 (6.6–8.3) | 30.5 ± 5.3 | 80.8 | NS        |
| Oh et al. [51]      | Austria | 63/156             |                    |              | 54.9        | 78.8 ± 7.1 vs. 74.7 ± 8.2 | Obesity: 30.6% vs. 28.1% | 55.6 vs. 56.5 | 32.2 vs. 11.9 | Increased |
|                     | Korea   | 4132/23,361        |                    |              | 54.1        | 73.3 ± 12.7 |                       |                  |         | NS        |
| Orioli et al. [53]  | Spain   | 180/1409           |                    |              | 63.9        | 67.6 ± 14.0 | 6.7 (1.9) | 29.4 ± 5.7 | 77.0 | 23.1 NS   |
|                     | Austria | 42/138             |                    |              | 54.9        | 76.7 ± 11.8 |                       |                  |         | NS        |
| Perez-Belmonte et al. [54] | Spain | 266/524           |                    |              | 47.1        | Obesity: 17.7% | 84.3 | 17.2 Decreased |
|                     | Spain   | 266/524           |                    |              | 47.1        | Obesity: 17.7% | 84.3 | 17.2 Decreased |
|                     | Russia  | 26/283             |                    |              |              | 66.0 vs. 74.1 | Obesity: 15.4% | 49.6 | NS        |
| Silveri et al. [62] | Italy   | 13/146             |                    |              | 36.3        | 69.7 ± 13.2 | 7.7 (6.8–9.0) | 28.4 (25.0–32.4) | 76.8 | NS        |
| Souri et al. [63]   | Spain   | 42/138             |                    |              | 60.7        | 66.3 ± 11.7 vs. 65.1 ± 13.0 | 7.8 ± 2.3 vs. 7.4 ± 2.5 | Obesity: 15% vs. 11.3% | 88.8 vs. 75.2 | 30.8 vs. 11.3 | NS        |
| Strollo et al. [64] | Italy   | 30/163             |                    |              | 56.2        | 65.4 ± 11.6 | 28.0 ± 5.1 | 65.4 | 7.9 NS    |
| Wander et al. [66]  | USA     | 5810/59,082        | White: 66.0, Black: 27.0, Hispanic: 9.0 |              | 64.0        | 67.7 | 89.0 | 36.0 NS    |
| Wargny et al. [69]  | France  | 615/2179           |                    |              | 30.7        | 65.1 ± 13.0 | 7.4 ± 2.5 | 28.0 ± 5.1 | 65.4 | 7.9 NS    |
| Wong et al. [70]    | China   | 107/1107           |                    |              | 53.1        | 65.4 ± 11.6 | 28.0 ± 5.1 | 65.4 | 7.9 NS    |
| Pazoki et al. [13]  | Iran    | 20/373             |                    |              | 36.3        | 69.7 ± 13.2 | 7.7 (6.8–9.0) | 28.4 (25.0–32.4) | 76.8 | NS        |
| SGLT-2 users/nonusers | Italy | 4/168              |                    |              | 45.6        | 63.3 ± 10.3 | 74.1 | 4.6 NS     |
| Germiglia et al. [19] | Italy | 56/376             |                    |              | 61.8        | 59.0 (52.0–68.0) | 8.2 ± 1.8 | 35.2 ± 7.8 | 77.3 | 16.3 Decreased |
| Elbodi et al. [36]  | Denmark | 274/654            |                    |              | 55.2        | 57.9 ± 11.7 | 8.3 ± 1.8 | 35.2 ± 7.8 | 77.3 | 16.3 Decreased |
| Israelsen et al. [32] | USA | 3665/8781        | White: 33.9 |              | 60.8        | 67.0 (57.0–77.0) | 75.4 | 75.4 Decreased |
| Kahkoska et al. [13] | USA | 266/505/2,584,960 | White: 66.8, Black: 36.3, Asian: 15.2 |              | 45.1        | 68.3 ± 11.9 | 24.2 ± 3.2 | 62.6 | 7.7 NS    |
| Iliadis et al. [19] | Korea   | 8/227              |                    |              | 48.2        | 60.9 ± 15.0 | 7.7 ± 2.1 | 32.8 ± 8.9 | 47.7 | 15.5 Decreased |
| Nyland et al. [50]  | USA     | 792/28,724         | White: 47.9, African American: 25.5, Asian: 3.1 |              | 64.0        | 67.7 | 89.0 | 36.0 NS    |
| Souri et al. [63]   | Belgium | 4/64               |                    |              | 48.0        | 69.0 ± 14.0 | 7.1 (6.6–8.3) | 30.5 ± 5.3 | 80.8 | 34.2 NS    |
| Ramos-Rincon et al. [56] | Spain | 45/745             |                    |              | 47.1        | Obesity: 17.7% | 84.3 | 17.2 NS    |
| Shetaskova et al. [61] | Russia | 13/296             |                    |              | 54.1        | 73.3 ± 12.7 |                       |                  |         | NS        |
| Silveri et al. [62] | Italy   | 4/155              |                    |              | 63.9        | 67.6 ± 14.0 | 6.7 (1.9) | 29.4 ± 5.7 | 77.0 | 23.1 NS   |
| Wander et al. [66]  | USA     | 5542/59,350        | White: 66.0, Black: 27.0, Hispanic: 9.0 |              | 64.0        | 67.7 | 89.0 | 36.0 NS    |
| Insulin users/nonusers | USA | 531/661            | White: 15.5, African American: 74.5 |              | 49.3        | 67.9 ± 13.7 | 7.5 ± 2.0 | 30.1 ± 7.5 | 90.9 | 42.5 Increased |
| Agarwal et al. [14] | USA     | 3461/6070          |                    |              | 46.0        | 71.6 ± 12.5 | 7.2 | 37 Increased |

(continued on next page)
| Study                     | Country       | Number of patients | Race/ethnicity (%) | Male sex (%) | Age (years) | HbA1C (%) | Body mass index (kg/m²) or obesity (%) | Hypertension (%) | CKD (%) | Mortality          |
|---------------------------|---------------|--------------------|-------------------|--------------|-------------|-----------|--------------------------------------|-----------------|---------|--------------------|
| Cernigliaro et al. [19]   | Italy         | 42/130             |                                 |              |             |           |                                      |                  |         |                    |
| Chen et al. [20]          | China         | 7/49               |                                 | 42.9         | 65.0        | 8.8       | 61.2                                 | 10.2            | NS      | Increased          |
| Cheng et al. [12]         | China         | 11/39              |                                 | 54.5 vs.     | 58.0        | 24.8      | 20.4                                 | 27.3 vs.        | 27.3    | NS                 |
| Crouse et al. [22]        | USA           | 87/133             |                                 | 50.6         | 62.0 ± 15.0| 32.9      | 78.4                                 | 21.3            | NS      |                    |
| Dave et al. [23]          | Africa        | 207/3635           |                                 | 39.3         | 55.0        | 24.2      | 62.6                                 | 7.7             | NS      |                    |
| Deng et al. [24]          | China         | 29/56              |                                 | 57.6         | 65.0        | 7.9 ± 2.3| 62.6                                 | 7.7             | NS      |                    |
| Giorda et al. [30]        | Italy         | 656/1226           |                                 | 50.9         | 60.0        | 32.9      | 84.4                                 | 60.1            | NS      |                    |
| Khunti et al. [34]        | England       | 350,960/2,500,505  | White: 71.1, Black: 4.7, Asian: 12.3 | 54.5 (57.0-77.0) | 67.0 | 24.2 vs. 32.9 | 78.4 | 21.3 | NS |
| Kim et al. [35]           | Korea         | 19/216             |                                 | 45.1         | 68.3 ± 11.9| 24.2      | 62.6                                 | 7.7             | NS      |                    |
| Kristan et al. [36]       | USA           | 281/351            |                                 | 51.0         | 62.0 ± 15.0| 32.9      | 78.4                                 | 21.3            | NS      |                    |
| Lally et al. [37]         | USA           | 103/190            | White: 54.4, Black: 40.8        | 97.1         | 73.3 ± 9.4 | 7.7 ± 1.5| 29.3 ± 3.0 | 52.4       | NS     |                    |
| Li et al. (1) [39]        | China         | 26/105             |                                 | 56.5         | 66.8 ± 11.6| 7.9 ± 1.9| 24.2 ± 3.4 | 59.5       | NS     |                    |
| Li et al. (2) [38]        | China         | 102/285            |                                 | 51.1         | 60.0        | 7.9 ± 1.9| 24.2 ± 3.4 | 48.6       | 1.0    |                    |
| Luk et al. [40]           | China         | 385/679            | Asian                          | 57.7         | 66.0 (58.5-73.1) vs. 65.3 | 7.7 ± 15.1 vs. 7.9 ± 1.3 | 22.9 | 69.4 vs. 48.5 | Increased |                  |
| Luo et al. [42]           | China         | 88/103             |                                 | 56.5         | 62.7 ± 11.0| 7.9 (6-9-9) | 22.9 | 69.4 vs. 48.5 | Increased |                  |
| Mansour et al. [44]       | Iran          | 25/86              |                                 | 55.9         | 63.6 ± 13.3| 7.9 ± 6.3 | Obesity: 51.7% | 31.0 | Increased |                  |
| Mirani et al. [46]        | Italy         | 29/61              |                                 | 72.4         | 72.0 ± 10.0 vs. 70.0 | 7.7 ± 2.1 | 32.8 | 15.5 | Increased |
| Nyland et al. [50]        | USA           | 9149/20,367        | White: 47.9, African American: 25.5, Asian: 3.1 | 48.2         | 60.9 ± 15.0| 7.7 ± 2.1 | 32.8 | 15.5 | Increased |
| Oh et al. [51]            | Korea         | 914/26,579         |                                 | 48.0         | 69 ± 14  | 7.1 (6.7-8.3) | 30.5 | 80.8 | 34.2 | NS |
| Orioli et al. [52]        | Belgium       | 31/37              |                                 | 48.0         | 69 ± 14  | 7.1 (6.7-8.3) | 30.5 | 80.8 | 34.2 | NS |
| Perez-Belmonte et al. [54] | Spain         | 292/1458           |                                 | 77.9 ± 9.0  | Obesity: 20.9% | vs. 28.8% | Obesity: 17.7% | 84.3 | 17.2 | NS |
| Ramos-Rincon et al. [56]  | Spain         | 225/565            |                                 | 47.1         | 66.4 ± 12.7| 8.6 ± 3.5 | 31.1 | 91.0 | 25.0 | Increased |
| Ribad et al. [58]         | USA           | 88/78              | White: 6.0, African American: 71.0 | 52.0         | 66.4 ± 12.7 | 31.1 | 91.0 | 25.0 | Increased |
| Satman et al. [59]        | Turkey        | 3340/15,318        |                                 | 42.3         | 53.0 (22.0) | 6.9 (2.3) | 30.0 (7.1) | 66.4 | 18.9 | Increased |
| Shetakova et al. [61]     | Russia        | 115/194            |                                 | 54.1         | 73.3 ± 12.7| 7.7 (8.8-9.0) | 7.7 (6.8-9.0) | 28.4 | 76.8 | Increased |
| Silveri et al. [62]       | Italy         | 43/116             |                                 | 63.9         | 67.6 ± 14.0| 6.7 | 29.4 | 77.0 | 23.1 | NS |
| Sourj et al. [63]         | Austria       | 41/139             |                                 | 64.0         | 67.7        | 89.0 | 36.0 | Increased |
| Wender et al. [66]        | USA           | 18,521/46,371      | White: 66.0, Black: 27.0, Hispanic: 9.0 | 36.3         | 69.7 ± 13.2| Obesity: 74.5% | Increased |                  |
(continued on next page)
medications in more homogenous populations. The results of metformin and insulin were consistently confirmed among various groups in terms of vulnerability, including advanced age, high BMI, and high rate of CKD (Figs. A.6–A.8 and A.25–A.27, respectively). Meanwhile, GLP-1RA and SGLT-2i were still beneficial compared to nonusers, albeit less pronounced in populations with a higher rate of comorbidities and older

Table 1 (continued)

| Study          | Country     | Number of patients | Race/ethnicity (%) | Male sex (%) | Age (years) | HbA1C (%) | Body mass index (kg/m²) or obesity (%) | Hypertension (%) | CKD (%) | Mortality |
|----------------|-------------|--------------------|--------------------|--------------|-------------|-----------|----------------------------------------|-----------------|---------|-----------|
| Yan et al. [71] | China       | 4/30               | White: 58.1, African: 17.4, Asian: 3.6 | 68.8         | 69.4 ± 9.9  | 7.2 (6.7–8.3) | 50.0                                      | 0.0             | Increased |
| Yuan et al. [72] | China       | 76/106             |                   | 47.4         | 66.0        | 8.6        | 23.7                                      | 57.9            | 2.6     | Increased |
| Pazoki et al. [13] | Iran       | 53/340             |                   | 56.2         | 65.4 ± 11.6 | 28.0 ± 5.1 | 65.4                                      | 7.9             | NS      |           |

Data are presented as mean ± SD or median (IQR). Abbreviation: AGI, alpha-glucosidase inhibitor; CKD, chronic kidney disease; DPP-4i, dipeptidyl peptidase inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; NS, not significant; SGLT-2i, sodium–glucose transporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

**Fig. 2.** Forest plot of the relationship between metformin and mortality in patients with COVID-19 having type 2 diabetes.
patients, respectively (Figs. A.15, A.17, and A.21). Despite overall mortal neutrality, SU might have mild benefits in younger and less vulnerable populations (Figs. A.9–A.12). In contrast, DPP-4i showed harm or at least no benefit (A.18–A.20).

3.3.4. Sensitivity analysis

We further performed a sensitivity analysis by using two methods. First, we identified outliers by implementing the outlier removal algorithm in the dmetar package to explore the influence of individual studies on pooled effects. After outliers were removed, the pooled OR did not significantly change (all p > 0.05). Next, we conducted the trim-and-fill method to impute missing effects and concluded that our main results were stable after extending additional effects (all p > 0.05; Table 3).

3.3.5. Dose-response meta-analysis

Metformin was the only medication that was reported the daily dosage in these original papers. Therefore, we performed a dose-response meta-analysis for metformin. We observed a significant linear dose-response association between metformin dose and odds ratio of mortality (estimate: 0.88, standard error: 0.22, p < 0.001) and no evidence of heterogeneity among studies (I² = 0%, p = 0.46; Fig. 5).

3.3.6. Comparison with previous meta-analyses

We next compared our results with those from other publications [4–7,73–88]. No published meta-analysis has analyzed the association between TZD or AGI and COVID-19-related mortality (Table 4).

4. Discussion

4.1. Summary of main findings

To the best of our knowledge, this timely study has been the most extensive systematic review and meta-analysis confirming that different antidiabetic medications could predispose individuals with COVID-19 to different prognoses. Compared with a previous publication [5], we observed significant roles of GLP-1RA and SGLT-2i, besides metformin, in protecting individuals from COVID-19-related death. Similar to most studies, we also identified a positive association between DPP-4i usage and mortality. Moreover, we are the first to report the pooled effect of TZD and the pooled effect of AGI. Similar to smaller meta-analyses [5,75,85], our data also indicated the inconsistent impact of SU. Finally, we are the first to perform a dose-response meta-analysis regarding the daily dose of metformin to predict the magnitude of the effect on mortality in patients with COVID-19 having diabetes. These findings can have a large impact on the outpatient management strategy.
**Table 2**

Meta-regression analysis on potentially confounding factors.

| Medication | Continent factor | Estimate | SE  | p-Value |
|------------|------------------|----------|-----|---------|
| Metformin  | Continent (vs. America) |          |     |         |
|            | Africa            | 0.274    | 0.482 | 0.57    |
|            | Asia              | -0.076   | 0.227 | 0.74    |
|            | Europe            | 0.096    | 0.235 | 0.68    |
|            | White race (%)    | 0.004    | 0.006 | 0.53    |
|            | Age (years)       | -0.003   | 0.013 | 0.81    |
|            | Male sex (%)      | -0.001   | 0.007 | 0.87    |
|            | HbA1C (%)         | -0.100   | 0.181 | 0.59    |
|            | Body mass index (kg/m²) | 0.043 | 0.037 | 0.26    |
|            | Hypertension (%)  | -0.001   | 0.006 | 0.87    |
|            | Chronic kidney disease (%) | 0.001 | 0.005 | 0.89    |
| Sulfonylurea| Continent (vs. America) |          |     |         |
|            | Africa            | -0.123   | 0.204 | 0.56    |
|            | Asia              | 0.075    | 0.185 | 0.69    |
|            | Europe            | 0.076    | 0.158 | 0.64    |
|            | White race (%)    | 0.017    | 0.003 | 0.02    |
|            | Age (years)       | 0.015    | 0.007 | 0.03    |
|            | Male sex (%)      | 0.009    | 0.003 | 0.01    |
|            | HbA1C (%)         | -0.753   | 0.551 | 0.55    |
|            | Body mass index (kg/m²) | -0.045 | 0.030 | 0.19    |
|            | Hypertension (%)  | 0.006    | 0.002 | 0.01    |
|            | Chronic kidney disease (%) | 0.009 | 0.003 | 0.02    |
| Thiazolidinedione| Continent (vs. America) |          |     |         |
|            | Asia              | 0.389    | 0.398 | 0.37    |
|            | Europe            | 0.182    | 0.350 | 0.62    |
|            | White race (%)    | 0.071    | 0.026 | 0.22    |
|            | Age (years)       | 0.099    | 0.063 | 0.19    |
|            | Male sex (%)      | -0.001   | 0.030 | 0.07    |
|            | HbA1C (%)         | Insufficient data for analysis |
|            | Body mass index (kg/m²) | Insufficient data for analysis |
|            | Hypertension (%)  | 0.025    | 0.008 | 0.05    |
|            | Chronic kidney disease (%) | 0.005 | 0.025 | 0.87    |
| Alpha-glucosidase inhibitor| Continent (vs. America) |          |     |         |
|            | Asia              | 0.073    | 1.966 | 0.97    |
|            | Europe            | 1.452    | 2.234 | 0.54    |
|            | White race (%)    | Insufficient data for analysis |
|            | Age (years)       | -0.078   | 0.067 | 0.28    |
|            | Male sex (%)      | -0.090   | 0.054 | 0.15    |
|            | HbA1C (%)         | 1.845    | 1.991 | 0.42    |
|            | Body mass index (kg/m²) | 0.108 | 0.174 | 0.65    |
|            | Hypertension (%)  | -0.007   | 0.027 | 0.81    |
|            | Chronic kidney disease (%) | 0.023 | 0.124 | 0.86    |
| Glucagon-peptide like-1 receptor agonist| Continent (vs. America) |          |     |         |
|            | Asia              | 1.707    | 1.459 | 0.27    |
|            | Europe            | -0.004   | 0.283 | 0.99    |
|            | White race (%)    | 0.033    | 0.027 | 0.30    |
|            | Age (years)       | 0.043    | 0.021 | 0.08    |
|            | Male sex (%)      | 0.032    | 0.010 | 0.01    |
|            | HbA1C (%)         | -1.000   | 0.361 | 0.07    |
|            | Body mass index (kg/m²) | -0.053 | 0.038 | 0.25    |
|            | Hypertension (%)  | 0.029    | 0.010 | 0.02    |
|            | Chronic kidney disease (%) | 0.008 | 0.007 | 0.32    |
| Dipeptidyl peptidase-4 inhibitor| Continent (vs. America) |          |     |         |
|            | Asia              | -0.183   | 0.247 | 0.47    |
|            | Europe            | -0.260   | 0.243 | 0.30    |
|            | White race (%)    | -0.003   | 0.018 | 0.90    |
|            | Age (years)       | -0.005   | 0.014 | 0.74    |

**Table 2 (continued)**

| Medication | Continent factor | Estimate | SE  | p-Value |
|------------|------------------|----------|-----|---------|
| Sodium-glucose transporter-2 inhibitor| Continent (vs. America) |          |     |         |
|           | Asia             | 0.675    | 0.381 | 0.11    |
|           | Europe           | -0.500   | 0.218 | 0.04    |
|           | White race (%)   | -0.006   | 0.017 | 0.77    |
|           | Age (years)      | 0.029    | 0.048 | 0.56    |
|           | Male sex (%)     | -0.031   | 0.023 | 0.21    |
|           | HbA1C (%)        | 0.565    | 0.124 | 0.35    |
|           | Body mass index (kg/m²) | -0.069 | 0.107 | 0.57    |
|           | Hypertension (%) | 0.011    | 0.012 | 0.38    |
|           | Chronic kidney disease (%) | 0.008 | 0.018 | 0.66    |
| Insulin   | Continent (vs. America) |          |     |         |
|           | Asia             | 0.217    | 0.576 | 0.71    |
|           | Europe           | 0.009    | 0.285 | 0.98    |
|           | White race (%)   | -0.221   | 0.280 | 0.44    |
|           | Age (years)      | -0.000   | 0.011 | 0.98    |
|           | Male sex (%)     | -0.001   | 0.011 | 0.97    |
|           | HbA1C (%)        | 0.029    | 0.347 | 0.93    |
|           | Body mass index (kg/m²) | 0.115 | 0.061 | 0.08    |
|           | Hypertension (%) | 0.011    | 0.008 | 0.19    |
|           | Chronic kidney disease (%) | 0.002 | 0.009 | 0.87    |

Abbreviations: SE, standard error.

of diabetes patients amid the COVID-19 pandemic. These results can be helpful for clinicians in terms of choosing proper glucose-lowering regimens and dosage for those patients to reduce the risk of in-hospital death, i.e. by promoting the prescription of metformin, GLP-1RA, and SGLT-2i in the absence of any contraindications. In contrast, caution should be exercised in long-term insulin use.

Metformin might decrease or did not significantly affect COVID-19 death in the original studies. However, when performing meta-analyses, it yielded the most consistent result, even in vulnerable patients. Our study corroborated previous publications highlighting the potential benefits of metformin in patients with COVID-19 and diabetes. Several mechanisms might explain the lower mortality from SARS-CoV-2 infections in individuals taking metformin. First, beyond the hypoglycemic effect, metformin could reduce the release of inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha, which play a vital role in COVID-19 pathophysiology [89]. Second, metformin is also involved in other pathways: angiotensin-converting enzyme-2 (ACE-2) modulation through adenosine monophosphate-activated protein kinase, decreased coagulation and thrombosis formation, mast cell stabilization, and improved endothelial function [18,90]. Therefore, several researchers are currently investigating metformin as a host-directed medication in patients with COVID-19 [91]. Our current study indicated that metformin is effective among different races, sexes, weight status, and levels of glucose control. The dosage of metformin also affected the risk of mortality. First, Cheng et al. indicated that preadmission metformin usage was associated with better outcomes in a dose-response manner. In that study, metformin median dose was 1000 (890–1220) mg/day [21]. Ghany et al. reported that individuals using metformin at a dose of ≥1000 mg/day had lower mortality than those on 500–850 mg/day [29]. Referenced to nonusers, Ong et al. reported the greatest benefit on mortality with the dose from 1000 to <2000 mg/day [52]. Our findings were consistent with these studies. Specifically, every
metformin is only 2550 mg/day (immediate-release form) and 2000 mg/day (extended-release form).

GLP-1RA and SGLT-2i are two novel classes of antidiabetic medications that have been approved for cardiorenal protection in type 2 diabetes patients. In the COVID-19 scenario, GLP-1RA can help reduce cytokine-induced lung injury by interfering with the NF-kB pathway or exerting anti-inflammatory effects [92,93]. Meanwhile, when hypoxemia and hypoxia occur, SGLT-2i reverses the acid-base cytokine balance by decreasing lactic acid accumulation, thereby inhibiting the lowering of cytosolic pH and preventing cell damage during COVID-19-induced cytokine storm [94]. These cardiorenal benefits can synergistically offer protection to vital organs to reduce the risk of severity progression accompanied by beta-cell dysfunction. Therefore, it was not insulin therapy, per se, that was associated with poor prognosis of patients with COVID-19 having type 2 diabetes, but rather that it represented a proxy of severity and duration of diabetes. However, notably, iatrogenic hyperinsulinemia caused by exogenous insulin use might lead to adverse effects, including insulin resistance due to downregulation of insulin receptors, vascular changes, and subsequent adverse cardiovascular outcomes [96]. Moreover, our subgroup analyses as well as those from previous publications controlling for severity markers did not eliminate the association, raising concerns about the actual harmful effects of insulin [17]. Like DPP-4i, the increased risk of death among insulin users should be cautiously interpreted.

Unlike two smaller meta-analyses demonstrating that SU could reduce mortality risk [5,75], our results indicated that SU was not significantly associated with COVID-19-related mortality. Moreover, our study conducted a meta-analysis of AGI, which has not been reported previously. Traditionally, these drugs were often considered cardiovas-
cular neutral. This characteristic makes them not a first-line treatment in several comorbidities who had a compelling need to minimize hypoglycemia. These characteristics promoted the prescription of DPP-4i and limited the indication of other antidiabetic medications [33,50,54]. On the other hand, our subgroup analyses showed that DPP-4i might have little or no benefit among patient groups differed by vulnerability, suggesting that DPP-4i might not be associated with favorable COVID-19-related outcomes. To summarize, higher mortality rates in DPP-4i users should be cautiously interpreted.

The association between insulin treatment and severity or mortality is more complex. This result may still be affected by a confounding factor regarding the late commencement of insulin at an advanced stage of diabetes and the heterogeneous effectiveness of different insulin regimens, such as basal, basal-bolus, or premixed therapies. We speculate that insulin therapy is likely a surrogate indicator of diabetes progression accompanied by beta-cell dysfunction. Therefore, it was not insulin therapy, per se, that was associated with poor prognosis of patients with COVID-19 having type 2 diabetes, but rather that it represented a proxy of severity and duration of diabetes. However, notably, iatrogenic hyperinsulinemia caused by exogenous insulin use might lead to adverse effects, including insulin resistance due to downregulation of insulin receptors, vascular changes, and subsequent adverse cardiovascular outcomes [96]. Moreover, our subgroup analyses as well as those from previous publications controlling for severity markers did not eliminate the association, raising concerns about the actual harmful effects of insulin [17]. Like DPP-4i, the increased risk of death among insulin users should be cautiously interpreted.

Fig. 5. Dose–response meta-analysis between daily metformin dosage and mortality in patients with COVID-19 with diabetes.

250 mg/day increase in metformin use was associated with a 19.7% lower odds of mortality. In summary, the minimum metformin dosage that was found beneficial was 500 mg/day, and the higher the dose, the higher the effect. However, notably, the maximum approved dose for metformin is only 2550 mg/day (immediate-release form) and 2000 mg/day (extended-release form).

Metformin, SGLT-2i, and GLP-1RA have been identified as promising therapeutic targets for COVID-19 treatment. Metformin can reduce mortality. DPP-4i has yielded both protective and harmful effects on the underlying mechanisms of SARS-CoV-2 infection and progression from preclinical studies [4,95]. Moreover, the controversial results of DPP-4i from various original studies and meta-analyses up to the present might be explained by the fact that the authors could not entirely exclude potential confounders, even with multivariate adjustment or propensity score matching. For example, we observed a trend toward higher use of DPP-4i in older fragile people and in patients with several comorbidities who had a compelling need to minimize hypoglycemia. These characteristics promoted the prescription of DPP-4i and limited the indication of other antidiabetic medications [33,50,54]. On the other hand, our subgroup analyses showed that DPP-4i might have little or no benefit among patient groups differed by vulnerability, suggesting that DPP-4i might not be associated with favorable COVID-19-related outcomes. To summarize, higher mortality rates in DPP-4i users should be cautiously interpreted.

Table 3
Sensitivity analysis.

| Medication                           | Main meta-analysis | Sensitivity analysis |
|--------------------------------------|--------------------|---------------------|
|                                      | OR (95% CI)        | I²                  | OR (95% CI) | I² | p value | OR (95% CI) | p value |
| Metformin                            | 0.54 (0.47–0.62)   | 86%                 | 0.50 (0.45–0.55) | 41% | 0.37   | 0.61 (0.54–0.70) | 0.17     |
| Sulfonylurea                          | 0.92 (0.83–1.01)   | 44%                 | 0.98 (0.90–1.06) | 18% | 0.31   | 0.93 (0.84–1.04) | 0.80     |
| Thiazolidinedione                     | 0.90 (0.71–1.14)   | 46%                 | No outlier    | 88.0 (0.70–1.11) | 91%     |
| Alpha-glucosidase inhibitor          | 0.61 (0.26–1.45)   | 77%                 | 1.13 (0.60–2.11) | 47% | 0.26   | 1.45 (0.57–3.74) | 0.18     |
| Glucagon-like peptide-1 receptor agonist | 0.51 (0.37–0.69)   | 85%                 | 0.54 (0.49–0.60) | 0%  | 0.70   | 0.62 (0.45–0.84) | 0.40     |
| Dipeptidyl peptidase-4 inhibitor     | 1.23 (1.07–1.42)   | 82%                 | 1.25 (1.14–1.37) | 37% | 0.86   | 1.29 (1.12–1.48) | 0.67     |
| Sodium-glucose transporter-2 inhibitor | 0.60 (0.40–0.88)   | 91%                 | 0.67 (0.52–0.85) | 47% | 0.63   | 0.54 (0.37–0.79) | 0.72     |
| Insulin                              | 1.70 (1.33–2.19)   | 97%                 | 1.60 (1.41–1.81) | 60% | 0.65   | 2.00 (1.58–2.52) | 0.37     |

a Comparison of OR before vs. after removing outliers.
b Comparison of OR before vs. after trimming and filling.

Fig. 5. Dose–response meta-analysis between daily metformin dosage and mortality in patients with COVID-19 with diabetes.

In contrast to previous smaller meta-analyses reporting that DPP-4i had no significant effect on COVID-19-related death [6,75,80,85], after incorporating a larger number of studies, we observed that preadmission DPP-4i users were associated with higher odds of in-hospital mortality.
lungs [97]. Moreover, evidence has shown that a TZD could downregulate A Disintegrin and Metalloproteinase-17 (ADAM-17), an ACE2 cleaving enzyme in human skeletal muscles [98]. This event, in turn, increased membrane ACE2 and facilitated cellular viral entry, raising concerns about increased susceptibility to SARS-CoV-2 infection. These hypotheses partially explained why TZD did not improve the mortality outcomes of patients with COVID-19 with diabetes in our study.

### 4.2. Strengths and limitations

Our study has several strengths. Despite the high heterogeneity related to some analyses, the robustness of our findings was confirmed through meta-regression, subgroup analysis, and sensitivity analysis. First, after outliers were identified and removed, the heterogeneity of all remaining studies drastically decreased without a significant change in OR (all p > 0.05). Second, after the trim-and-fill method was performed, the OR did not significantly change (all p > 0.05), indicating that our pooled odds ratio still reflected the actual effect size. In other words, our results were reliable and stable, even in the presence of high heterogeneity. Third, we only included preadmission-usage studies instead of combining both preadmission and in-hospital use like some meta-analyses, leading to a more consistent data interpretation. Moreover, unlike some publications, we updated the most recent and completed data instead of using ongoing data or pooling two studies from the same cohort. Next, we recruited relatively diverse samples from multicenter and multinational cohorts, thus increasing the ability to generalize to a larger population. Finally, we could present a dose-response meta-analysis to predict the effect of daily metformin doses on COVID-19 mortality.

Our study nevertheless has some limitations. First, we could include only observational studies because no randomized controlled trial was conducted on the topic of interest at the time of analysis. Any conclusions, therefore, should be cautiously drawn (considering indication bias). However, we recruited the largest number of participants from various papers of acceptable quality, making our systematic review and meta-analysis have high internal validity. Second, due to the observational nature of the studies, the multidrug issue could not be excluded. An investigation of specific combination therapies was necessary, an investigation that was not possible with the available data. Third, we could only perform a single meta-analysis to predict the effect of daily metformin doses on COVID-19 mortality.

### Table 4
Comparison with previous meta-analyses.

| Medication                      | Study                        | Medication use setting | Number of studies | OR/RR  | Conclusion |
|--------------------------------|------------------------------|------------------------|-------------------|--------|------------|
| Metformin                       | Our current study            | Preadmission           | 42                | 0.54   | Decreased  |
|                                 | Han et al. [5]               | Preadmission + in-hospital | 20               | 0.62   | Decreased  |
|                                 | Hariyanto et al. [74]        | Preadmission           | 5                 | 0.54   | Decreased  |
|                                 | Kan et al. [75]              | Preadmission + in-hospital | 15               | 0.69   | Decreased  |
|                                 | Kow et al. [76]              | Preadmission           | 5                 | 0.62   | Decreased  |
|                                 | Li et al. [77]               | Preadmission + in-hospital | 19               | 0.66   | Decreased  |
|                                 | Lukito et al. [78]           | Preadmission           | 6                 | 0.64   | Decreased  |
|                                 | Oshana et al. [79]           | Preadmission + in-hospital | 22               | 0.56   | Decreased  |
|                                 | Poly et al. [82]             | Preadmission + in-hospital | 16               | 0.66   | Decreased  |
|                                 | Schein et al. [84]           | Preadmission           | 4                 | 0.75   | Decreased  |
|                                 | Schlesinger et al. [85]      | ND                     | 4                 | 0.50   | Decreased  |
|                                 | Sun et al. [86]              | Preadmission           | 7                 | 0.54   | Decreased  |
|                                 | Yang et al. [87]             | Preadmission + in-hospital | 17               | 0.63   | Decreased  |
| Sulfonylurea                     | Our current study            | Preadmission           | 21                | 0.92   | NS         |
|                                 | Han et al. [5]               | Preadmission           | 4                 | 0.93   | Decreased  |
|                                 | Kan et al. [75]              | Preadmission + in-hospital | 5               | 0.80   | Decreased  |
|                                 | Schlesinger et al. [85]      | ND                     | 2                 | 0.73   | NS         |
| Thiazolidinedione                | Our current study            | Preadmission           | 8                 | 0.90   | NS         |
|                                 | No published meta-analysis   |                        |                   |        |            |
| Alpha-glucosidase inhibitor      | Our current study            | Preadmission           | 8                 | 0.61   | NS         |
|                                 | No published meta-analysis   |                        |                   |        |            |
| Glucagon-like peptide-1 receptor agonist | Our current study      | Preadmission           | 12                | 0.51   | Decreased  |
|                                 | Han et al. [5]               | Preadmission + in-hospital | 3               | 0.92   | NS         |
|                                 | Hariyanto et al. [7]         | Preadmission           | 9                 | 0.53   | Decreased  |
| Dipeptidyl peptidase-4 inhibitor | Our current study            | Preadmission           | 28                | 1.23   | Increased  |
|                                 | Bonora et al. [73]           | Preadmission           | 7                 | 0.81   | NS         |
|                                 | Han et al. [5]               | Preadmission + in-hospital | 11               | 0.95   | NS         |
|                                 | Hariyanto et al. [6]         | Preadmission           | 7                 | 1.14   | NS         |
|                                 | Kan et al. [75]              | Preadmission + in-hospital | 8               | 0.72   | NS         |
|                                 | Pal et al. [80]              | Preadmission           | 4                 | 1.21   | NS         |
|                                 | Patouis et al. [81]          | Preadmission           | 8                 | 1.14   | NS         |
|                                 | Rahmat et al. [83]           | Preadmission + in-hospital | 9               | 0.76   | NS         |
|                                 | Schlesinger et al. [85]      | ND                     | 2                 | 0.90   | NS         |
|                                 | Yang et al. [4]              | Preadmission + in-hospital | 4               | 0.58   | NS         |
| Sodium-glucose transporter-2 inhibitor | Our current study         | Preadmission           | 13                | 0.60   | Decreased  |
|                                 | Han et al. [5]               | Preadmission + in-hospital | 3               | 1.04   | NS         |
| Insulin                         | Our current study            | Preadmission           | 33                | 1.70   | Increased  |
|                                 | Kan et al. [75]              | Preadmission + in-hospital | 7               | 2.20   | Increased  |
|                                 | Schlesinger et al. [85]      | ND                     | 5                 | 1.75   | Increased  |
|                                 | Yang et al. [88]             | Preadmission + in-hospital | 12               | 2.10   | Increased  |

Abbreviations: ND, not defined; NS, not significant.
drugs used during hospitalization, both of which are especially critical for mortality modeling. Fifth, it is impossible to completely rule out unmeasured confounders, such as smoking or socioeconomic status, although the original studies tried to adjust for these factors to a certain extent. Therefore, further studies with a strictly controlled design are warranted to confirm the relationships between therapies and mortality among patients with COVID-19 having type 2 diabetes. Last, because of the high publication rate regarding the COVID-19 topic within the past three years, there is a possibility that some studies might have been missed and therefore were not included in our current review. Although it is unavoidable, we minimized that issue by assigning three researchers to systematically search and select studies and another reviewer to be consulted to reach a final decision if needed.

5. Conclusions

The preadmission prescription of glucose-lowering therapies was associated with different outcomes in patients with COVID-19 having type 2 diabetes. Specifically, metformin, GLP-1RA, and SGLT-2i were more likely to be beneficial regarding in-hospital death. By contrast, DPP-4i and insulin were associated with increased mortality. However, SU, TZD, and AGI were mortality neutral.

Abbreviations

ACE-2 Angiotensin-converting enzyme-2
ADAM-17 A Disintegrin And Metalloproteinase-17
AGI Alpha-glucosidase inhibitor
CKD Chronic kidney disease
COVID-19 Coronavirus disease of 2019
DPP-4i Dipeptidyl peptidase-4 inhibitor
GLP-1RA Glucagon-like peptide-1 receptor agonist
NF-kB Nuclear factor kappa-light-chain-enhancer of activated B cell
SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2
SGLT-2i Sodium–glucose transporter-2 inhibitor
SU Sulfonylurea
TZD Thiazolidinedione

CRediT authorship contribution statement

NNN conceived of the original idea, performed meta-analyses, meta-regression, sensitivity analyses, interpreted data, and wrote the first manuscript. DSH, HSN, and DKNH performed the systematic search, study selection, risk of bias assessment, and data extraction. HYC and YCC verified the analytical methods, supervised the findings of this study, and contributed to the revisions of the final manuscript. HYC and CYL provided clinical advice on the interpretation of the data and contributed to the revisions of the final manuscript. All authors approved the final manuscript as submitted and have agreed to be accountable for all aspects of the work. YCC is the guarantor of this work.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose. All authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

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Data availability

Data were extracted from published research papers, all of which are available and accessible. All datasets generated during the current study are available upon reasonable request from the corresponding authors. The study protocol has been published (PROSPERO ID: CRD42021293064; www.crd.york.ac.uk/PROSPERO/) and is unrestrictedly available.

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Appendix A. Supplementary data

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