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.

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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), I^2 86%], glucagon-like peptide-1 receptor agonist (GLP-1RA) [0.51 (0.37–0.69), I^2 85%], and sodium–glucose transporter-2 inhibitor (SGLT-2i) [0.60 (0.40–0.88), I^2 91%]. Dipeptidyl peptidase-4 inhibitor (DPP-4i) [1.23 (1.07–1.42), I^2 82%] and insulin [1.70 (1.33–2.19), 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, I^2 44%), 0.90 (95% CI 0.71–1.14, I^2 46%), and 0.61 (95% CI 0.26–1.45, 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,

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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 preadmission 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 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-kB) 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 current use of antidiabetic medications was recorded at the time of recruitment. The interventional therapies considered were one of the following medications: metformin, sulfonylurea (SU), meglitinide (glinide), thiazolidinedione (TZD), alpha-glucosidase inhibitor (AGI), GLP-1RA, DPP-4i, sodium–glucose transporter-2 inhibitor (SGLT-2i), and insulin. Specific-agent users were defined as those who have been on a current prescription. The comparator included nonusers of specific antidiabetic medications. Our primary outcome was in-hospital mortality or mortality within 90 days, confirmed with the medical record.

We planned to include randomized and nonrandomized controlled trials and observational studies, including prospective and retrospective cohort studies and case-control studies, which were either peer-reviewed or published as abstracts or preprints. If an official publication has already replaced a preprint, the publication was chosen instead of a preprint. We excluded case reports and review articles.

Based on the predetermined inclusion criteria, three independent reviewers (DSH, HSN, and DKNH) searched, screened, reviewed, extracted, and recorded data. In case of discrepancy, a fourth reviewer (NNN) was consulted to reach a final consensus. We verified transparent reporting following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist because we only found observational studies relevant to this topic.

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 A.1 (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 I^2 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 I^2 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 prespecified 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 re-analyzed 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, I^2 86%), GLP-1RA (OR 0.51, 95% CI 0.37–0.69, I^2 85%), and SGLT-2i (OR 0.60, 95% CI 0.40–0.88, I^2 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, I^2 82%) and insulin (OR 1.70, 95% CI 1.33–2.19, I^2 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, I^2 44%), TZD (0.90, 95% CI 0.71–1.14, I^2 46%), and AGI (OR 0.61, 95% 0.26–1.45, I^2 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

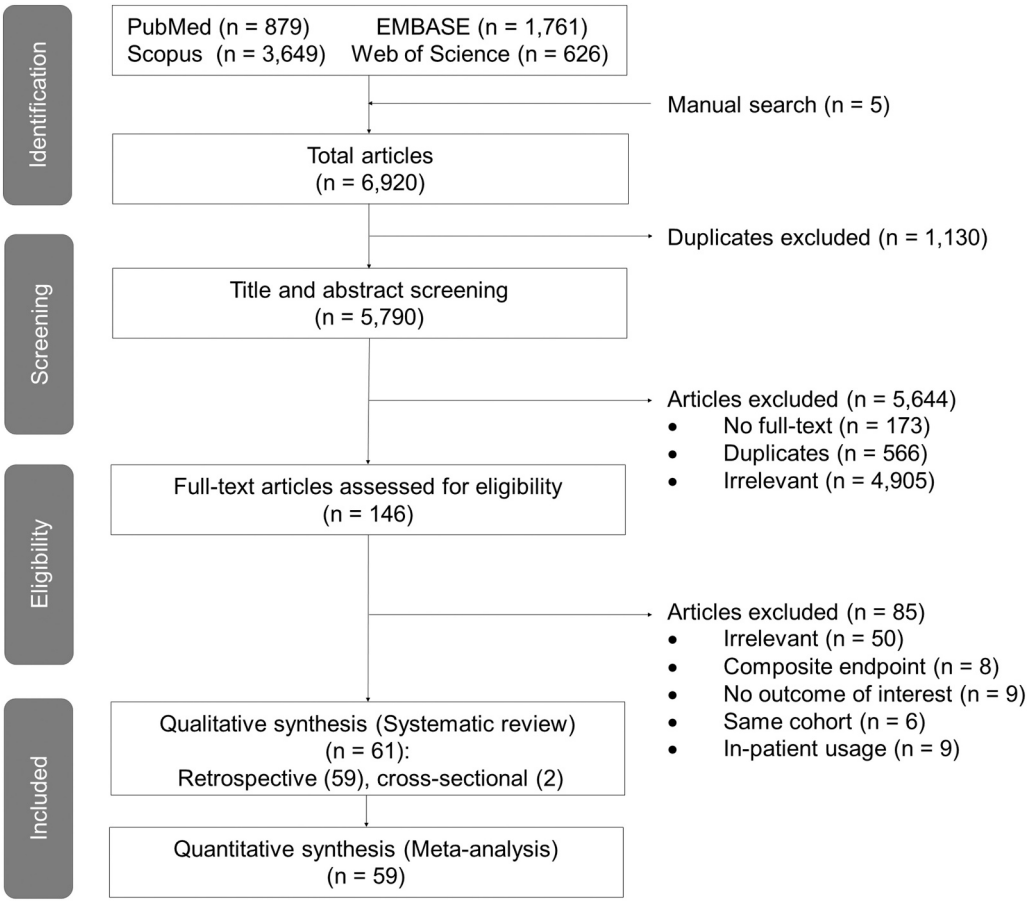

Fig. 1. PRISMA flowchart summarizing the study selection process.

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			18.2	0.8	NS
Bliden et al. [16]	USA	34/41				8.9 ± 2.3 vs. 8.4 ± 1.8				NS
Bramante et al. [18]	USA	2333/3923		51.6 vs. 44.6	73.0 (66.0–80.0) vs. 76.0 (67.0–84.0)		Obesity: 4.8% vs. 9.0%	56.3 vs. 60.4	6.3 vs. 18.6	NS
Cernigliaro et al. [19]	Italy	82/90								Decreased
Chen et al. [20]	China	43/77		42.9	62.0 (56.0–69.0) vs. 67.0 (57.5–73.0)	7.7 (6.9–9.1) vs. 8.4 (7.4–10.7)		61.2	10.2	NS
Cheng et al. [21]	China	18/32		66.7 vs. 46.9	48.0 (40.5–56.5) vs. 58.0 (49.5–66.5)		25.9 (24.7–26.9) vs. 24.5 (21.3–28.0)	22.2 vs. 43.8	27.8 vs. 37.5	NS
Crouse et al. [22]	USA	76/144	White: 27.6, African American: 64.9	50.6		8.0 ± 2.6 vs. 7.0 ± 1.8	35.2 ± 9.4 vs. 33.6 ± 8.7	91.6		Decreased
Dave et al. [23]	Africa	4084/1624		39.3	55.0 (46.0–63.0)			55.5	9.2	Decreased
Do et al. [25]	Korea	469/1396		51.8 vs. 42.1	64.8 ± 11.4 vs. 67.4 ± 12.1			73.8 vs. 82.1	29.4 vs. 47.4	NS
Eliboi et al. [26]	Turkey	379/53		45.6	63.3 ± 10.3			74.1	4.6	NS
Ghany et al. [29]	USA	243/350	Black: 71.0 vs. 70.0	39.0 vs. 41.0	70.9 ± 8.9 vs. 71.2 ± 8.9	7.7 ± 1.5 vs. 6.4 ± 1.5	33.2 ± 7.7 vs. 31.7 ± 9.6	60.0 vs. 50.0		Decreased
Goodall et al. [31]	England	210/166	White: 25.5, Black: 13.9, Asian: 37.8	64.3	69.0 (56.0–80.0)			49.6		NS
Khunti et al. [34]	England	1,800,005/ 1,051,460	White: 64.5, Black: 4.8, Asian: 16.0	58.1	67.0 (57.0–77.0)				78.0	Decreased
Kim et al. [35]	Korea	113/122		45.1	68.3 ± 11.9		24.2 ± 3.2	62.6	7.7	NS
Lally et al. [37]	USA	127/172	White: 61.4, Black: 30.7	98.4 vs. 98.6	72.3 ± 8.3 vs. 75.6 ± 9.2	7.5 ± 1.4 vs. 6.5 ± 1.3	29.7 ± 6.6 vs. 28.0.2 ± 7.0		13.4	Decreased
Li et al. (1) [39]	China	37/94		59.5 vs. 55.3	64.6 ± 11.2 vs. 67.7 ± 11.7	9.2 ± 4.6 vs.9.0 ± 4.6	24.2 ± 3.3 vs. 24.2 ± 3.7	62.2 vs. 58.5		Decreased
Li et al. (2) [38]	China	142/245		51.1	60.0 (49.0–68.0)			48.6	1.0	NS
Luk et al. [40]	China	737/254	Asian	55.0 vs. 51.6	65.6 (57.7–72.6) vs. 68.9 (61.3–79.7)	7.3 (6.6–8.5) vs. 6.6 (6.1–7.8)	24.1 (21.5–27.7) vs. 23.7 (22.2–27.0)	63.1 vs. 56.7	19.5 vs. 37.8	Decreased
Luo et al. (1) [41]	China	104/179		51.0 vs. 57.5	63.0 (55.8–68.3) vs. 65.0 (57.5–71.0)			59.6 vs. 57.0		Decreased
Luo et al. (2) [42]	China	54/137		54.0 vs. 54.0	61.0 (56.0–69.0) vs. 61.0 (57.8–68.3)	8.0 ± 1.9 vs. 6.7 ± 1.9		55.5	2.0 vs. 2.0	Decreased
Ma et al. [43]	USA	361/995	White: 72.6, Black: 12.2, Asian: 1.9	60.4 vs. 54.1				79.5 vs. 85.0		Decreased
Mirani et al. [46]	Italy	69/21		72.5 vs. 71.4	69.0 ± 13.0 vs. 75.0 ± 8.0		Obesity: 47.8% vs. 47.6%	72.5 vs. 90.5	11.6 vs. 42.9	NS
Mirsoleymani et al. [47]	Iran	36/69		72.4	59.8 ± 17.2			37.1		NS
Nafakhi et al. [48]	Iraq	35/32		43.0	60.0 ± 10.0		29.8 ± 5.0	66.0		Decreased
Nyland et al. [50]	USA	5077/ 24,439	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	Decreased

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Table 1 (*continued*)

Study	Country	Number of patients	Race/ethnicity (%)	Male sex (%)	Age (years)	HbA1C (%)	Body mass index (kg/m^2) or obesity (%)	Hypertension (%)	CKD (%)	Mortality
Oh et al. [51]	Korea	7204/ 20,289		44.7 vs. 38.2					3.4 vs. 4.1	NS
Ong et al. [52]	Philippines	186/169		58.6 vs. 52.7	61.6 ± 11.6 vs. 63.9 ± 12.8	7.0 ± 2.4 vs. 7.6 ± 1.9	Obesity: 62.0% vs. 65.1%	73.1 vs. 76.3	4.8 vs. 21.9	Decreased
Orioli et al. [53]	Belgium	45/23		48.0	69.0 ± 14.0	7.1 (6.6–8.3)	30.5 ± 5.3	80.8	34.2	Decreased
Perez-Belmonte et al. [54]	Spain	825/663		65.7 vs. 57.2	74.8 ± 7.9 vs. 77.1 ± 7.1		Obesity: 26.4% vs. 26.1%	74.2 vs. 79.5	4.7 vs. 29.0	NS
Philipose et al. [55]	England	100/59	White: 45.5, Afro-Caribbean: 20.2, Asian: 19.1	59.0				50.2		NS
Ramos-Rincon et al. [56]	Spain	421/369		47.1			Obesity: 17.7%	84.3	17.2	NS
Ravindra et al. [57]	India	53/313		63.2	46.7 ± 17.1			28.7	0.9	NS
Saygili et al. [60]	Turkey	432/154		49.8 vs. 50.2	65.0 ± 11.2 vs. 68.9 ± 13.5	8.0 (6.8–9.9) vs. 7.7 (6.7–10.1)		67.1 vs. 70.1	0.0	Decreased
Shetaskova et al. [61]	Russia	196/113								Decreased
Silverii et al. [62]	Italy	76/83		54.1	73.3 ± 12.7					Decreased
Sourij et al. [63]	Austria	77/103		63.9	67.6 ± 14.0	6.7 (1.9)	29.4 ± 5.7	77.0	23.1	NS
Tamura et al. [65]	Brazil	116/72		63.5 vs. 61.6	62.1 ± 15.1 vs. 68.6 ± 17.3		29.2 ± 5.3 vs. 29.4 ± 5.1	60.3 vs. 76.4	1.7 vs. 12.3	Decreased
Wander et al. [66]	USA	29,685/ 64,892	White: 66.0, Black: 27.0, Hispanic: 9.0	64.0	67.7			89.0	36.0	Decreased
Wang et al. (1) [67]	USA	9/7	African American: 23.0, Hispanic: 16.0	52.0	67 (12.5)		27.6	64.0	24.0	NS
Wang et al. (2) [68]	England	110/54		61.9 vs. 52.0	64.8 ± 11.7 vs. 67.8 ± 13.1		32.1 ± 6.7 vs. 31.8 ± 6.8	59.1 vs. 60.7	13.0 vs. 24.2	NS
Wargny et al. [69]	France	1553/1241	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		Decreased
Cheng et al. [12]	China	678/553		53.8 vs. 49.9	62.0 (55.0–68.0) vs. 64.0 (58.0–70.0)	8.1 (7.0–9.9) vs. 7.6 (6.7–8.9)	24.3 (22.0–25.9) vs. 24.5 (22.6–26.2)		2.4 vs. 2.6	NS
Yuan et al. [72]	China	73/109		52.1	62.0 (55.0–70.0)	8.3 (7.2–9.9)	23.7 (22.0–25.4)	52.1	0.0	Decreased
Pazoki et al. [13]	Iran	177/216		56.2	65.4 ± 11.6		28.0 ± 5.1	65.4	7.9	NS
SU users/nonusers										
An et al. [15]	Korea	212/809		39.9	45.0 ± 19.9			18.2	0.8	NS
Cernigliaro et al. [19]	Italy	35/137								NS
Chen et al. [20]	China	53/67		42.9	66.0 (60.0–72.5) vs. 65.0 (55.0–73.0)	8.3 (7.4–9.5) vs. 7.7 (7.1–10.4)		61.2	10.2	NS
Dave et al. [23]	Africa	2110/3598		39.3	55.0 (46.0–63.0)			55.5	9.2	NS
Eliboi et al. [26]	Turkey	66/366		45.6	63.3 ± 10.3			74.1	4.6	NS
Khunti et al. [34]	England	561,290/ 2,290,175	White: 63.7, Black: 5.0, Asian: 17.2	60.5	67.0 (57.0–77.0)			80.7		Decreased
Kim et al. [35]	Korea	60/175		45.1	68.3 ± 11.9		24.2 ± 3.2	62.6	7.7	NS
Li et al. (1) [39]	China	22/109		56.5	66.8 ± 11.6	7.9 ± 1.9	24.2 ± 3.4	59.5		NS
Li et al. (2) [38]	China	91/296		51.1	60.0 (49.0–68.0)			48.6	1.0	NS
Luk et al. [40]	China	385/679	Asian	57.7 vs. 51.5	66.0 (58.5–73.1) vs.	7.7 (6.9–9.1) vs. 6.9 (6.4–8.2)	24.4 (21.8–27.8) vs.	69.4 vs. 48.5	25.5 vs. 19.9	NS

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Table 1 (*continued*)

Study	Country	Number of patients	Race/ethnicity (%)	Male sex (%)	Age (years)	HbA1C (%)	Body mass index (kg/m^2) or obesity (%)	Hypertension (%)	CKD (%)	Mortality
					65.3 (57.3–73.6)		23.5 (21.5–27.0)			
Luo et al. [42]	China	37/154		56.5	62.7 ± 11.0	7.9 (6.3–9.0)		55.5	3.0	Decreased
Mirani et al. [46]	Italy	10/80		60.0 vs. 73.8	75.0 ± 8.0 vs. 70.0 ± 12.0		Obesity: 50.0% vs. 47.5%	80.0 vs. 76.3	0.0 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	Decreased
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	NS
Shetaskova et al. [61]	Russia	129/180								NS
Silverii 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	NS
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 (60.0–73.0)	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		28.0 ± 5.1	65.4	7.9	NS
TZD users/nonusers										
Cernigliaro et al. [19]	Italy	10/162								NS
Eliboi et al. [26]	Turkey	27/405		45.6	63.3 ± 10.3			74.1	4.6	NS
Khunti et al. [34]	England	60,085/2,791,380	White: 63.5, Black: 3.7, Asian: 18.4	63.4	67.0 (57.0–77.0)			80.5		NS
Luo et al. [42]	China	7/184		56.5	62.7 ± 11.0	7.9 (6.3–9.0)		55.5	3.0	NS
Nyland et al. [50]	USA	469/23,714	White:52.4, African American: 23.2, Asian: 3.5	53.3 vs. 48.8	63.1 ± 12.5 vs. 60.9 ± 15.3	8.2 ± 2.0 vs. 7.5 ± 2.1	34.3 ± 9.0 vs. 32.3 ± 8.7	52.1 vs. 44.9	17.4 vs. 14.9	NS
Oh et al. [51]	Korea	1264/26,229								NS
Silverii et al. [62]	Italy	8/151		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										
An et al. [15]	Korea	7/1014		39.9	45.0 ± 19.9			18.2	0.8	Increased
Chen et al. [20]	China	69/51		42.9	66.0 (57.5–73.0) vs. 65.0 (56.0–72.0)	8.4 (7.4–10.3) vs. 7.9 (6.9–9.1)		61.2	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 (57.0–77.0)			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		NS
Li et al. (2) [38]	China	140/247		51.1	60.0 (49.0–68.0)			48.6	1.0	NS
Luo et al. [42]	China	77/114		65.0 vs. 63.0	62.3 ± 9.6 vs. 61.9 ± 9.4	7.9 ± 1.8 vs. 8.3 ± 2.0		55.5	2.2 vs. 0.0	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	Decreased

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Table 1 (*continued*)

Study	Country	Number of patients	Race/ethnicity (%)	Male sex (%)	Age (years)	HbA1C (%)	Body mass index (kg/m^2) or obesity (%)	Hypertension (%)	CKD (%)	Mortality
					66.0 (57.0–72.0)		23.7 (22.0–25.4)			
GLP-1RA users/nonusers										
Cernigliaro et al. [19]	Italy	8/164								NS
Israelsen et al. [32]	Denmark	370/558		53.0	59.0 (51.0–70.0)		Obesity: 29.2%	56.2		NS
Kahkoska et al. [33]	US	6692/5854	White: 64.1	40.9	55.7 ± 12.6	8.0 ± 2.0	37.2 ± 8.1	74.9 vs. 76.0	18.5	Decreased
Khunti et al. [34]	England	100,820/ 2,750,645	White: 76.3, Black: 3.3, Asian: 7.9	51.7	67.0 (57.0–77.0)				83.1	NS
Nyland et al. [50]	USA	1774/ 23,714	White: 52.3, Black: 28.7, Asian: 0.9	39.2 vs. 48.8	55.0 ± 12.7 vs. 60.9 ± 15.3	8.4 ± 2.2 vs. 7.5 ± 2.1	37.5 ± 9.3 vs. 32.3 ± 8.7	55.9 vs. 44.9	12.9 vs. 14.9	Decreased
Orioli et al. [53]	Belgium	5/63		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	37/753		47.1			Obesity: 17.7%	84.3	17.2	NS
Shetaskova et al. [61]	Russia	1/308								NS
Silverii et al. [62]	Italy	7/152		54.1	73.3 ± 12.7					NS
Sourij et al. [63]	Austria	3/177		63.9	67.6 ± 14.0	6.7 (1.9)	29.4 ± 5.7	77.0	23.1	NS
Wander et al. [66]	USA	4737/ 60,155	White: 66.0, Black: 27.0, Hispanic: 9.0	64.0	67.7			89.0	36.0	NS
Wargny et al. [69]	France	254/2540	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
DPP-4i users/nonusers										
An et al. [15]	Korea	229/792		39.9	45.0 ± 19.9			18.2	0.8	NS
Cernigliaro et al. [19]	Italy	13/159								NS
Chen et al. [20]	China	20/100		42.9	66.0 (56.0–73.0) vs. 65.0 (57.0–72.0)	7.8 (6.8–10.6) vs. 8.3 (7.3–9.5)		61.2	10.2	NS
Eliboi et al. [26]	Turkey	246/186		45.6	63.3 ± 10.3			74.1	4.6	NS
Emral et al. [27]	Turkey	6846/ 26,632		42.0 vs. 41.3	60.0 (16.0) vs. 52.0 (24.0)	8.1 (2.7) vs. 6.4 (1.6)	30.8 (6.7) vs. 29.4 (7.3)	85.6 vs. 64.0		Decreased
Fanidi et al. [28]	Italy	9/72			72.2 ± 12.8 vs. 70.1 ± 13.3	7.5 ± 3.3 vs. 7.6 ± 4.3		88.9 vs. 67.1	11.2 vs. 15.8	NS
Israelsen et al. [32]	Denmark	284/644		60.9	67.0 (57.0–76.0)		Obesity: 12.3%	61.6		NS
Kahkoska et al. [33]	USA	3511/8935	White: 57.4	49.9	64.1 ± 12.9 vs. 58.6 ± 13.1	7.8 ± 1.9 vs. 8.0 ± 1.9	36.0 ± 6.2 vs. 35.4 ± 8.2	78.7 vs. 76.0	31.6	Increased
Khunti et al. [34]	England	479,555/ 2,371,910	White: 65.5, Black: 4.7, Asian: 15.7	58.3	67.0 (57.0–77.0)			81.6		Increased
Kim et al. [35]	Korea	85/150		45.1	68.3 ± 11.9		24.2 ± 3.2	62.6	7.7	NS
Kristan et al. [36]	USA	76/756	White: 32.7, African American: 52.0, Asian: 1.4	51.0	62.0 ± 15.0	7.9 ± 2.3	32.9 ± 8.6	78.4	21.3	NS
Luk et al. [40]	China	199/952	Asian	59.3 vs. 53.2	67.0 (58.4–75.5) vs. 65.1 (56.8–72.2)	7.6 (6.8–8.9) vs. 7.2 (6.5–8.9)	25.0 (18.7–27.0) vs. 23.3 (21.6–27.4)	61.8 vs. 52.3	36.2 vs. 17.2	NS
Luo et al. [42]	China	11/180		56.5	62.7 ± 11.0	7.9 (6.3–9.0)		55.5	3.0	NS
Meijer et al. [45]	Netherlands	28/537		60.7 vs. 64.2	66.9 ± 12.4 vs. 69.5 ± 12.5		29.1 ± 6.0 vs. 29.8 ± 6.3	66.7 vs. 70.0	25.9 vs. 14.4	NS
Mirani et al. [46]	Italy	11/79		90.9 vs. 69.6	70.0 ± 13.0 vs. 71.0 ± 12.0		Obesity: 27.3% vs. 50.6%	54.6 vs. 79.8	18.2 vs. 19.0	Decreased
Noh et al. [49]	Korea	453/133								NS

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Table 1 (*continued*)

Study	Country	Number of patients	Race/ethnicity (%)	Male sex (%)	Age (years)	HbA1C (%)	Body mass index (kg/m^2) or obesity (%)	Hypertension (%)	CKD (%)	Mortality
				49.2 vs. 55.6					21.2 vs. 18.0	
Nyland et al. [50]	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	22.4 vs. 14.9	Increased
Oh et al. [51]	Korea	4132/ 23,361								NS
Orioli et al. [53]	Belgium	4/64		48.0	69.0 ± 14.0	7.1 (6.6–8.3)	30.5 ± 5.3	80.8	34.2	NS
Perez-Belmonte et al. [54]	Spain	180/1409		59.4 vs. 62.9	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
Ramos-Rincon et al. [56]	Spain	266/524		47.1			Obesity: 17.7%	84.3	17.2	Decreased
Shetaskova et al. [61]	Russia	26/283								NS
Silverii et al. [62]	Italy	13/146		54.1	73.3 ± 12.7					NS
Sourij et al. [63]	Austria	42/138		63.9	67.6 ± 14.0	6.7 (1.9)	29.4 ± 5.7	77.0	23.1	NS
Strollo et al. [64]	Italy	30/163		54.9	76.7 ± 11.8					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	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
Wong et al. [70]	China	107/1107		60.7 vs. 53.7	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
Pazoki et al. [13]	Iran	20/373		56.2	65.4 ± 11.6		28.0 ± 5.1	65.4	7.9	NS
SGLT-2i users/nonusers										
Cernigliaro et al. [19]	Italy	4/168								Decreased
Eliboi et al. [26]	Turkey	56/376		45.6	63.3 ± 10.3			74.1	4.6	NS
Israelsen et al. [32]	Denmark	274/654		61.8	59.0 (52.0–68.0)		Obesity: 15.4%	49.6		NS
Kahkoska et al. [33]	USA	3665/8781	White: 33.9	55.2	57.9 ± 11.7	8.2 ± 1.8	35.2 ± 7.8	77.3	16.3	Decreased
Khunti et al. [34]	England	266,505/ 2,584,960	White: 66.8, Black: 3.6, Asian: 15.2	60.8	67.0 (57.0–77.0)			75.4		Decreased
Kim et al. [35]	Korea	8/227		45.1	68.3 ± 11.9		24.2 ± 3.2	62.6	7.7	NS
Nyland et al. [50]	USA	792/28,724	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	Decreased
Orioli et al. [53]	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								NS
Silverii et al. [62]	Italy	4/155		54.1	73.3 ± 12.7					NS
Sourij et al. [63]	Austria	24/156		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	Decreased
Insulin users/nonusers										
Agarwal et al. [14]	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
Boye et al. [17]	USA	3461/6070		46.0	71.6 ± 12.5	7.2			37	Increased

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Table 1 (*continued*)

Study	Country	Number of patients	Race/ethnicity (%)	Male sex (%)	Age (years)	HbA1C (%)	Body mass index (kg/m^2) or obesity (%)	Hypertension (%)	CKD (%)	Mortality
			Caucasian: 47, African American: 31, Asian: 2, Hispanic: 5							
Cernigliaro et al. [19]	Italy	42/130								NS
Chen et al. [20]	China	7/49		42.9	65.0 (57.0–72.0) vs. 65.0 (56.0–73.0)	8.8 (7.4–10.9) vs. 7.5 (6.8–8.3)		61.2	10.2	Increased
Cheng et al. [12]	China	11/39		54.5 vs. 53.8	58.0 (54.0–60.0) vs. 52.0 (44.0–65.0)		24.8 (19.9–25.6) vs. 26.0 (23.8–27.2)	27.3 vs. 38.5	27.3 vs. 35.9	NS
Crouse et al. [22]	USA	87/133	White: 27.6, African American: 64.9	50.6			Obesity: 74.5%	91.6		NS
Dave et al. [23]	Africa	2073/3635		39.3	55.0 (46.0–63.0)			55.5	9.2	Increased
Deng et al. [24]	China	29/56		57.6	65.0 (34.0–91.0)			68.2	7.1	NS
Giorda et al. [30]	Italy	656/1226		50.9				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	67.0 (57.0–77.0)			85.2		Increased
Kim et al. [35]	Korea	19/216		45.1	68.3 ± 11.9		24.2 ± 3.2	62.6	7.7	NS
Kristan et al. [36]	USA	281/551	White: 32.7, African American: 52.0, Asian: 1.4	51.0	62.0 ± 15.0	7.9 ± 2.3	32.9 ± 8.6	78.4	21.3	NS
Lally et al. [37]	USA	103/190	White: 54.4, Black: 40.8	97.1	73.3 ± 9.4 vs. 75.6 ± 9.2	7.7 ± 1.5 vs. 6.5 ± 1.3	29.3 ± 3.0 vs. 28.0.2 ± 7.0		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 (49.0–68.0)			48.6	1.0	NS
Luk et al. [40]	China	385/679	Asian	57.7 vs. 51.5	66.0 (58.5–73.1) vs. 65.3 (57.3–73.6)	7.7 (6.9–9.1) vs. 6.9 (6.4–8.2)	22.9 (19.8–25.9) vs. 24.4 (22.2–27.4)	69.4 vs. 48.5	25.5 vs. 19.9	Increased
Luo et al. [42]	China	88/103		56.5	62.7 ± 11.0	7.9 (6.3–9.0)		55.5	3.0	NS
Mansour et al. [44]	Iran	25/86		55.9	63.6 ± 13.3		28.2 ± 5.6	57.7	9.0	NS
Mirani et al. [46]	Italy	29/61		72.4 vs. 72.1	72.0 ± 10.0 vs. 70.0 ± 13.0		Obesity: 51.7% vs. 45.9%	79.3 vs. 75.4	31.0 vs. 13.1	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 ± 8.9	47.7	15.5	Increased
Oh et al. [51]	Korea	914/26,579								NS
Orioli et al. [53]	Belgium	31/37		48.0	69 ± 14	7.1 (6.6–8.3)	30.5 ± 5.3	80.8	34.2	NS
Perez-Belmonte et al. [54]	Spain	292/1458			77.9 ± 9.0		Obesity: 20.9% vs. 28.8%	50.0 vs. 57.8		Increased
Ramos-Rincon et al. [56]	Spain	225/565		47.1			Obesity: 17.7%	84.3	17.2	NS
Riahl et al. [58]	USA	88/78	White: 6.0, African American: 71.0	52.0	66.4 ± 12.7	8.6 ± 2.5 vs. 7.0 ± 1.7	31.1 ± 8.5	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
Shetaskova et al. [61]	Russia	115/194								Increased
Silverii et al. [62]	Italy	43/116		54.1	73.3 ± 12.7					NS
Sourij et al. [63]	Austria	41/139		63.9	67.6 ± 14.0	6.7 (1.9)	29.4 ± 5.7	77.0	23.1	NS
Wander et al. [66]	USA	18,521/ 46,371	White: 66.0, Black: 27.0, Hispanic: 9.0	64.0	67.7			89.0	36.0	Increased
Wargny et al. [69]	France	1039/1757		36.3	69.7 ± 13.2	7.7 (6.8–9.0)	28.4 (25.0–32.4)	76.8		Increased

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Table 1 (*continued*)

Study	Country	Number of patients	Race/ethnicity (%)	Male sex (%)	Age (years)	HbA1C (%)	Body mass index (kg/m^2) or obesity (%)	Hypertension (%)	CKD (%)	Mortality
			White: 58.1, African: 17.4, Asian: 3.6							
Yan et al. [71]	China	4/30		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 (61.0–72.0)	8.6 (7.9–10.0)	23.7 (22.0–25.4)	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.

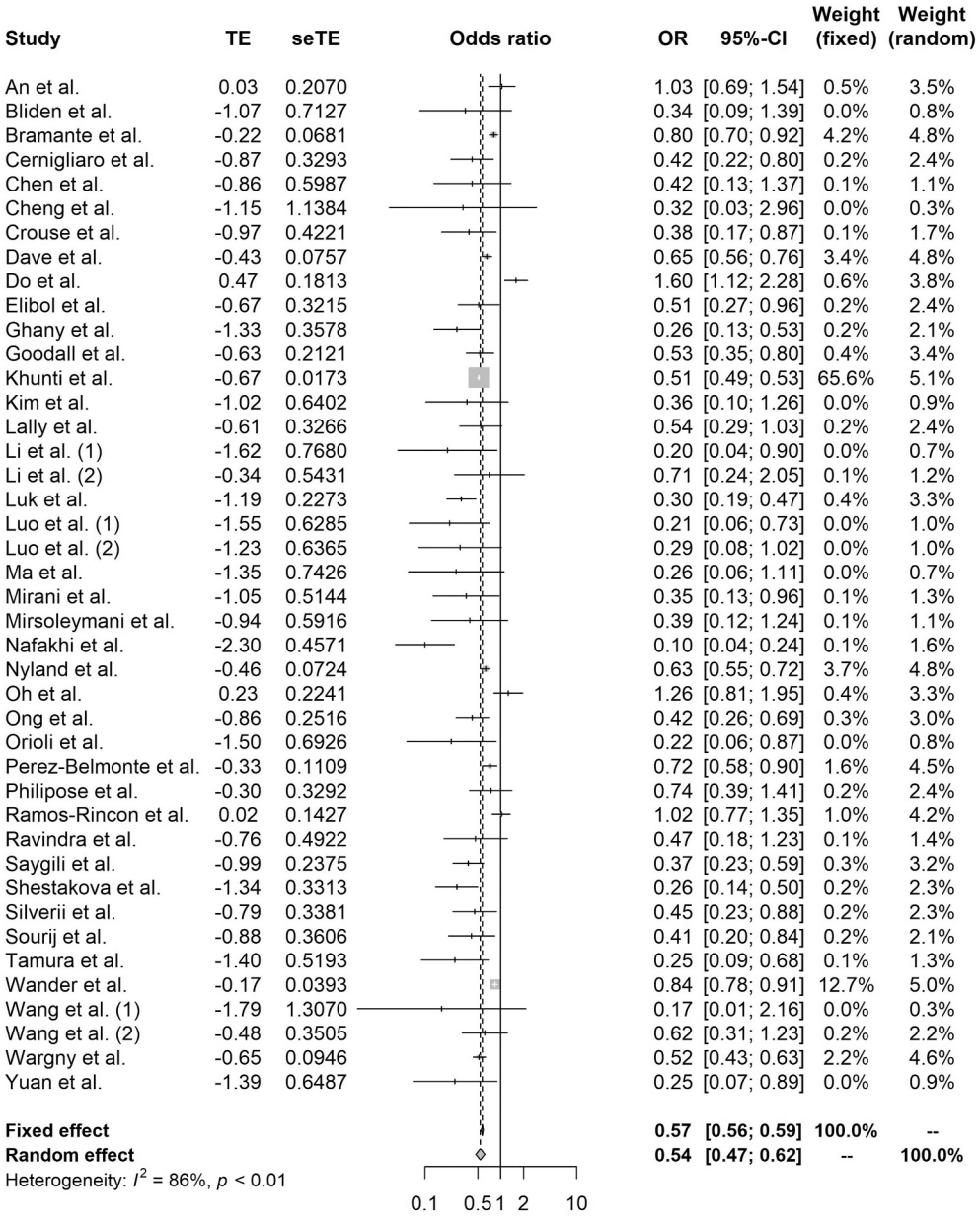

Fig. 2. Forest plot of the relationship between metformin and mortality in patients with COVID-19 having type 2 diabetes.

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

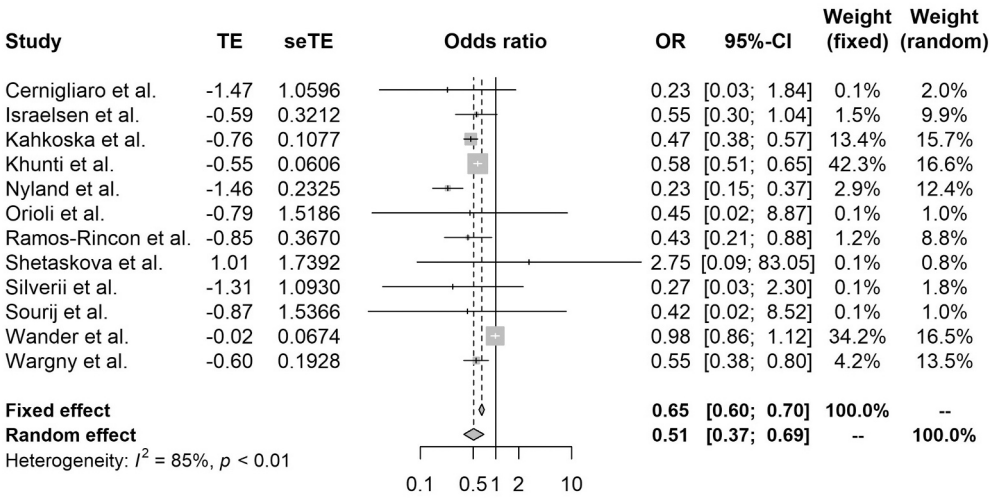

Fig. 3. Forest plot of the relationship between GLP-1RA and mortality in patients with COVID-19 having type 2 diabetes.

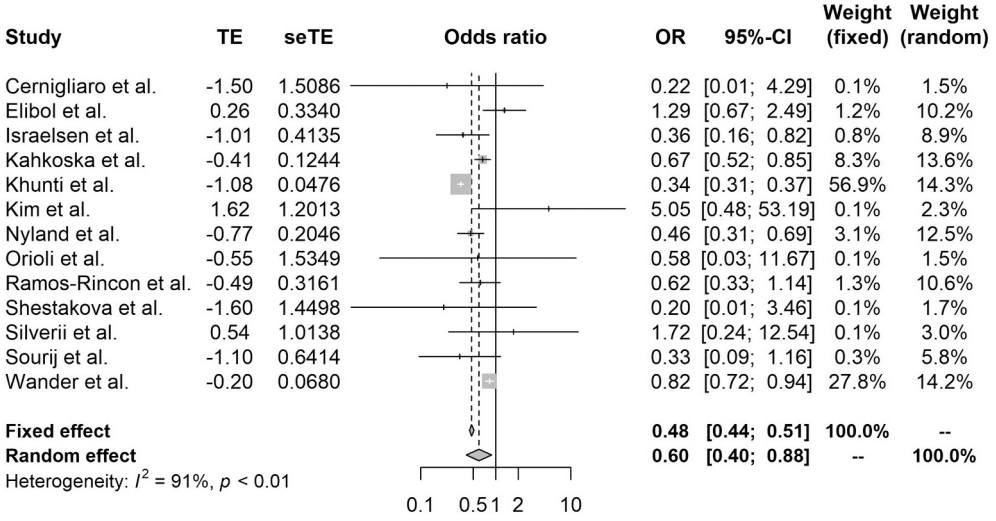

Fig. 4. Forest plot of the relationship between SGLT-2i and mortality in patients with COVID-19 having type 2 diabetes.

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 ($I^2 = 0\%$, $p = 0.46$; 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	Confounding 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/m^2)	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/m^2)	−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	0.97
	HbA1C (%)	Insufficient data for analysis		
	Body mass index (kg/m^2)	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/m^2)	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/m^2)	−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
	Male sex (%)	0.000	0.012	1.00
	HbA1C (%)	0.005	0.347	0.99
	Body mass index (kg/m^2)	0.087	0.030	0.02
	Hypertension (%)	−0.001	0.006	0.87
	Chronic kidney disease (%)	0.009	0.010	0.39
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	0.128	0.05
	Body mass index (kg/m^2)	−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)			
	Africa	−0.217	0.576	0.71
	Asia	0.009	0.285	0.98
	Europe	−0.221	0.280	0.44
	White race (%)	−0.000	0.011	0.98
	Age (years)	−0.032	0.020	0.12
	Male sex (%)	−0.001	0.011	0.97
	HbA1C (%)	0.029	0.347	0.93
	Body mass index (kg/m^2)	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

Table 3
Sensitivity analysis.

Medication	Main meta-analysis		Sensitivity analysis				
			Outlier removal method			Trim-and-fill method	
	OR (95% CI)	I^2	OR (95% CI)	I^2	p value[a]	OR (95% CI)	p value[b]
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			0.88 (0.70–1.11)	0.91
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.

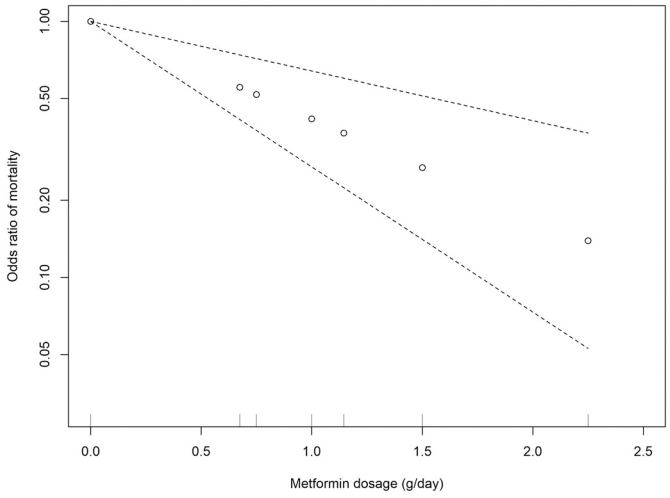

Fig. 5. Dose–response meta-analysis between daily metformin dosage and mortality in patients with COVID-19 with diabetes.

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).

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 and death in the context of SARS-CoV-2 infection. It was not surprised from our findings that SGLT-2i might have more obvious impacts on those with high baseline BMI or history of CKD due to the renal-metabolic benefits of this class. Consistently, SGLT-2i was more beneficial in a subgroup with a history of cardiovascular disease [34]. It should be noted that, however, this benefit might be less pronounced in vulnerable patients.

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 pre-admission DPP-4i users were associated with higher odds of in-hospital mortality. DPP-4i has yielded both putative 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.

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.

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 cardiovascular neutral. This characteristic makes them not a first-line treatment in patients with type 2 diabetes in general. Therefore, it is reasonable that they did not affect mortality in the COVID-19 setting, where cardiovascular events caused by hyperinflammation and hypercoagulation were the leading causes of intensive care unit admission, mechanical ventilation, and death. Although TZD could alleviate the long-term progressive atherosclerosis and inhibit the macrophage training, both of which were associated with the development of severe COVID-19, its benefit might be counteracted by the putative harmful effect regarding the fluid retention that could exacerbate pulmonary congestion in acute

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 (0.47–0.62)**	**Decreased**
	Han et al. [5]	Preadmission + in-hospital	20	0.62 (0.50–0.76)	Decreased
	Hariyanto et al. [74]	Preadmission	5	0.54 (0.32–0.90)	Decreased
	Kan et al. [75]	Preadmission + in-hospital	15	0.69 (0.55–0.86)	Decreased
	Kow et al. [76]	Preadmission	5	0.62 (0.43–0.89)	Decreased
	Li et al. [77]	Preadmission + in-hospital	19	0.66 (0.56–0.78)	Decreased
	Lukito et al. [78]	Preadmission	6	0.64 (0.43–0.97)	Decreased
	Oscanoa et al. [79]	Preadmission + in-hospital	22	0.56 (0.45–0.68)	Decreased
	Poly et al. [82]	Preadmission + in-hospital	16	0.66 (0.54–0.80)	Decreased
	Scheen et al. [84]	Preadmission	4	0.75 (0.67–0.85)	Decreased
	Schlesinger et al. [85]	ND	4	0.50 (0.28–0.90)	Decreased
	Sun et al. [86]	Preadmission	7	0.54 (0.35–0.84)	Decreased
	Yang et al. [87]	Preadmission + in-hospital	17	0.63 (0.51–0.79)	Decreased
Sulfonylurea	**Our current study**	**Preadmission**	**21**	**0.92 (0.83–1.01)**	**NS**
	Han et al. [5]	Preadmission + in-hospital	4	0.93 (0.89–0.98)	Decreased
	Kan et al. [75]	Preadmission + in-hospital	5	0.80 (0.66–0.96)	Decreased
	Schlesinger et al. [85]	ND	2	0.73 (0.49–1.09)	NS
Thiazolidinedione	**Our current study**	**Preadmission**	**8**	**0.90 (0.71–1.14)**	**NS**
	No published meta-analysis				
Alpha-glucosidase inhibitor	**Our current study**	**Preadmission**	**8**	**0.61 (0.26–1.45)**	**NS**
	No published meta-analysis				
Glucagon-like peptide-1 receptor agonist	**Our current study**	**Preadmission**	**12**	**0.51 (0.37–0.69)**	**Decreased**
	Han et al. [5]	Preadmission + in-hospital	3	0.92 (0.80–1.04)	NS
	Hariyanto et al. [7]	Preadmission	9	0.53 (0.43–0.66)	Decreased
Dipeptidyl peptidase-4 inhibitor	**Our current study**	**Preadmission**	**28**	**1.23 (1.07–1.42)**	**Increased**
	Bonora et al. [73]	Preadmission	7	0.81 (0.57–1.15)	NS
	Han et al. [5]	Preadmission + in-hospital	11	0.95 (0.72–1.26)	NS
	Hariyanto et al. [6]	Preadmission	7	1.14 (0.87–1.51)	NS
	Kan et al. [75]	Preadmission + in-hospital	8	0.72 (0.51–1.51)	NS
	Pal et al. [80]	Preadmission	4	1.21 (0.72–2.03)	NS
	Patoulias et al. [81]	Preadmission	8	1.14 (0.78–1.66)	NS
	Rakhmat et al. [83]	Preadmission + in-hospital	9	0.76 (0.60–0.97)	Decreased
	Schlesinger et al. [85]	ND	2	0.90 (0.59–1.36)	NS
	Yang et al. [4]	Preadmission + in-hospital	4	0.58 (0.34–0.99)	Decreased
Sodium–glucose transporter-2 inhibitor	**Our current study**	**Preadmission**	**13**	**0.60 (0.40–0.88)**	**Decreased**
	Han et al. [5]	Preadmission + in-hospital	3	1.04 (0.56–1.92)	NS
Insulin	**Our current study**	**Preadmission**	**33**	**1.70 (1.33–2.19)**	**Increased**
	Kan et al. [75]	Preadmission + in-hospital	7	2.20 (1.34–3.60)	Increased
	Schlesinger et al. [85]	ND	5	1.75 (1.01–3.03)	Increased
	Yang et al. [88]	Preadmission + in-hospital	12	2.10 (1.51–2.93)	Increased

Abbreviations: ND, not defined; NS, not significant.

lung disease [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 because a large proportion of diabetic patients need two or more glucose-lowering agents (either oral or injectable medications) to achieve glycemic targets. However, it was not feasible to perform such analysis due to limited raw data from original studies, even after we contacted the authors, because of the complexity of current diabetes treatment algorithms that would require additional mining of the original sources. Third, we were also unable to exclude the possibility of using medications beyond the hospital admission. However, our findings still reflected effects received before admission rather than short-term in-hospital effects because several included studies predefined medication users as those who had received a prescription that lasted at least 90–180 days, which is considered enough to exert their long-term effects. Fourth, because the COVID-19 treatment protocol has not been published as an international consensus among medical centers and countries, we lacked standardized severity assessment and concomitant

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
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 work, and contributed to the revisions of the final manuscript. HYL 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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