Dipeptidyl peptidase-4 inhibitor use and mortality in COVID-19 patients with diabetes mellitus: an updated systematic review and meta-analysis

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Abstract

Background: Few observational studies have shown a beneficial effect of dipeptidyl peptidase-4 inhibitors (DPP4i) in patients with coronavirus disease 2019 (COVID-19), although results are not consistent. The present systematic review and meta-analysis was undertaken to provide a precise summary of the effect of DPP4i use (preadmission or in-hospital) and mortality in COVID-19 patients with diabetes mellitus (DM).

Methods: PubMed and Google Scholar databases were systematically searched using appropriate keywords to 4 January 2021, to identify observational studies reporting mortality in COVID-19 patients with DM using DPP4i *versus* those not using DPP4i. Preadmission and in-hospital use of DPP4i were considered. Study quality was assessed using the Newcastle–Ottawa Scale. Unadjusted and adjusted pooled odds ratio (OR) with 95% confidence intervals (CIs) were calculated. Subgroup analysis was performed for studies reporting preadmission and in-hospital use of DPP4i.

Results: We identified nine observational studies of high quality pooling data retrieved from 7008 COVID-19 patients with DM. The pooled analysis of unadjusted and adjusted data did not show any significant association between DPP4i use and mortality in COVID-19 patients with DM. However, on subgroup analysis, we found that in-hospital (and not preadmission) DPP4i use was associated with reduced mortality (unadjusted OR 0.37, 95% CI 0.23, 0.58, $p < 0.0001$, $I^2 = 0$% and adjusted OR 0.27, 95% CI 0.13, 0.55, $p = 0.0003$, $I^2 = 12$%).

Conclusions: In-hospital use of DPP4i is associated with a significant reduction in COVID-19 mortality. Hence, it would be prudent to initiate or continue DPP4i in COVID-19 patients with DM if not contraindicated.

Keywords: COVID-19, dipeptidyl peptidase-4 inhibitors, DPP4, mortality, SARS-CoV-2

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Introduction

Patients with diabetes mellitus are at a high risk of severe disease, acute respiratory distress syndrome, intensive care unit (ICU) admission, and mortality from the novel coronavirus disease 2019 (COVID-19).[1,2] Potential pathogenetic links between diabetes mellitus and COVID-19 include hyperglycemia-mediated viral proliferation, dysregulated immune system and altered renin–angiotensin–aldosterone system (RAAS).[1–3]

In the absence of any robust therapy, multiple pre-existing drugs have been repurposed to treat COVID-19.[4] One such class of drug, the dipeptidyl peptidase-4 inhibitors (DPP4i), has evoked much interest in the scientific community.[5,6] Both experimental and human studies have shown that DPP4i exert a potent anti-inflammatory effect by reducing pro-inflammatory cytokines. Intuitively, this may appear to help curb the inflammatory storm seen in patients with severe COVID-19.[7] Besides, it has also

been postulated that dipeptidyl peptidase-4 (DPP4) may facilitate SARS-CoV-2 entry into host cells due to its remarkable homology with the Middle East respiratory syndrome (MERS) coronavirus. The interplay between the SARS-CoV-2 spike protein S1 and human DPP4 may promote SARS-CoV-2 virulence; inhibition of this interaction may improve clinical outcomes in COVID-19.[8]

Hitherto, evidence about the use of DPP4i and clinical outcomes in COVID-19 patients with diabetes mellitus is limited only to observational studies.[9–22] Apart from the variable clinical outcomes reported across the studies, the results are highly incongruous. While some studies found no association between DPP4i use and clinical outcomes in COVID-19,[9,11,13–17] a few authors have reported an improved outcome[10,12,22] and others have reported worse outcomes[18] in COVID-19 patients with DPP4i use. Considering the remarkable heterogeneity in the available clinical evidence, the present systematic review and meta-analysis was undertaken to provide a precise summary and collate the effect of DPP4i use (preadmission or in-hospital) on mortality in COVID-19 patients with diabetes mellitus.

Methods

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[23]

Search strategy

Two investigators (RP and MB) independently performed a systematic search of the literature across the PubMed and Google Scholar databases from inception to 4 January 2021, using the following keywords interposed with appropriate Boolean operators: 'COVID-19' OR 'SARS-CoV-2' AND 'dipeptidyl peptidase-4 inhibitor' OR 'DPP4 inhibitor' OR 'gliptin' OR 'glucose-lowering drug'. The language was restricted to English only. The references of relevant reviews and retrieved articles were also screened for potentially eligible articles. For missing data, the corresponding authors of the potentially eligible studies were contacted whenever possible.

Eligibility and exclusion criteria

Eligibility criteria were set as follows:

1. In the absence of randomized controlled trials (RCTs), we planned to include observational studies (prospective or retrospective, cohort or case–control design).
2. Studies should include COVID-19 patients with diabetes mellitus, a proportion who must have been taking DPP4i before hospitalization. Studies reporting in-hospital DPP4i use in COVID-19 patients were also included.
3. Studies should report the data comparing the rate of occurrence of mortality (as the number of 'events') among DPP4i users compared to DPP4i non-users.
4. In addition, studies reporting the adjusted odds ratio (OR) of mortality in DPP4i users compared to DPP4i non-users were also included.

Exclusion criteria were set as follows:

1. Studies reporting clinical outcomes of COVID-19 patients other than mortality
2. Reviews, comments, editorials, letters to the editor
3. Non-peer-reviewed studies published as preprints
4. Incompleteness in data.

Data extraction

Two investigators (RP and MB) independently scanned titles and/or abstracts to exclude duplicate studies and studies that failed to meet the eligibility criteria. Potentially eligible studies were full-text assessed. Any discrepancies between the afore-mentioned investigators were solved by discussion, consensus, or arbitration by a third senior investigator (SKB). Studies thus selected were reviewed, and the following data were extracted from full-text reports for further assessment: study characteristics, preadmission or in-hospital use of DPP4i, the number of patients using DPP4i, the number of DPP4i users *versus* non-users who had died (i.e. the number of events in DPP4i users *versus* non-users) and the adjusted OR of mortality in DPP4i users as compared to DPP4i non-users.

Assessment of study quality

The Newcastle–Ottawa Scale (NOS) was used to assess the quality and risk of bias of the included observational studies. The scale assesses three

quality parameters, namely, selection, comparability, and outcome divided across eight specific items which slightly differ when scoring case–control and cohort studies.[24] The maximum score on NOS is 9. Any score ⩾7 qualifies as high quality with a low risk of bias while a score of <5 is categorized as low quality with a high risk of inherent bias. Any score in between is rated as moderate quality.[25] The assessment of study quality was independently conducted by two investigators (RP and MB). Any discrepancy was solved by a discussion with a third senior investigator (SKB).

Statistical analysis

Being a dichotomous variable, the difference in the rate of occurrence of mortality (events) in DPP4i users *versus* DPP4i non-users in COVID-19 patients was calculated using the OR (unadjusted) with 95% confidence intervals (CIs) after implementation of the Mantel–Haenszel (M–H) fixed-effects model. Adjusted ORs for mortality reported in each study, whenever available, were also pooled together using the generic inverse variance method with the fixed-effects model. We also performed a subgroup analysis of studies reporting the use of DPP4i prior to admission (preadmission) and those reporting the use of the drug in hospital.

Statistical heterogeneity among studies was assessed using I^2 statistics. Heterogeneity was quantified as low, moderate, and high with upper limits of 25%, 50%, and 75% for I^2, respectively.[26] In the present meta-analysis, significant heterogeneity was considered when the I^2 value was ⩾50%, with a p value < 0.05. Outcomes with significant heterogeneity were re-analyzed and reported using the random effects model. A $p < 0.05$ was considered to be statistically significant.

Statistical analysis was performed using the RevMan 5.4 software.

Results

After a scrupulous literature search and a meticulous study selection process, we included nine observational studies in our meta-analysis pooling data retrieved from 7008 COVID-19 patients with diabetes mellitus (Figure 1).[9–17] Three pertinent studies were excluded as clinical outcomes were reported either in terms of disease severity,[19] intubation,[20] or ICU admission[18] rather than in terms of mortality. Furthermore, two related studies had to be excluded due to incomplete data.[21,22] Among the nine studies included, only the studies by Solerte *et al.*[12] and Zhou *et al.*[16] catered to the in-hospital use of DPP4i while the rest of the studies had reported on the use of DPP4i before hospitalization (preadmission). Besides, in the study by Mirani *et al.*,[10] DPP4i were continued after hospitalization in all the COVID-19 patients who had been on the drug prior to admission. None of the other studies concerning the preadmission use of DPP4i had clearly stated whether the drug was continued after hospitalization.

The primary characteristics of the included studies and the NOS scores have been summarized in Table 1. All the studies were of high quality. The results of the meta-analysis have been summarized under the following headings.
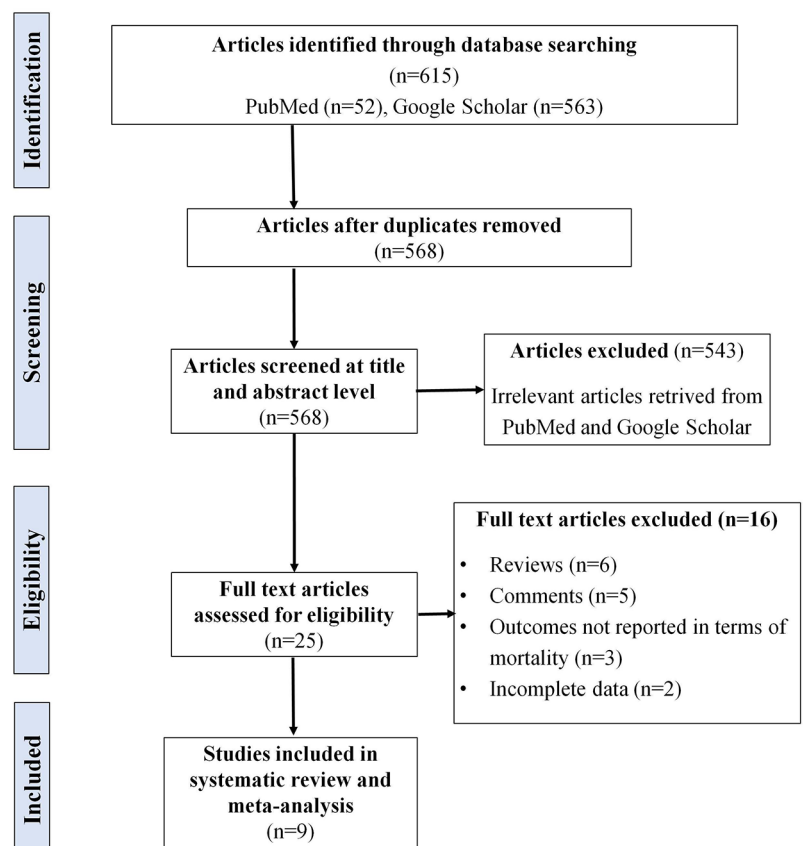
Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart showing the study selection process.

Table 1. Showing characteristics and risk of bias assessment of the included observation studies.

Authors (reference)	Number of participants	Statin use	Mortality			Covariates adjusted for	NOS[a]
	Design		DPP4i user	DPP4i non-user	Adjusted estimate		
	Place of study						
Pérez-Belmonte et al.[9]	2666 Retrospective, observational Spain	Preadmission	75/180 (41.7%)	440/1409 (31.2%)	OR = 1.39 (0.64, 1.67)	Age, sex, comorbidities, Barthel index score, Charlson comorbidity index score, use of medications, admission BG, creatinine, transaminase levels	8/9
Mirani et al.[10]	90 Retrospective, observational Italy	Preadmission and continued in-hospital	1/11 (9.1%)	37/79 (46.8%)	HR = 0.13 (0.02, 0.92)	Age, sex	7/9
Chen et al.[11]	904[b] Retrospective, observational China	Preadmission	5/20 (25.0%)	14/100 (14.0%)	OR = 1.48 (0.40, 5.53)	Age, albumin, creatinine, CRP, BG	8/9
Solerte et al.[12]	338 Retrospective, observational Italy	In-hospital	31/169 (18.0%)	63/169 (37.0%)	OR = 0.23 (0.12, 0.46)	Age, sex, cancer, CVD, CKD, use of HCQ, antiviral agents	8/9
Cariou et al.[13]	1317[c] Prospective, observational France	Preadmission	NR/285	NR/1032	OR = 0.85 (0.55, 1.32)	Age, sex	8/9
Fadini et al.[14]	403[d] Retrospective, observational Italy	Preadmission	1/9 (11.1%)	10/72 (13.9%)	NR	–	7/9
Kim et al.[15]	1082[e] Retrospective, observational Korea	Preadmission	NR/85	NR/150	OR = 1.47 (0.45, 4.78)	Age, sex, presence of underlying diseases	7/9
Zhou et al.[16]	2563 Retrospective, observational China	In-hospital	2/111 (1.8%)	11/333 (3.3%)	OR = 0.58[f] (0.12, 2.68)	Incidence of increased CRP	8/9

(Continued)

Table 1. (Continued)

Authors (reference)	Number of participants	Statin use	Mortality			Covariates adjusted for	NOS[a]
	Design		DPP4i user	DPP4i non-user	Adjusted estimate		
	Place of study						
Wargny *et al.*[17]	2796 Prospective, observational France	Preadmission	113/615 (18.3%)	464/2179 (21.3%)	OR = 0.83 (0.65, 1.05)	Age	8/9

Clinical outcome data reported as *n/N* (%).
OR/HR presented as ratio (95% confidence interval).
[a]Risk of bias assesssment was performed using the Newcastle–Ottawa scale (NOS).
[b]Out of 904 patients with COVID-19, 136 had diabetes mellitus. Out of 136 patients with diabetes mellitus, glucose-lowering medication history was available in 120 subjects.
[c]285 patients were on DPP4i therapy.
[d]85 patients had type 2 diabetes mellitus.
[e]Out of 1082 patients, 235 had diabetes mellitus of whom, 85 were on DPP4i therapy.
[f]OR calculated based on propensity score-matched analysis.
BG, blood glucose; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; DPP4i, dipeptidylpeptidase 4 inhibitor; HCQ, hydroxychloroquine; HR, hazard ratio; HTN, hypertension; NR, not reported; OR, odds ratio.

Pooled analysis using the rate of occurrence of mortality (i.e. number of events) in DPP4i users versus DPP4i non-users

Data on the rate of occurrence of mortality in DPP4i users *versus* non-users were available from seven studies comprising 5456 COVID-19 patients with diabetes mellitus.[9–12,14,16,17] Pooled analysis did not show any significant association between DPP4i use and mortality (OR 0.79, 95% CI 0.46, 1.36, $p = 0.39$, $I^2 = 80\%$, random effects model). Subgroup analysis, however, showed that in-hospital use of DPP4i was associated with reduced mortality (OR 0.37, 95% CI 0.23, 0.58, $p < 0.0001$, $I^2 = 0\%$, random effects model) (Figure 2).

### Pooled analysis using adjusted ORs of mortality in DPP4i users versus DPP4i non-users

The adjusted OR of mortality in DPP4i users *versus* non-users was reported in seven studies,[9,11–13,15–17] pooling data from 6837 COVID-19 patients with diabetes mellitus. Data pooled using the generic inverse variance method also showed no statistically significant association between DPP4i use and COVID-19 mortality (adjusted OR 0.78, 95% CI 0.50, 1.22, $p = 0.28$, $I^2 = 67\%$, random effects model). Subgroup analysis revealed that preadmission DPP4i use was not significantly associated with mortality (adjusted OR 0.89, 95% CI 0.73, 1.09, $p = 0.25$, $I^2 = 0\%$,

random effects model). In contrast, in-hospital use was found to be associated with a statistically significant reduction in mortality in COVID-19 patients with diabetes mellitus (adjusted OR 0.27, 95% CI 0.13, 0.55, $p = 0.0003$, $I^2 = 12\%$, random effects model) (Figure 3).

Discussion

The present systematic review and meta-analysis shows that in-hospital use of DPP4i in patients with diabetes mellitus is associated with reduced mortality in COVID-19. However, preadmission use of the drug as a home medication had no significant association with mortality.

The COVID-19 pandemic has posed a significant threat to patients with pre-existing comorbidities.[27] Likewise, diabetes mellitus has emerged as a distinct comorbidity associated with severe disease, acute respiratory distress syndrome and increased mortality in COVID-19. The pathogenetic mechanisms linking diabetes mellitus with COVID-19 severity include hyperglycemia-mediated viral proliferation, dysregulated immune system, increased predisposition to cytokine storm, and altered renin–angiotensin–aldosterone system.[1–3] Besides, the presence of typical complications of diabetes mellitus (cardiovascular disease, heart failure, and chronic kidney disease) also contributes to COVID-19 mortality.[3,28]
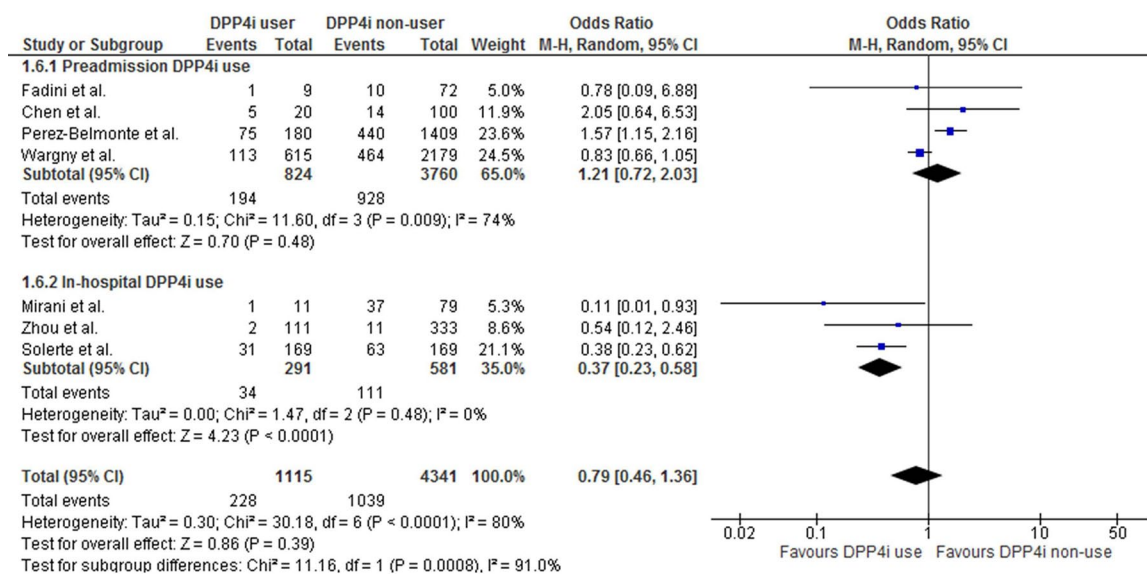
Figure 2. Forest plot with subgroup analysis showing the effect (unadjusted) of dipeptidyl peptidase-4 inhibitor (DPP4i) use on mortality in the novel coronavirus disease (COVID-19) patients with diabetes mellitus as compared to non-use of the drug.
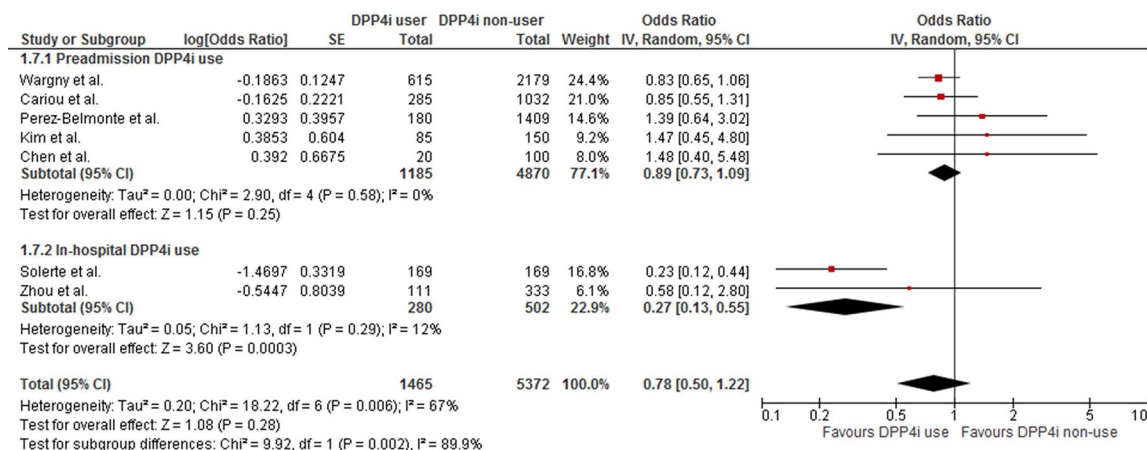
Figure 3. Forest plot with subgroup analysis showing the effect (adjusted) of dipeptidyl peptidase-4 inhibitor (DPP4i) use on mortality in the novel coronavirus disease (COVID-19) patients with diabetes mellitus as compared to non-use of the drug.

Aggressive management of COVID-19 patients with diabetes mellitus is essential; however, hitherto, only low-dose dexamethasone has been shown to lower mortality in patients with COVID-19 on invasive mechanical ventilation or those requiring oxygen.[29] However, dexamethasone use would lead to worsening of hyperglycemia and good glycemic control is essential as it is associated with a lower rate of complications and all-cause mortality in COVID-19.[30] In this regard, DPP4i has emerged as a unique class of oral antidiabetic drugs that has been postulated to exert beneficial effects in COVID-19 patients with diabetes mellitus. Available clinical evidence is, however, limited to only observational studies and the existing data are contradictory.

In this systematic review and meta-analysis that had included nine up-to-date observational studies, we have derived pooled estimates of mortality concerning DPP4i use in COVID-19 patients with diabetes mellitus. We found that preadmission use of DPP4i was not associated with any change in mortality on unadjusted as well as adjusted analyses. However, the use of DPP4i during hospitalization led to a significant reduction in mortality. DPP4i use in hospital was associated with a 63% and 73% reduction in mortality on unadjusted and adjusted analyses, respectively. The results are encouraging and warrant consideration of the initiation or continuation of DPP4i in all COVID-19 patients with type 2 diabetes mellitus (T2D), unless otherwise contraindicated. The use of DPP4i in modified doses can also be contemplated in COVID-19 patients with diabetes with varying degrees of renal impairment. Besides, DPP4i (apart from saxagliptin) are neutral in terms of major adverse cardiovascular events including stroke,[31,32] and hence can be safely used even in T2D patients with prior atherosclerotic cardiovascular disease (ASCVD) or at a high risk of ASCVD.[3]

The mechanisms underlying the association between DPP4i use and improved clinical outcomes in COVID-19 patients with diabetes mellitus are speculative. There is little doubt that DPP4, also known as CD26, plays a role as a receptor for the MERS coronavirus.[33] Due to its remarkable homology with the MERS coronavirus, it has been postulated that DPP4 may also facilitate the SARS-CoV-2 docking process and subsequent entry into the host cells.[8] The use of DPP4i might induce a conformational change in the DPP4 molecule and thereby interfere with the interaction between SARS-CoV-2 spike S1 protein and human DPP4.[12,34]

An alternative explanation would be an alteration in the expression of soluble dipeptidyl peptidase-4 (sDPP4). A recent report from Germany has shown that circulating levels of sDPP4 are reduced in patients hospitalized with severe COVID-19.[35] A similar reduction in sDPP4 was reported in the plasma of patients infected with the MERS coronavirus. The authors also stated that sDPP4 could act as a decoy receptor for MERS coronavirus and prevent vital replication.[36] The same might be applicable to SARS-CoV-2. A higher relative abundance of sDPP4 could bind SARS-CoV-2 and thus prevent attachment of the coronaviruses

to membrane-bound DPP4 as in pneumocytes or other cells relevant for viral spread and replication.[34] In this context, a recent study has demonstrated a significant rise in sDPP4 by 50–100% on exposure of mice to various DPP4i.[37] Hence, DPP4i, apart from interfering with viral entry, could possibly promote sequestration of the viral particles in the circulation by raising sDPP4 levels and thereby limit viral proliferation in humans. The dichotomous findings in COVID-19 patients who used DPP4i in hospital against those who had been using the drug preadmission could be explained on similar grounds. Although not explicitly mentioned in the studies, it could be assumed that the preadmission anti-diabetic medications were stopped at hospital admission and most of the COVID-19 patients were shifted to insulin. Discontinuation of DPP4i perhaps leads to rapid normalization of sDPP4 levels, thereby, negating the effect of prior DPP4i use.

Other potential reasons that make DPP4i a potential armamentarium against COVID-19 are their anti-inflammatory, anti-fibrotic and immunomodulatory properties. Both experimental and human studies have shown that DPP4i exert a potent anti-inflammatory effect by reducing pro-inflammatory cytokines. Consequently, this may be instrumental in curbing the inflammatory storm seen in patients with severe COVID-19.[7]

The present meta-analysis had included all the available up-to-date observational studies reporting clinical outcomes in COVID-19 patients with DPP4i use. However, we had included only those studies that had reported COVID-19 clinical outcomes in terms of mortality for uniformity. Besides, unlike the hitherto published only meta-analysis reporting preadmission DPP4i use and risk of a fatal or severe course of illness in patients with COVID-19,[38] we have provided pooled analyses of both unadjusted and adjusted ORs, making the results more robust and reproducible.

The meta-analysis does have certain limitations. Adjusted estimates were either not reported or reported as hazard ratios (instead of ORs) in some studies; hence, they could not be included in the adjusted pooled analysis. In addition, the ORs derived from various studies were adjusted for different covariates. Furthermore, most studies do not mention the type and dosage of DPP4i treatment in their studied samples that can be an independent source of potential bias. Besides, as

has already been mentioned, most of the studies reporting the preadmission use of DPP4i are silent as to whether the drug was discontinued after hospitalization. Finally, the cause of mortality was not mentioned in any of the included studies.

In conclusion, the present meta-analysis of all hitherto available observational studies has shown that in-hospital use of DPP4i is associated with a significant reduction in mortality in COVID-19 patients with diabetes mellitus. Hence, if not contraindicated, it would be prudent to initiate or continue DPP4i in COVID-19 patients with diabetes mellitus. Besides, several RCTs in this regard are underway (NCT04365517, NCT04341935, NCT04371978).

Author contributions
Rimesh Pal: Data curation; formal analysis; methodology; writing-original draft.

Mainak Banerjee: Data curation; formal analysis; methodology; writing-review and editing.

Soham Mukherjee: Writing-review and editing; visualization

Ranjitpal Singh Bhogal: Writing-review and editing

Amanpreet Kaur: Writing-review and editing; visualization

Sanjay Kumar Bhadada: Conceptualization; supervision; writing-review and editing.

Conflict of interest
The authors declare that there is no conflict of interest.

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