Dipeptidyl peptidase 4 (DPP4) inhibitor and outcome from coronavirus disease 2019 (COVID-19) in diabetic patients: a systematic review, meta-analysis, and meta-regression

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Abstract

Background One of the drugs which is commonly used in diabetic patients is Dipeptidyl Peptidase-4 (DPP-4) inhibitor. Currently, the association between DPP-4 inhibitor and coronavirus disease 2019 (COVID-19) outcome is not yet established. This study aims to analyze the potential association between DPP-4 inhibitor and the composite poor outcome of COVID-19.

Methods We systematically searched the PubMed and Europe PMC database using specific keywords related to our aims until November 29th, 2020. All articles published on COVID-19 and DPP-4 inhibitor were retrieved. Statistical analysis was done using Review Manager 5.4 and Comprehensive Meta-Analysis version 3 software.

Results Our pooled analysis showed that DPP-4 inhibitor use was not associated with composite poor outcomes of COVID-19 [OR 1.09 (95% CI 0.93–1.28), $p = 0.29$, $I^2 = 0\%$, random-effect modelling], and its subgroup which comprised of severe COVID-19 [OR 1.07 (95% CI 0.87–1.31), $p = 0.54$, $I^2 = 0\%$, random-effect modelling], and mortality [OR 1.14 (95% CI 0.87–1.51), $p = 0.35$, $I^2 = 8\%$, random-effect modelling]. Meta-regression showed that the association was not influenced by age ($p = 0.663$), hypertension ($p = 0.454$), and admission blood glucose ($p = 0.310$). Subgroup analysis showed that the association was weaker in East Asian populations (OR 1.02) compared to European populations (OR 1.11).

Conclusion DPP-4 inhibitor in diabetic patients did not alter the outcomes from COVID-19. Our study suggest that the use of DPP-4 inhibitor in COVID-19 patients with diabetes may still be continued according to the patients' need.

Keywords Diabetes · Medications · DPP-4 · Coronavirus · COVID-19

Introduction

Eight months have passed since coronavirus disease 2019 (COVID-19) was declared as a pandemic by the World Health Organization (WHO), but the number of positive cases and death cases is still increasing. This global pandemic disease has caused a significant impact on the economic and health aspects around the world. The manifestation of this disease can be varied from asymptomatic or consist of mild symptoms such as cough and fever to severe and life-threatening acute respiratory distress syndrome (ARDS), sepsis, multi-organ failure, and death [1, 2]. There are several comorbid conditions which are associated with the development of severe outcome and mortality from COVID-19, including diabetes [3–8]. Patients with diabetes have a higher risk of severe COVID-19 because of the increased expression of angiotensin II converting enzyme-2 (ACE-2) and Dipeptidyl Peptidase-4 (DPP-4) mediating infection [9]. Moreover, patients with diabetes are thought to have elevated pro-inflammatory cytokine levels such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [10]. Several efforts have been made to minimize the risk of progression into severe COVID-19 and mortality in patients with diabetes based on the beforementioned pathophysiology. The previous meta-analysis has shown that metformin administration is associated with a reduction of mortality rate from COVID-19 because of its ability to decrease binding between ACE2 receptor and SARS-CoV-2 Receptor Binding Domain (RBD) through AMP-activated protein kinase (AMPK)-

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mediated phosphorylation of ACE2 [11]. Not only that, metformin can inhibit the inflammatory response that could potentially contribute to mortality through a mechanism such as a cytokine storm and vascular damage [11]. Besides metformin, one of the drugs which are commonly used by patients with diabetes is the dipeptidyl peptidase-4 (DPP-4) inhibitor. This drug has been proposed to help in reducing the severity and mortality from COVID-19 because of its ability to modulate the DPP4/CD26 activity and block the host CD26 receptor, thus disabling SARS–CoV-2 way to enter T cells [12]. DPP-4 inhibitor is also believed to have an effect on the reduction of cytokines overproduction, downregulation of macrophages activity/function, and enhancement of Glucagon Like Peptide-1 (GLP-1) anti-inflammatory activity, therefore can improve the poor outcomes from COVID-19 [9, 12]. However, these arguments are not supported by enough evidence on COVID-19 patients. Several observational studies still showed conflicting results. This study aims to analyze the association between DPP-4 inhibitor use and composite poor outcomes from COVID-19 in patients with diabetes mellitus to give better evidence regarding its efficacy and safety in COVID-19 patients.

Materials and methods

Search strategy and study selection

A systematic search of the literature was conducted on PubMed and Europe PMC using the keywords "DPP-4" OR "dipeptidyl peptidase 4" OR "medications" AND "diabetes" OR "diabetes mellitus" AND "coronavirus disease 2019" OR "COVID-19", until the present time (November 29th, 2020) with language restricted to English only. We assessed the title, abstract, and full text of all articles identified that matched the search criteria, and those reporting the rate of DPP-4 inhibitor in COVID-19 patients with a clinically validated definition of "severe disease" and "mortality" were included in this meta-analysis. The references of all identified studies were also analyzed (forward and backward citation tracking) to identify other potentially eligible articles. The study was carried out per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

Eligibility criteria

Studies were included in this review if met the following inclusion criteria: representation for clinical questions (P: patients with diabetes who have positive/confirmed cases of COVID-19; I: a group of patients with DPP-4 inhibitor as their medication; C: a group of patients without DPP-4

inhibitor usage; O: severe COVID-19 and mortality, type of study was a randomized control trial, cohort, clinical trial, case-cohort, and cross-over design, and if the full-text article was available. The following types of articles were excluded: articles other than original research (e.g., review articles, letters, or commentaries); case reports; articles not in the English language; articles on research in pediatric populations (17 years of age or younger); and articles on research in pregnant women.

Data extraction and quality assessment

Data extraction was performed independently by two authors, we used standardized forms that include author, year, study design, number of participants, age, gender, hypertension, cardiovascular disease, DPP-4 inhibitor, admission blood glucose levels, severe COVID-19, and mortality.

The outcome of interest was the composite poor outcome which comprised of severe COVID-19 and mortality. Severe COVID-19 was defined as patients who had any of the following features at the time of, or after, admission: (1) respiratory distress (≥30 breaths per min); (2) oxygen saturation at rest ≤93%; (3) ratio of the partial pressure of arterial oxygen (PaO2) to a fractional concentration of oxygen inspired air (fiO2) ≤300 mmHg; or (4) critical complication (respiratory failure, septic shock, and or multiple organ dysfunction/failure) or admission into ICU. Mortality outcome was defined as the number of patients who died because of COVID-19.

Two investigators independently evaluated the quality of the included cohort and case-control studies using the Newcastle–Ottawa Scale (NOS) [14]. The selection, comparability, and exposure of each study were broadly assessed and studies were assigned a score from zero to nine. Studies with scores ≥7 were considered of good quality.

Statistical analysis

Review Manager 5.4 (Cochrane Collaboration) and Comprehensive Meta-Analysis version 3 software were used to perform the meta-analysis. We used the Generic Inverse Variance formula with random-effects models to calculate each outcome's risk. The heterogeneity was assessed by using the I^2 statistic with a value of <25%, 26–50%, and > 50% were considered as low, moderate, and high degrees of heterogeneity, respectively. The effect estimate was reported as odds ratio (OR) along with its 95% confidence intervals (CIs) for dichotomous variables, respectively. P value was two-tailed, and the statistical significance was set at ≤0.05. Random effects meta-regression was performed using a restricted-maximum likelihood for pre-specified variables including age, gender, hypertension, cardiovascular disease, and admission

Table 1 Characteristics of included studies

Study	Sample size	Design	Overall age mean±SD	Male n (%)	Hypertension n (%)	Cardiovascular diseasen (%)	DPP4 inhibitor n (%)	Admission blood glucose mg/dL
Cariou B et al. [16] 2020 (France)	1317	Retrospective cohort	69.8 ± 13	855 (64.9%)	1003 (76.1%)	336 (25.5%)	285 (21.6%)	171.8±77.6
Chen Y et al. [17] 2020 (China)	120	Retrospective cohort	66.6 ± 9.6	64 (53.3%)	84 (70%)	29 (24.1%)	20 (16.6%)	165.7±103.7
Fadini GP et al. [18] 2020 (Italy)	85	Retrospective cohort	70.3 ± 13.3	55 (64.7%)	59 (69.4%)	23 (27.1%)	9 (10.5%)	228.8±109.9
Izzi-Engbeaya C et al. [19] 2020 (England)	889	Retrospective cohort	65.8 ± 17.5	534 (60%)	418 (47%)	231 (25.9%)	93 (10.4%)	180.9±99.8
Kim MK et al. [20] 2020 (South Korea)	235	Retrospective cohort	68.3 ± 11.9	106 (45.1%)	147 (62.6%)	27 (11.5%)	85 (36.2%)	186.7±101.1
Perez-Belmonte LM et al. [21] 2020 (Spain)	2666	Retrospective cohort	74.9 ± 8.4	1647 (61.9%)	2026 (76.2%)	1499 (56.2%)	791 (30.2%)	153±45.7
Rhee SY et al. [22] 2020 (South Korea)	832	Retrospective cohort	63.6 ± 12.1	445 (53.4%)	568 (68.2%)	227 (27.2%)	263 (31.6%)	N/A
Sourij H et al. [23] 2020 (Austria)	238	Retrospective cohort	71.1 ± 12.9	152 (63.9%)	169 (71%)	63 (26.5%)	42 (17.7%)	127±61.4
Yan H et al. [24] 2020 (China)	578	Retrospective cohort	49.1 ± 14.1	293 (50.7%)	130 (22.4%)	15 (2.6%)	6 (1%)	N/A
Zhang N et al. [25] 2020 (China)	52	Retrospective cohort	66.4 ± 8.7	33 (63.5%)	34 (65.4%)	14 (26.9%)	4 (7.7%)	166.3±56

blood glucose levels. Subgroup analysis was done to compare the outcomes in European populations and East Asian populations. We performed Begg's funnel-plot analysis and Egger's weighted regression method [15] to assess the risk of publication bias ($p < 0.05$ was considered statistically significant).

Results

Study selection and characteristics

A total of 4982 records were obtained through systematic electronic searches. After the removal of duplicates, 4610

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart
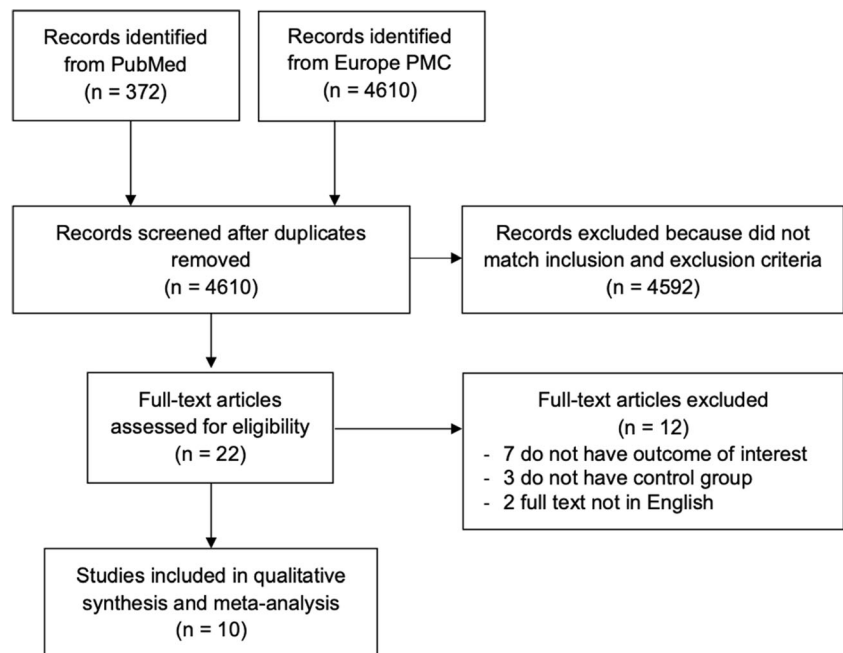
Table 2 Newcastle-Ottawa quality assessment of observational studies

First author, year	Study design	Selection	Comparability	Outcome	Total score	Result
Cariou B et al. [16] 2020	Cohort	****	**	***	9	Good
Chen Y et al. [17] 2020	Cohort	***	**	***	8	Good
Fadini GP et al. [18] 2020	Cohort	***	**	***	8	Good
Izzi-Engbeaya C et al. [19] 2020	Cohort	***	**	***	8	Good
Kim MK et al. [20] 2020	Cohort	***	**	****	9	Good
Perez-Belmonte LM et al. [21] 2020	Cohort	***	**	***	8	Good
Rhee SY et al. [22] 2020	Cohort	***	**	***	8	Good
Sourij H et al. [23] 2020	Cohort	****	**	***	9	Good
Yan H et al. [24] 2020	Cohort	***	**	****	9	Good
Zhang N et al. [25] 2020	Cohort	***	**	***	8	Good

records remained. A total of 4592 records were excluded after screening the titles/abstracts because they did not match our inclusion and exclusion criteria. After evaluating 22 full-texts for eligibility, 7 full-text articles were excluded because they do not have the outcome of interest (severe COVID-19 or mortality), 3 full-text articles were excluded because they do not have the control/comparison group, 2 articles were excluded because the full text not in English, and finally, 10 studies [16–25] with a total of 7012 COVID-19 patients with diabetes were included in the meta-analysis (Fig. 1). Of a total of 10 included studies, all were retrospective cohort. The essential characteristics of the included studies are summarized in Table 1.

Quality of study assessment

Studies with various study designs including cohort and case-control were included in this review and assessed accordingly with the appropriate scale or tool. Newcastle Ottawa Scales (NOS) were used to assess the cohort and case-control studies (Table 2). All included studies were rated 'good'. In conclusion, all studies were seemed fit to be included in the meta-analysis.

DPP-4 inhibitor and outcome

Our pooled analysis showed that DPP-4 inhibitor use was not associated with composite poor outcomes of COVID-19, with
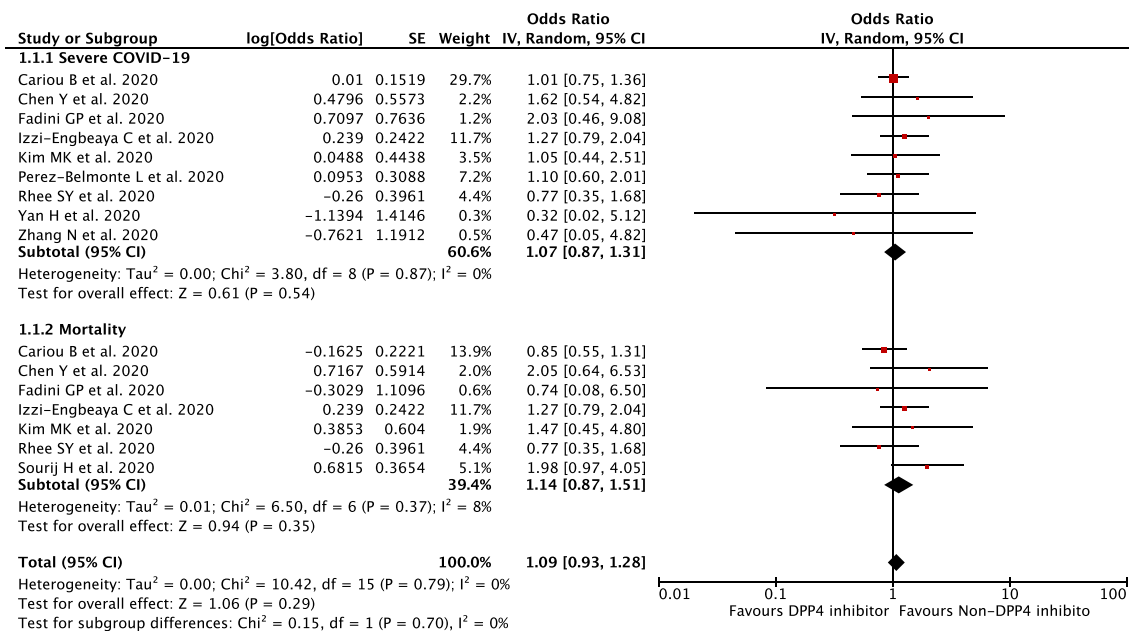

Fig. 2 Forest plot that demonstrates the association of the DPP-4 inhibitor with composite poor outcome and its subgroup which comprised of severe COVID-19 and mortality

Fig. 3 Bubble-plot for Meta-regression. Meta-regression analysis showed that the association between DPP-4 inhibitor and composite poor outcome was not affected by age (**a**), cardiovascular disease (**b**), and admission blood glucose levels (**c**)
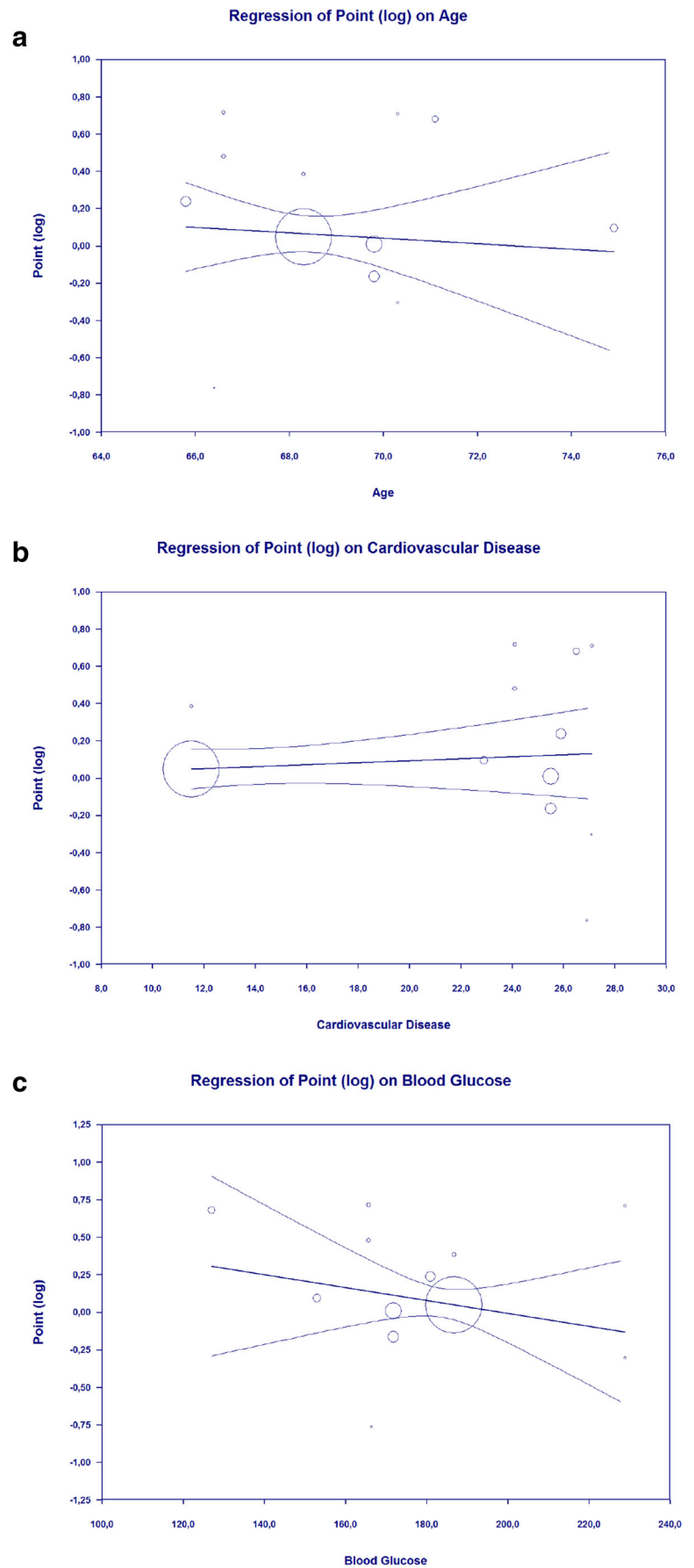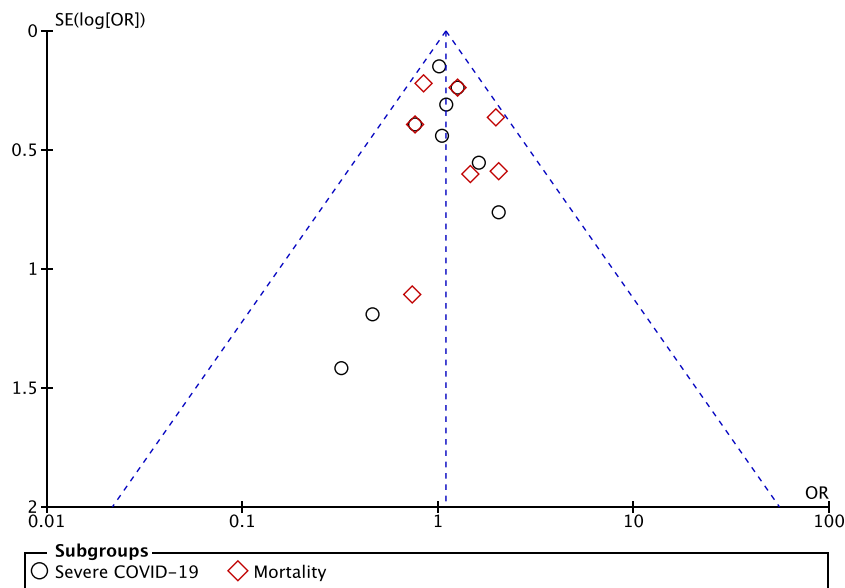
Fig. 4 Begg's funnel-plot analysis showed a qualitatively symmetrical inverted funnel-plot for the association of DPP-4 inhibitor with composite poor outcome of COVID-19

no relevant heterogeneity [OR 1.09 (95% CI 0.93–1.28), $p = 0.29$, $I^2 = 0\%$, random-effect modelling] (Fig. 2). Subgroup analysis showed that DPP-4 inhibitor did not alter the severity of COVID-19 [OR 1.07 (95% CI 0.87–1.31), $p = 0.54$, $I^2 = 0\%$, random-effect modelling], nor mortality from COVID-19 [OR 1.14 (95% CI 0.87–1.51), $p = 0.35$, $I^2 = 8\%$, random-effect modelling].

Meta-regression

Meta-regression showed that the association between DPP-4 inhibitor and composite poor outcome of COVID-19 was not affected by age ($p = 0.663$) (Fig. 3a), gender ($p = 0.679$), hypertension ($p = 0.538$), cardiovascular disease ($p = 0.454$) (Fig. 3b), and admission blood glucose levels ($p = 0.310$) (Fig. 3c).

Subgroup analysis

Subgroup analysis for studies from European populations [OR 1.11 (95% CI 0.93–1.33), $p = 0.26$, $I^2 = 0\%$, random-effect modelling] showed a higher OR for composite poor outcomes of COVID-19 compared to East Asian populations [OR 1.02 (95% CI 0.70–1.47), $p = 0.93$, $I^2 = 0\%$, random-effect modelling].

Publication Bias

The funnel-plot analysis showed a qualitatively symmetrical inverted funnel-plot (Fig. 4) and regression-based Egger's test were not statistically significant ($p = 0.759$) for the association between DPP-4 inhibitor and composite poor outcome of COVID-19, showing no indication of publication bias.

Discussion

This is the first systematic review and meta-analysis which not only analyzes the association between DPP-4 inhibitor and composite poor outcome of COVID-19, but also elaborate the effect of the confounding factors such as age, gender, hypertension, cardiovascular disease, and admission blood glucose which may influence the association between DPP-4 inhibitor and composite poor outcome of COVID-19. This comprehensive meta-analysis of 10 studies showed that DPP-4 inhibitor was not associated with composite poor outcome of COVID-19, therefore it cannot alter the severity of COVID-19 and mortality from COVID-19. This association was not influenced by age, gender, hypertension, cardiovascular disease, and admission blood glucose. From the subgroup analysis, it is also revealed that the magnitude of risk linked to DPP-4 inhibitor as single factor was greater in studies with European populations compared with Asian populations. This was probably caused by the Neanderthal core haplotype which presents higher in the European populations (France, Italy, England, Austria) at an allele frequency of 8%, while in East Asia populations (China, South Korea) the Neanderthal risk haplotype are almost absent [26]. The Neanderthal core haplotype is found to be the major genetic risk factor for severe COVID-19 [26].

Several reasons can be proposed to explain why DPP-4 inhibitor use cannot alter the severity nor mortality outcome of COVID-19. First, although a recent publication demonstrated that the S1 domain of the SARS-CoV-2 spike glycoprotein might interact with membrane-bound human DPP-4 [27], but functional assays study has suggested that ACE2 to be the major binding partner for COVID-19 and DPP-4 did not play a significant role for

SARS-CoV-2 internalization into host cells [28]. Therefore, administration of DPP-4 inhibitor cannot make a significant change into the course of COVID-19. Second, a recently published experimental study showed that the levels of pro-inflammatory cytokines such as IFN-γ, IL-10, IL-5, IL-6, CXCL1, IL-1β, and IL-4 were not different in a calorie deficit (CD) vs. high fat, fructose, and cholesterol (HFFC) diet after 14-days administration of DPP-4 inhibitor, despite the simultaneous reduction of DPP-4 activity and induction of DPP-4 protein levels [29]. These findings suggest that the levels of DPP-4 activity and soluble DPP-4 (sDPP-4) were not associated with cytokine levels in plasma, liver, or adipose tissue of high-fat diet-fed mice treated with DPP-4 inhibitor and further questions the anti-inflammatory effect of DPP-4 inhibitors. Moreover, the same study also analyzed the DPP4 activity, sDPP4 protein, and levels of inflammatory markers in plasma samples from 600 subjects with type 2 diabetes (T2D) treated with or without sitagliptin for 12 months from The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trial [29, 30]. This study showed no differences, relative to baseline values, in the sDPP4 protein levels and in circulating levels of IL-6, TNF-α, and CRP, which were the marker of severe COVID-19, at 12 months in the subjects receiving sitagliptin [29, 31]. Administration of DPP-4 inhibitor in patients with diabetes who have COVID-19 cannot reduce the inflammation and prevent the cytokine storm, thus cannot alter the severity and mortality outcome from COVID-19.

Despite DPP-4 inhibitor has no significant advantage for improving the composite poor outcomes of COVID-19, due to its important role in the control of diabetes, it should be prescribed according to patients' need. Physicians may still be using these drugs for type 2 diabetes patients who already received a benefit from using this drug or may also opt to change into metformin which has beneficial effects in reducing the mortality rate from COVID-19. Finally, anti-diabetes medications, including DPP-4 inhibitor shall be regarded as an important factor in future risk stratification models for COVID-19 in patients with diabetes.

This study has several limitations. First, data on the duration of DPP-4 inhibitor usage and the compliance to medications were lacking in the included studies, hence, cannot be analyzed. Second, we include some pre-print studies to minimize the risk of publication bias, however, the authors have made exhaustive efforts to ensure that only sound studies were included and we expect that most of those studies currently available in pre-print form will eventually be published and that we will identify them through ongoing electronic literature surveillances. We hope that this study can still give early insight into further risk stratification for COVID-19.

Declarations

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