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Review

Dipeptidyl peptidase-4 (DPP-4) inhibitor and mortality in coronavirus disease 2019 (COVID-19) – A systematic review, meta-analysis, and meta-regression

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ABSTRACT

Background and aims: This study aims to synthesize evidence on dipeptidyl peptidase-4 (DPP-4) inhibitor and mortality in COVID-19 patients and factors affecting it.
Methods: We performed a systematic literature search from PubMed, Scopus, and Embase databases from inception of databases up until 7 March 2021. Studies that met all of the following criteria were included: 1) observational studies or randomized controlled trials that report COVID-19 patients, 2) reporting DPP-4 inhibitor use, 3) mortality, and 4) mortality based on DPP-4 inhibitor use. The exposure was DPP-4 inhibitor, defined as DPP-4 inhibitor use that started prior to COVID-19 hospitalization. The control group was patients with no exposure to DPP-4 inhibitor. The outcome was mortality. The pooled effect estimate was reported as risk ratio (RR).
Results: There were 4,477 patients from 9 studies in this systematic review and meta-analysis. 31% of (15%, 46%) the patients use DPP-4 inhibitor. Mortality occurs in 23% (15%, 31%) of the patients. DPP-4 inhibitor was associated with lower mortality in patients with COVID-19 (RR 0.76 [0.60, 0.97], $p = 0.030$, I2: 44.5%, $p = 0.072$). Meta-regression analysis showed that the association between DPP-4 inhibitor and mortality was significantly affected by metformin (RR 1.02 [1.00, 1.04], $p = 0.048$) and angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB) use (RR 1.04 [1.01, 1.07], $p = 0.006$), but not age ($p = 0.759$), sex (reference: male, $p = 0.148$), and hypertension ($p = 0.218$).
Conclusion: DPP-4 inhibitor use was associated with lower mortality in COVID-19 patients, and the association was weaker in patients who were also taking metformin and/or ACE inhibitors.

1. Background

Coronavirus disease 2019 (COVID-19) has affected more than a hundred millions of people and causes more than a million death globally [1]. Although most COVID-19 patients have mild symptoms or even asymptomatic, there a significant proportion of patients that will experience multiple complications resulting in death [2]. Diabetes has been shown to increase mortality in patients with COVID-19 [3]. During the pandemic, questions on whether we should discontinue drugs routinely used for other comorbidities such as hypertension and diabetes in patients hospitalized with COVID-19. Moreover, many drugs that have been touted for treating COVID-19 fails. Thus, more importantly, can we repurpose these

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drugs to reduce in-hospital mortality in patients with COVID-19?

Dipeptidyl peptidase-4 (DPP-4) enzyme is a serine exopeptidase expressed in various tissues and plays a crucial part in the metabolism of glucose and insulin. Dipeptidyl peptidase-4 inhibitor inhibitor exerts anti-inflammatory, anti-fibrotic, and anti-adipogenic properties, which may be useful in delaying the progression to hyper-inflammation in severe COVID-19 cases [4–6]. A multicenter study have shown that DPP-4 inhibitor was associated with lower mortality [7], while other studies did not [8,9]. This study aims to synthesize evidence on DPP-4 inhibitor and mortality in COVID-19 patients and factors affecting it.

2. Material and methods

This is a Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) compliant systematic review and meta-analysis. This study is registered in PROSPERO (CRD42021241347).

2.1. Search strategy and study selection

We performed a systematic literature search from PubMed, Scopus, and Embase databases using keywords "(SARS-CoV-2 OR COVID-19 OR 2019-nCoV) AND (dipeptidyl peptidase-4 inhibitor OR dipeptidyl peptidase-IV inhibitor OR DPP-4 inhibitor OR DPP-IV inhibitor OR gliptin OR DPP-4 OR DPP-IV)" from inception of databases up until 7 March 2021. Screening of title/abstracts were performed independently by two authors. Potentially eligible articles were assessed for inclusion and exclusion criteria. Discrepancies that arises were resolved by discussion.

2.2. Inclusion and exclusion criteria

Studies that met all following criteria were included: 1) observational studies or randomized controlled trials that reported COVID-19 patients, 2) reporting DPP-4 inhibitor use, 3) mortality, and 4) mortality based on DPP-4 inhibitor use.

Studies that met one of the following criteria were excluded: 1) conference papers, 2) abstracts, 3) commentaries, and 4) letters. There was no language restriction.

2.3. Data extraction

Two independent authors extracted studies for the first author, study design, sample size, age, sex, hypertension, statin use, metformin use, angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB) use, the exposure, and mortality. Discrepancies were resolved by discussion.

Two independent authors performed risk of bias assessment of the included studies using the Newcastle-Ottawa Scale (NOS). Discrepancies that arose were resolved by discussion.

2.4. Intervention and outcome

The exposure was DPP-4 inhibitor, defined as DPP-4 inhibitor use that started prior to COVID-19 hospitalization. The control group was patients with no exposure to DPP-4 inhibitor. The outcome was mortality, defined as death/non-survivor. The pooled effect estimate was reported as risk ratio (RR).

2.5. Statistical analysis

STATA version 16.0 was used to perform meta-analysis. We pooled the risk ratio (RR) for DPP-4 inhibitor use and mortality, calculated from each of the included studies using the DerSimonian Laird random-effects meta-analysis. P-values below or equal to 0.05 was considered as statistically significant. Cochran's Q test and I^2 statistic tests were performed to assess heterogeneity, in which I^2 values above 50% and p-value below 0.10 indicates significant heterogeneity. Qualitative funnel-plot analysis and quantitative regression-based Egger's test were performed to evaluate the risk of publication bias and small-study effects. Meta-regression analysis was performed to evaluate the effect of age, sex, hypertension, ACEI/ARB use, and metformin use on the association between DPP-4 inhibitor and mortality.

3. Results

There were 4,477 patients from 9 studies in this systematic review and meta-analysis [7] [–] [16] [Fig. 1]. 31% of (15%, 46%) the patients used DPP-4 inhibitor. Mortality occurs in 23% (15%, 31%) of the patients. Baseline characteristics of the included studies is available in Table 1.

3.1. DPP-4 inhibitor and mortality

DPP-4 inhibitor was associated with lower mortality in patients with COVID-19 (RR 0.76 [0.60, 0.97], p = 0.030, I^2: 44.5%, p = 0.072) [Fig. 2]. Meta-regression analysis showed that the association between DPP-4 inhibitor and mortality was significantly affected by metformin (OR 1.02 [1.00, 1.04], p = 0.048) and ACEI/ARB use (OR 1.04 [1.01, 1.07], p = 0.006), but not age (p = 0.759), sex (reference: male, p = 0.148), and hypertension (p = 0.218).

3.2. Publication bias

Funnel-plot was asymmetrical [Fig. 3A] and non-parametric trim-and-fill analysis showed that imputation of one study on the right side of the plot resulted in RR of 0.78 [0.609, 1.00] [Fig. 3B]. There was no indication of small-study effects (p = 0.745).

4. Discussion

In this pooled analysis, we found that DPP-4 inhibitor use was associated with lower mortality in COVID-19 patients. Meta-regression analysis showed that the association between DPP4 inhibitor use and reduced mortality was weaker in patients who were also taking metformin and/or ACE inhibitors.

Metformin and ACE/ARB have been shown to reduce mortality in patients with COVID-19 [17,18], these drugs are frequently prescribed in patients with diabetes. Possible explanation is that, the benefit of DPP-4 inhibitor in terms of mortality is reduced by the presence of the two drugs. Further analysis of individual patient data is required to evaluate whether DPP-4 inhibitor benefit is independent of metformin and ACE/ARB use.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may use angiotensin-converting enzyme 2 (ACE2) receptor by binding its spike (S) glycoprotein to enter human cells [19]. It has also been observed that the human DPP-4/CD26 receptor can also be used by the SARS-CoV-2 spike glycoprotein to invade respiratory cells, suggesting the role of DPP-4 in the hijacking and virulence of the novel coronavirus [20,21]. Both ACE2 and DPP-4 membrane proteins appear to be correlated and relevant in the pathophysiology of the COVID-19 [6,19].

DPP-4 enzyme is a serine exopeptidase expressed in various tissues, such as pulmonary, cardiac, hepatic, renal, gastrointestinal, and immune cells. This enzyme plays a crucial part in the metabolism of glucose and insulin. DPP-4 inhibitor exerts anti-inflammatory, anti-fibrotic, and anti-adipogenic properties, which may be useful in delaying the progression to hyperinflammation in severe COVID-19 cases [4–6]. Hyperactivation of immune response

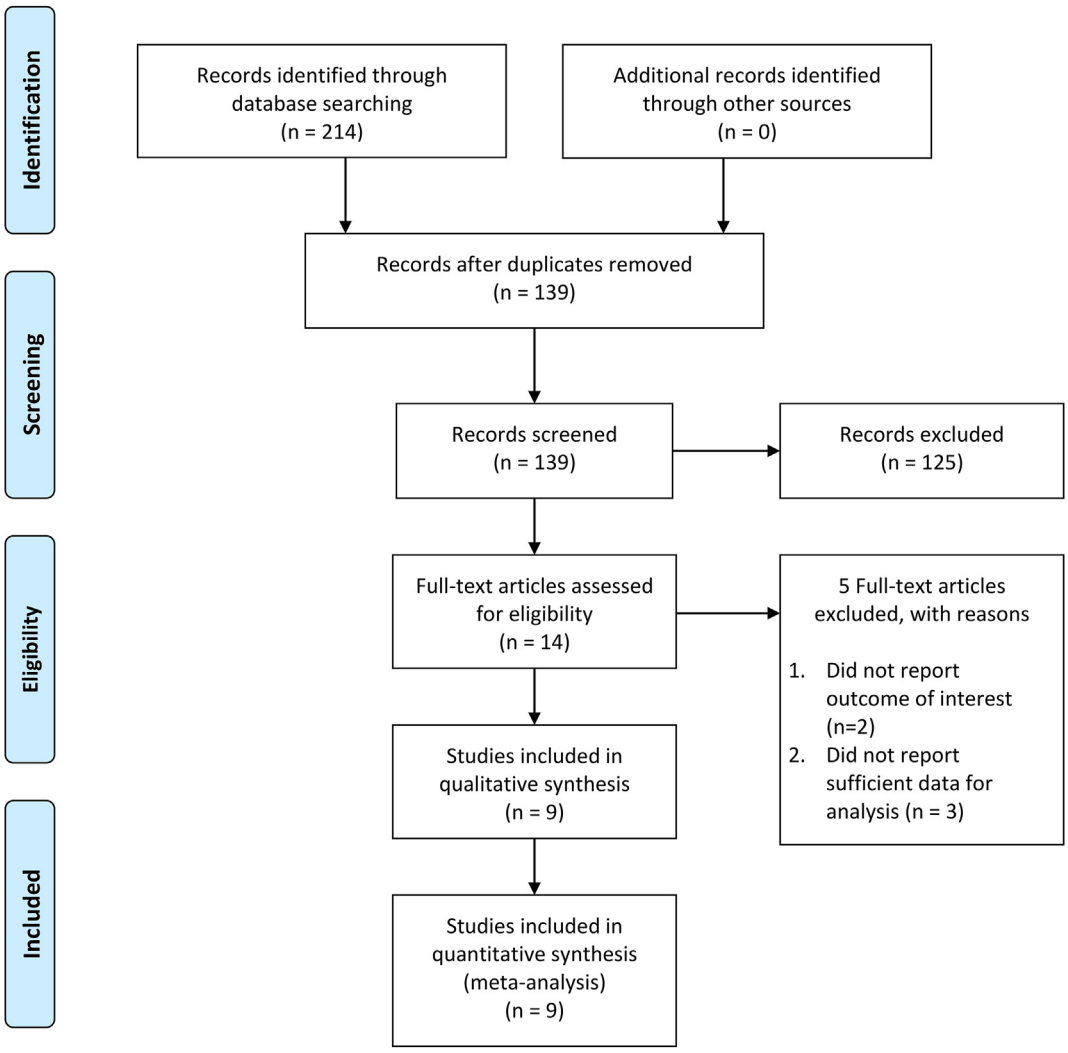

Fig. 1. Prisma flowchart.

Table 1
Baseline characteristics of the included studies.

Author	Design	Sample	Age (years)	Male (%)	Hypertension (%)	Statin (%)	Metformin (%)	ACEI/ARB (%)	NOS
Chen 2020	RC	904	66	47	33	NA	NA	NA	8
Fadini 2020	RC	403	70	65	69	37.6	NA	42.2	6
Mirani 2020	Case Series	498	71	72	77	NA	76.7	44.4	7
Noh 2021	Cohort	586	NA	50.7	NA	NA	NA	NA	6
Perez-Belmonte 2020	RC	2666	75	62	76	58	60.8	57.3	8
Roussel 2021	Cohort (PSM)	2449	70.9	64	80.2	48.7	61.1	58.1	9
Silverii 2020	RC	159	73	54	NA	NA	47.8	NA	6
Solerte 2020	RC	338	69	70	70	NA	42	44	8
Zhou 2020	RC (PSM 1:3)	2563	64	49	NA	NA	NA	NA	8

leading to cytokine storm is considered responsible for the pathogenesis of severe COVID-19 accompanied with serious complications, such as cardiorespiratory collapse, sepsis, disseminated intravascular coagulation (DIC), and multiple organ failure (MOF) [22]. This condition is characterized by elevated inflammatory biomarkers, including procalcitonin, ferritin, D-dimer, C-reactive protein (CRP), tumor-necrosis factor (TNF) -α and interleukin (IL) [23,24].

DPP-4 inhibitor, also known as gliptin, is an oral hypoglycemic agent that normally used in treating diabetic people, which is one of the risk factors for developing severe SARS-CoV-2 infection [3]. A number of non-communicable diseases such as hypertension, cardiovascular and cerebrovascular disease, chronic kidney disease, and chronic lung disease are also considered comorbidities for COVID-19, as well as increasing age, body mass index, and frailty conditions [25–31]. Recent evidences suggested that the use metformin, another anti-diabetic drug, and renin-angiotensin system (RAS) inhibitor were associated with lower severity and mortality in COVID-19 patients [17,32]. While these medications hamper hyperinflammation by affecting the ACE2 receptor, gliptin works by

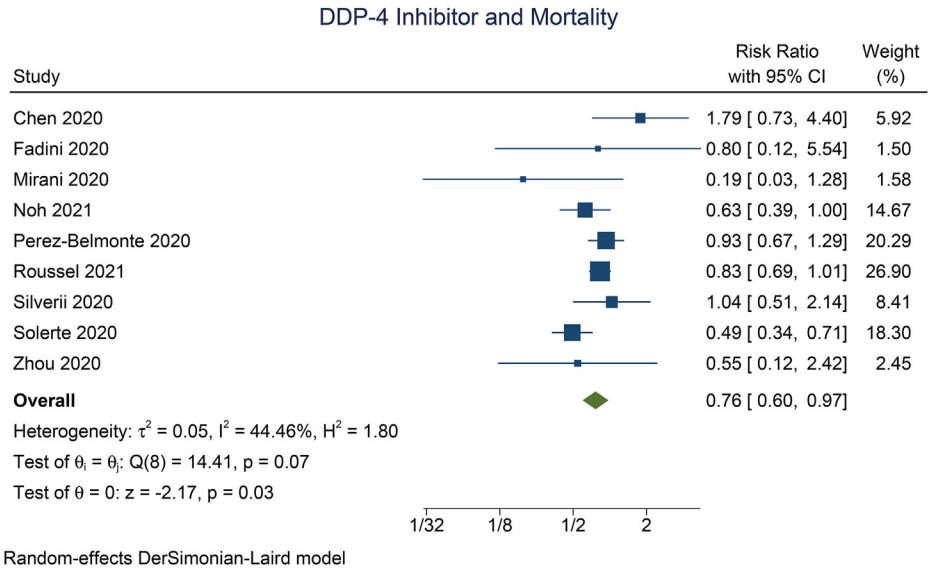

Fig. 2. DPP-4 Inhibitor use and Mortality.

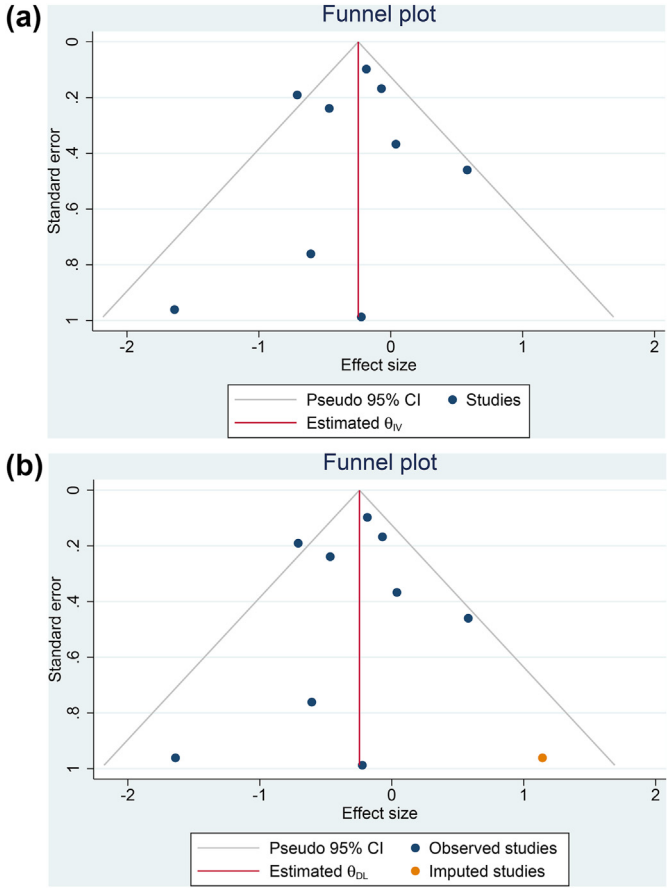

Fig. 3. Funnel-plot analysis (A) and non-parametric trim-and-fill analysis (B).

inhibiting DPP-4 [4–6,19].

Diabetes, as well as other diseases, contribute to a low-grade, chronic, systemic inflammation which exacerbates the SARS-CoV-2 infection [3,22,26]. The pro-inflammatory state negatively influences peripheral insulin sensitivity and homeostatic glucose control, hence chronic hyperglycemia and hyperinflammation aggravate each other and lead to poor immune function, including reduced leukocytes mobilization, chemotaxis, and phagocytic activity, decreased cytokines secretion (IL-1 and IL-6) in response to lipopolysaccharides, inhibition of tumor necrosis factor (TNF) activity and immunoglobulin glycation [5].

Normally, DPP-4 causes lower insulin secretion and abnormal visceral fat metabolism by degrading incretins such as glucagon like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide. DPP-4 inhibition and GLP-1 activation could antagonize hyperinflammation, insulin resistance, and macrophage infiltration via GLP-1 dependent signaling and M1/M2 macrophage polarization [5,19]. Higher expression of DPP-4 in visceral fat tissue contributes to insulin resistance and adipocyte inflammation. DPP-4 regulates the immune system by activating T-cells, enhancing lymphocyte proliferation, increasing the expression of CD86, and modulating NF-κB pathway [5,21]. This enzyme also promotes cleavage and affects the function of certain chemokines, cytokines, and growth factors [5].

Altered DPP-4 expression as seen in patients with comorbidities may favor SARS-CoV-2 to cause severe symptoms with complications [21]. Considering all potential beneficial effects, the inhibition of DPP-4 with gliptin might represent a promising option in lowering the risk of severity and mortality of COVID-19 patients with or without diabetes. As the evidence stands, it is recommended to continue the medication in patients using it routinely. However, more studies are required before repurposing it for COVID-19 therapy.

4.1. Limitations

The number of studies were small and many of them did not adequately report the potential confounding factors. Meta-regression analysis for ACEI/ARB and metformin use was based on small-number of studies. Association does not equal to causation, whether DPP-4 inhibitor can be repurposed requires further trials.

5. Conclusion

DPP-4 inhibitor use was associated with lower mortality in

COVID-19 patients, and the association was weaker in patients who were also taking metformin and/or ACE inhibitors.

Declaration of competing interest

None.

Abbreviations index

ACEI	Angiotensin Converting Enzyme inhibitor
ARB	Angiotensin Receptor Blocker
COVID-19	Coronavirus Disease 2019
DIC	Disseminated Intravascular Coagulation
DPP-4	Dipeptidyl Peptidase-4
GLP-1	Glucagon Like Peptide 1
IL:	Interleukin
MOF	Multiple Organ failure
NOS	Newcastle-Ottawa Scale
RAS	Renin-angiotensin System
RR	Risk Ratio
TNF	Tumor Necrosis Factor

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Ethical approval

Not Applicable.

Contributorship statement

IIR, YYK, and RP were involved in the conceptualization and design of the manuscript. DRH, HJ, ENN, YYK, IIR, AW, MAL, and RP participated in data curation and investigation. RP performed data analysis, formal analysis, and statistical analysis. DRH, HJ, ENN, YYK, and IIR drafted the manuscript. MAL, AW and RP review and edited the manuscript.

Informed consent

Not Applicable.

Data availability

Data are available on reasonable request.

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