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Brief Report

# Use of DPP4 inhibitors in Italy does not correlate with diabetes prevalence among COVID-19 deaths

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ABSTRACT

In a nationwide study of 3818 charts from patients with fatal COVID-19, we found that geographical differences in Dipeptidyl peptidase 4 (DPP4) inhibitors use did not correlate with diabetes prevalence among COVID-19 deaths, thus not supporting the hypothesis of a clinically relevant involvement of DPP4 inhibition in COVID-19 development and progression.


## 1. Introduction

Dipeptidyl peptidase 4 (DPP4) is a serine exopeptidase which regulates immune responses by acting as a co-stimulatory molecule on T-cells [1]. It is a pharmacological target of DPP4 inhibitors (DPP4i), a class of drugs widely used for the management of type 2 diabetes (T2D). It has been proposed that DPP4 might sterically interact with the S1 domain of the SARS-CoV-2 spike glycoprotein [2]. Moreover, DPP4i modulate inflammation by suppressing Th17 activity and proin-

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flammatory cytokines [3–5], two features of severe COVID-19 [6,7]. In an experimental model of Acute Respiratory Distress Syndrome (ARDS), a main cause of COVID-19 death, DPP4 inhibition alleviated histological findings of lung injury by inhibiting proinflammatory cytokines IL-1β, TNFα, and IL-6 [8]. Therefore, DPP4 inhibition may have a role in limiting two steps of COVID-19 immunopathogenesis: 1) by altering a potential SARS-CoV-2/DPP4 interaction; 2) by halting disease progression towards hyperinflammation. Under the hypothesis that treatment with DPP4i could prevent COVID-19 progression in subjects with diabetes, the aim of this analysis is to examine the association between DPP4i use among those with diabetes and COVID-19 deaths across regions of Italy during the pandemic.

## 2. Materials and methods

A COVID-19 surveillance system was launched by the Italian National Institute of Health (Istituto Superiore di Sanità [ISS]) in line with the Ministry of Health circular published in February 2020. Medical charts of people who died from COVID-19 in Italy were randomly sampled from the 21 Italian sanitary districts proportional to the total number of COVID-19 deaths which occurred in each district (the higher the number of deaths in one district, the higher was the number of medical charts reviewed in that district). As of the time of this analysis (June 17th, 2020) no medical charts were available from Valle D'Aosta, therefore, relevant data from only 20 Sanitary districts were provided by the ISS. Demographics of the population living in each district and diabetes prevalence in each region were obtained from the 2019 Italian statistical yearbook by the ISTAT [9]. Drug use was estimated for each sanitary district using data provided by IQVIA®. An additional primary source (Osservatorio per la Salute, Autonomous Province of Bolzano) that had access to all cases of COVID-19 deaths registered to April 27th, 2020 (n = 269), was used to validate data about DPP4i use in the general population and among patients with COVID-19 (Supplementary Material). As DPP4i are only available through specialist in a monitored process these data are likely more accurate than other drug use reports. Exposure in the population is expressed as the proportion of daily DPP4i units sold per 100 patients per year assuming 100% compliance. Spearman's rank correlation test was used to evaluate linear relationships between continuous variables. The analysis conducted on the 20 sanitary districts provided 80% power to detect an effect size of 0.55. Type I error threshold was set at two-tailed $p < 0.05$. Stata/IC 12.1 and Prism 8.0d were used for analysis and figures.

## 3. Results

A sample of 3818 medical charts from individuals who died of COVID-19 had been reviewed by the ISS by the time of this analysis; 467 were excluded due to unknown diabetes status resulting 87.8% (n = 3351) being used in the analysis. As the number of COVID-19 deaths varied by region, the ISS sampling algorithm dictates the number of medical charts reviewed from each sanitary district: from Lombardy n = 1813 were sampled (54.1% of deaths), Emilia Romagna (n = 507; 15.21%) and Veneto (n = 200; 6.0%). The median [IQR] number of medical charts reviewed in each region was 41 [8–108].

Of the charts reviewed of individuals who died from COVID-19, 1089 (32.5%) patients had diabetes. Diabetes prevalence among COVID-19 deaths varied substantially by the districts: the highest was in Trento (54.8%), then Molise (50.0%), Sardinia (40.0%), while the lowest was in Calabria (16.7%) and Abruzzo (12.5%). No cases of diabetes were registered among the seven medical charts of patients died in Umbria. Deaths from COVID-19 were not associated with diabetes prevalence across the individual districts used in this analysis. (*rho* = 0.153, p = 0.52). The total number of medical charts reviewed in each district did not correlate with the prevalence of diabetes among COVID-19 deaths (*rho* = 0.002, p = 0.99).

The median percentage use of DPP4i among diabetic people in the sanitary districts was 11.4% [10.2–12.5]; Sicily was the lowest (5.7%), while Bolzano and Sardinia showed the highest percentages (16.9% and 16.8%, respectively) (Table S1). The percentage use of DPP4i in each district was unrelated to diabetes prevalence among those who died from COVID-19 (*rho*=-0.247, p = 0.29; Fig. 1). No significant differ-

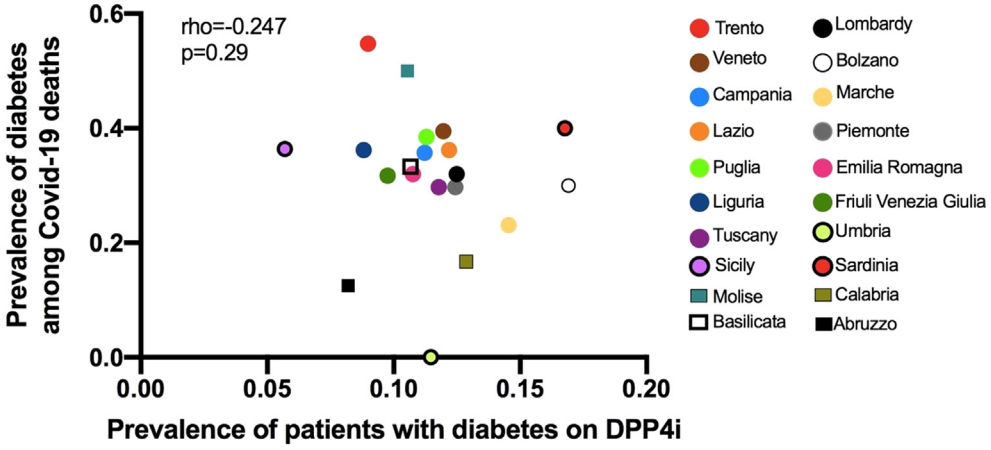


**Fig. 1 – Relationship between estimated overall DPP4i prevalence use in individuals with diabetes and proportion of patients with comorbid diabetes among COVID-19 deaths.**

ences in the use of DPP4i were found between alive and deceased T2D patients with COVID-19 in the Autonomous Province of Bolzano according to the data from "Osservatorio per la Salute" (25/149 [16.8%] vs 5/44 [11.4%], repsectively, p = 0.48; Table S2).

## 4. Discussion

In this study, over one third of individuals who died of COVID-19 had diabetes. Geographical differences in DPP4i use did not correlate with diabetes prevalence among COVID-19 deaths.

Our data extend findings from two recent reports that evaluated the association between DPP4i treatment and COVID-19 fatality. In an Italian case-control study involving 85 T2D individuals hospitalized for COVID-19, previous DPP4i treatment (nine patients) was unrelated to COVID-19 death [10]. In the CORONADO study, a larger, nationwide observational study of 1317 diabetic people hospitalized for COVID-19, DPP4i treatment before admission (285 subjects) did not improve the primary outcome (invasive respiratory support or death within seven days from admission) [11]. However, the small sample size stands out as major limitation in the former, while the latter study was not specifically designed to assess the relationship between DPP4i and COVID-19. Main strengths of our study include the large number of cases assessed nationwide and the use of hard endpoint which can be measured unambiguously. Due to its ecologic nature, our study is limited to the biases inherent these types of studies, and by the lack of data on glucose control and other comorbidities.

In conclusion, our findings suggest that pharmacological inhibition of DPP4 may not have a role in preventing SARS-CoV-2 infection and/or COVID-19 progression.

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## Author contribution

PP conceived the study, contributed to data collection, interpretation of the data and edited the manuscript. RS contributed to study conception, wrote the first draft of the manuscript and contribute to data interpretation. EM analyzed the data, wrote the first draft of the manuscript and contributed to data interpretation. RB contribute to study conception, data interpretation and edited the manuscript. MD contribute to data interpretation, data collection and edited the manuscript. CP contributed to data analyses and data interpretation. All authors critically revised the manuscript for intellectual content. All authors have seen and approved the final draft.

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## Conflict of interests

RS, MD and CP have no conflict of interest to declare for the preparation of this manuscript.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108444.

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