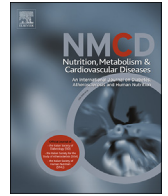




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## SHORT COMMUNICATION

## Are diabetes and its medications risk factors for the development of COVID-19? Data from a population-based study in Sicily

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**Abstract** *Background and aims:* Diabetes mellitus (DM) has been associated with higher incidence of severe cases of COVID-19 in hospitalized patients, but it is unknown whether DM is a risk factor for the overall COVID-19 incidence. The aim of present study was to investigate whether there is an association of DM with COVID-19 prevalence and case fatality, and between different DM medications and risk for COVID-19 infection and death.

*Methods and results:* retrospective observational study on all SARS-CoV-2 positive (SARS-CoV-2<sup>+</sup>) cases and deaths in Sicily up to 2020, May 14th. No difference in COVID-19 prevalence was found between people with and without DM (RR 0.92 [0.79–1.09]). Case fatality was significantly higher in SARS-CoV-2<sup>+</sup> with DM (RR 4.5 [3.55–5.71]). No diabetes medication was associated with differences in risk for SARS-Cov2 infection.

*Conclusions:* in Sicily, DM was not a risk factor for COVID-19 infection, whereas it was associated with a higher case fatality.

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**Introduction**

Since the beginning of the Sars-Cov-2 epidemics, Diabetes Mellitus (DM) has been associated with a higher incidence of severe cases of COVID-19. A recent meta-analysis of 83 observational studies enrolling 78,874 hospitalized patients with laboratory-confirmed COVID-19 showed a pooled prevalence of established diabetes of 14.34%; pre-

existing diabetes was associated with higher risk of severe COVID-19 illness and in-hospital mortality [1]. The prevalence of diabetes in patients deceased with COVID-19 was reported to be higher than in the general population [2], and the use of drugs for diabetes was associated with a higher risk of developing diagnosed COVID-19 in Lombardy [3]. In Italy, a report from the national Institute of Health (Istituto Superiore di Sanità, ISS) found that in a sample of patients with COVID-19 who died in Italy up to May 21st, 2020, 30.1% had DM [4]. On the other hand, as most studies focus on hospitalized cases, little information is available on the association of diabetes with COVID-19 in

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**Table 1** Difference in prevalence and case-fatality for Sars-CoV2 in Sicily between people with and without DM in different age and sex groups (95% CI RR: 95% confidence interval relative risk).

	Age	Men			Women		
		DM	Non DM	95% CI RR	DM	Non DM	95% CI RR
Prevalence	0–79	61/132,570 (46 × 100,000)	1217/2,180,805 53 × 100,000	0.83 (0.64–1.07)	43/81,792 (53 × 100,000)	1171/2,289,832 (50.2 × 100,000)	1.03 (0.76–1.39)
	≥80	26/22,624 (115 × 100,000)	105/97,719 (105 × 100,000)	1.1 (0.72–1.69)	30/32,805 (91.4 × 100,000)	198/162,873 (119.7 × 100,000)	0.76 (0.52–1.12)
Case Fatality	0–79	20/61 (33%)	71/1217 (4%)	5.62 (3.68–8.59)	8/43 (19%)	33/1171 (3%)	6.6 (3.25–13.43)
	≥80	15/26 (58%)	54/105 (51%)	1.12 (0.77–1.64)	16/30 (53%)	64/198 (35%)	1.65 (1.12–2.44)

outpatients. Furthermore, it is unknown whether DM is a risk factor for the overall incidence of COVID-19. In addition, most studies on COVID-19 have been performed in high-incidence areas, where the proportion of underdiagnosis in milder cases is likely to be higher. The assessment of the association of diabetes with COVID-19 in a low-risk Region, such as Sicily, in which a more accurate diagnosis of oligosymptomatic cases of COVID-19 could have been possible, could yield some relevant information.

## Methods

We performed a retrospective observational study on all SARS-CoV-2 positive (SARS-CoV-2<sup>+</sup>) cases and deaths in Sicily region, up to 2020, May 14th.

Our primary endpoint was the association of diabetes with COVID-19 prevalence and case fatality. We also explored the association between different diabetes medications and risk for COVID-19 infection and death. Data for all SARS-CoV-2<sup>+</sup> cases and deaths in the region were obtained from the Italian SARS-CoV-2<sup>+</sup> surveillance system, which is coordinated by the ISS and, as regards to the Sicilian region, it is managed by the Sicilian Epidemiologic Observatory; information on sex, age groups, and diabetes status (yes/no) prior to COVID-19 diagnosis were available for all patients. Information on medications for diabetes at December 31st, 2019, was obtained from regional reimbursement database on drug prescription. Each patient was given a code, so that all data were kept anonymous.

Unadjusted Relative risks (RR) with 95% confidence intervals (95% CI) were calculated to assess differences between people with and without diabetes or people with or without SARS-CoV-2 infection. RR was calculated for SARS-CoV-2 positivity in general population, comparing subjects exposed or unexposed to different diabetes drugs; a similar analysis was performed for case fatality among patients with diabetes. Chi-Square analysis was performed to investigate differential characteristics of people with diabetes and SARS-CoV-2 infection. Analysis were performed using SPSS and Microsoft Excel.

## Results

Of the 159 SARS-CoV-2<sup>+</sup> people with DM in Sicily up to May, 14th, 59 had died. Mean age was 73.31 (12.66) years: 78.66 (9.94) in those who died, 70.15 (13.06) in those who

survived ( $p < 0.001$  between the groups). Men were 54.1%, 59.3% of the dead and 51% of the survivors ( $p = 0.197$ ). Of the 2692 SARS-CoV-2<sup>+</sup> people without DM, 222 had died. The overall prevalence of COVID-19 was  $53.33 \times 100,000$  in the 298,140 people with DM, and  $57.6 \times 100,000$  in the 4,670,860 people without. No difference in COVID-19 prevalence was found between people with and without DM (RR 0.92 [0.79–1.09]), in any sex and age group (Table 1). Case fatality was significantly higher in those with DM 37.1% versus 8.2%; (RR 4.5 [3.55–5.71]), particularly among younger individuals (Table 1). No medication for diabetes was associated with differences in either risk of COVID-19 or case fatality, with the only exception of metformin, which was associated with a lower case fatality (Table 2).

## Discussion

In our study, Diabetes was not a risk factor for COVID-19, although it was associated with a higher case fatality. This is in line with previous suggestions that diabetes could be a negative prognostic factor, more than a risk factor for infection [2]. It has been speculated that diabetes could facilitate SARS-Cov2 infection either through an aspecific effect of hyperglycemia on infections, or through other, more specific mechanisms, such as the modulation of ACE2 receptor expression into lung cells [5]. In fact, prior studies reporting a higher prevalence of diabetes in COVID-19 patients included only hospitalized patients [6], whereas our sample includes the whole population; moreover, the incidence of Covid-19 was relatively low in Sicily, thus allowing a wider diagnosis of milder cases than in higher prevalence regions of Italy. In fact, in Sicily reported case fatality was 8.2%, which is lower than national rate of 14%, and much lower than the 18.2% of Lombardy for the same period [7]; this was probably due to a greater proportion of diagnosis in milder cases, rather than to differences in the actual prognosis of infected individuals. It is conceivable that the apparent higher prevalence among people with DM in hospitalized patients is due to a higher disease severity, rather than to increased incidence. Case fatality was increased in patients with diabetes, but the lack of information on comorbidities affecting mortality (e.g., obesity, renal and cardiovascular disease) [8] suggests caution in the interpretation of data. Unfortunately, information on weight, comorbidities and glycemic control during the disease was not available in our sample, and this is a major limitation of the present study. In

**Table 2** Differential characteristics between dead and survived as regards to diabetes medications intake (p for differences between groups). Association between diabetes medication intake and risk for Sars-Cov2 Positivity and Sars-COV2 Case fatality (95% CI RR).

Medications:	All (N = 159)	Dead (N = 59)	Survived (N = 100)	p	RR of Sars-Cov2 positivity (in GP)	RR of COVID19 Case fatality (in DM)
Metformin	76 (47.8%)	21 (35.6%)	55 (55%)	0.014	0.92 (0.72–1.15)	0.6 (0.39–0.93)
Metformin only	28 (17.6%)	8(13.6%)	20 (20%)		1.03 (0.51–2.08)	0.62 (0.33–1.17)
Metformin in combination	48 (30.2%)	13 (22%)	35 (35%)		0.81 (0.61–1.08)	0.65 (0.39–1.09)
Pioglitazone	8 (5%)	4 (6.8%)	4 (4%)	0.337	1.35 (0.68–2.71)	1.37 (0.67–2.83)
Insulin	43 (27%)	18 (30.5%)	25 (25%)	0.283	0.76 (0.56–1.03)	1.18 (0.77–1.82)
Insulin only	21 (13.2%)	10 (16.9%)	11(11%)		0.78 (0.5–1.2)	1.34 (0.81–2.25)
Sulphonylureas/ Glinides	33 (20.8%)	13 (22%)	20 (20%)	0.465	0.77 (0.55–1.08)	1.08 (0.67–1.75)
DPP-4 inhibitors	13 (8.2%)	5 (8.5%)	8 (8%)	0.568	1.33 (0.67–2.3)	1.0 (0.51–2.14)
SGLT-2 inhibitors	4 (2.5%)	2 (3.4%)	2 (2%)	0.153	0.63 (0.24–1.69)	1.36 (0.49–3.7)
GLP-1 Receptor agonists	7 (4.4%)	1 (1.7%)	6 (6%)	0.194	1.14 (0.54–2.38)	0.32 (0.05–2.06)

GP = General Population.

particular, cases of steroid-related diabetes during COVID19 and cases of COVID-19-induced diabetes [9] were not classified as diabetes in the present database. Diabetic medications do not seem to have either protective or detrimental effect on COVID-19 incidence and severity; in particular, we found no effect of DPP4-inhibitors, which were previously highlighted as possible Covid-19 disease modifiers [10]. This result is in line with a previous report on a small series of patients hospitalized for COVID19 [11].

In conclusion, in Sicily, during the epidemic outbreak of COVID-19 between February and May 14, diabetes mellitus was not a risk factor for the development of COVID-19, although it was associated with a higher case fatality. The reported association of diabetes with a greater risk of COVID-19 in other studies could be an artefact determined by a selective diagnosis of more severe cases.

### Declaration of Competing Interest

G.A. Silverii reports personal fees from Astra Zeneca, Novo Nordisk outside the submitted work; M. Monami reports personal fees from Astra Zeneca, Boehringer-Ingelheim, from Eli-Lilly, Novo Nordisk, Sanofi, Takeda outside the submitted work; E. Mannucci reports grants and personal fees from Astra Zeneca, Boehringer Ingelheim, Novo Nordisk, Eli Lilly, grants from Genentech, Molteni, personal fees from Merck, Abbott, Sanofi outside the submitted work. A. Cernigliaro, S. Scodotto, A.V. Allotta, C. Giordano, E. Vigneri and V. Guarnotta have nothing to declare. M. Conti is presently employee of Novo Nordisk.

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This research was performed as a part of the institutional activity of the unit, with no specific funding. All expenses, including salaries of the investigators, were covered by public research funds assigned to the unit.

### Access to data and data analysis

The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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