Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice
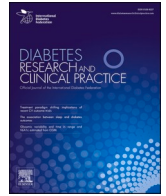
Diabetes and COVID-19 testing, positivity, and mortality: A population-wide study in Northern Italy

Olivera Djuric [a,b,*], Marta Ottone [a], Massimo Vicentini [a], Francesco Venturelli [c], Annamaria Pezzarossi [a], Valeria Manicardi [d], Marina Greci [e], Paolo Giorgi Rossi [a], the Reggio Emilia Covid-19 Working Group [1]

[a] *Epidemiology Unit, Azienda USL – IRCCS di Reggio Emilia, 42122 Reggio Emilia, Italy*
[b] *Centre for Environmental, Nutritional and Genetic Epidemiology (CREAGEN), Section of Public Health, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, 41125 Modena, Italy*
[c] *Public Health Unit, Azienda USL – IRCCS di Reggio Emilia, 42122 Reggio Emilia, Italy*
[d] *Medical Diabetologist Association Coordinator, Diabetologist, Salus Hospital, 42122 Reggio Emilia, Italy*
[e] *Primary Health Care Department, Azienda USL – IRCCS di Reggio Emilia, 42122 Reggio Emilia, Italy*

ARTICLE INFO

ABSTRACT

AIMS: To assess if patients with type 2 diabetes mellitus (DM2) are: a) at excess risk of undergoing testing, contracting, and dying from SARS-CoV-2 infection compared to the general population; b) whether cardiovascular diseases (CAVDs) contribute to COVID-19-related death; and c) what is the effect of DM2 duration and control on COVID-19-related death.

METHODS: This population-based study involved all 449,440 adult residents of the Reggio Emilia province, Italy. DM2 patients were divided in groups by COVID testing, presence of CAVDs and COVID death. Several mediation analyses were performed.

RESULTS: Patients with DM2 had an increased likelihood of being tested (Odds ratio, OR 1.27 95 %CI 1.23–1.30), testing positive (OR 1.21 95 %CI 1.16–1.26) and dying from COVID-19 (OR 1.75 95 %CI 1.54–2.00). COVID-19-related death was almost three times higher among obese vs non-obese patients with DM2 (OR 4.3 vs 1.6, respectively). For COVID-19 death, CAVDs mediated a) just 5.1 % of the total effect of DM2, b) 40 % of the effect of DM2 duration, and c) did not mediate the effect of glycemic control.

CONCLUSIONS: For COVID-19-related deaths in DM2 patients, the effect is mostly direct, obesity amplifies it, DM2 control and duration are important predictors, while CAVDs only slightly mediates it.

1. Introduction

Ever since Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS COV 2), has been declared a public health emergency of international concern at the beginning of 2020 [1], it continues to impact the health, economy, and quality of life of individuals and societies globally. Risk factors for severe

COVID-19 disease and mortality were one of the main research targets to achieve clinical and public health decision making, such as triage of hospitalized patients or tailoring vaccination strategies.

Diabetes mellitus (DM), hypertension, cancer, and respiratory and kidney diseases have been identified, together with age, obesity, and impaired immune status, as major factors contributing to an increased risk of severe illness from COVID-19 and death [2]. DM appeared to be

---

the most frequent comorbidity, after hypertension, in patients with severe illness [2,3], and the predominant underlying comorbidity amongst the COVID-19 non-survivors [4,5].

Although subsequent *meta*-analyses supported these results [6–12], the association between cardiometabolic risk factors and COVID-19 adverse outcomes in observational hospitalized-based studies are based on the prevalence of DM among hospitalized patients, which can lead to collider bias [13]. In fact, in studies that considered all patients with COVID-19, irrespective of the disease severity or hospitalization, the prevalence of DM was similar to the DM prevalence in the general population in the corresponding age group [14,15]. It is therefore important to consider the entire general population and to estimate first whether people with DM have an increased likelihood of being tested with respect to the general population.

The role of obesity, diabetes therapy and glucose control and cardiovascular diseases (CAVDs) in adverse COVID-19 outcomes is still unknown. Thus, there are several important questions still unanswered regarding this complex association: whether diabetes type 1 (DM1) and type 2 (DM2) increase the risk of COVID-19 death and if so, is that through increased testing or an increased risk of contracting the virus? Is the effect of DM2 different in different levels of obesity and cardiovascular diseases (effect modifier) or is part of the association conferred through their effect (mediator)? Whether DM2 duration and control affect COVID-19-related death and whether part of this effect is going through CAVDs?

In the present study, we tried to answer these questions by assessing whether people with DM1 and DM2 have an excess risk of being tested and of contracting SARS-CoV-2 infection, as well as whether they are at greater risk of death once they are diagnosed with COVID-19. The second aim was to investigate whether CAVDs are a mediator in the association between DM2 and death in people with COVID-19. In a subset of people with DM2 who have COVID-19, we aimed at estimating whether DM2 duration and control lead to the increased risk of COVID-19-related death and whether CAVDs are a mediator in the association.

2. Material and methods

2.1. Study design and population

A population-based study was conducted including all residents of the Reggio Emilia Province on December 31, 2019 (people over 18 years of age) according to the resident population registry of the local health authority. The cohort with diabetes mellitus comprised all prevalent cases of diabetes mellitus on December 31, 2019, according to the provincial diabetes registry. Women with gestational diabetes or women receiving treatment for the polycystic ovarian syndrome are excluded from the registry.

2.2. Data sources and variables

Data linkage was performed according to the unique identification number assigned to each resident, linking general population data, the diabetes registry, the cancer registry, local administrative databases, data on SARS-CoV-2 tests, as well as hospital, clinical, and pharmacological data.

Date of SARS-CoV-2 tests and death were retrieved from the COVID-19 Surveillance Registry, coordinated by the Italian National Institute of Health, and implemented in each Local Health Authority. The whole list of cases tested for SARS-CoV-2 (positive and negative) from February 26, 2020, up to August 10, 2021, was linked to the resident population.

DM status, together with the most recent value of BMI and glycated haemoglobin A1c (HbA1c), diabetic drugs and duration of diabetes was retrieved from the provincial diabetes registry. The methods applied to set up the diabetes registry have been described previously [16].

Cancer was defined through linkage with two sources: hospital admissions in the previous five years; or the local Cancer Registry (period

2015–2019), which registers all new cancer diagnoses occurring in people residing in the Reggio Emilia Province.

Information on recent comorbidities, such as CAVDs (Ischemic cardiopathy, heart failure, arrhythmias, vascular diseases, and cerebrovascular diseases), hypertension, dementia, chronic kidney failure and obesity were collected from hospital discharge databases (2015–2019). Charlson comorbidity index (CCI) was calculated based on hospital admissions in the previous ten years and it is used to evaluate the impact of comorbidity on selected outcomes [17]. Our CCI is a measure that incorporates 17 different comorbidity diseases, each of which was weighted according to its potential impact on mortality.

The highest value of triglycerides was retrieved from the laboratory information system. The most recent HbA1c concentration in the period between January 1, 2018, and December 31, 2019, was used as a measure of glycaemic control.

2.3. Outcomes

Outcomes of interest were: (a) being tested for SARS-CoV-2 (at least one PCR test performed); (b) resulting positive for SARS-CoV-2 in a PCR test (definition for COVID-19 cases as adopted by the Italian Ministry of Health); (c) death within 45 days from the COVID-19 diagnosis (first positive swab) and before the double negative swab result (two consecutive negative swabs even with a one-day distance). Reinfections and reinfection-related deaths were not included in the analysis.

2.4. Statistical analysis

Categorical variables are reported as proportions and continuous variables, such as lipid profile variables, are reported as median and interquartile ranges. BMI and triglycerides were categorized based on quartiles. Logistic regression models were used to estimate the associations between each putative risk factor and the outcome, first by univariable model and then by adjusting for age and sex. Odds Ratios (OR) with 95 % confidence intervals (95 % CI) were calculated.

A direct acyclic graph (DAG) was created in order to identify a bias-minimized model of the associations between diabetes and COVID-19-related death (Supplementary figure).

Among people with a positive SARS-CoV-2 PCR test, we investigated the possible modification effect of CAVDs and DM2 on death. An interaction term was added to the model and the odds ratios for each of the two levels of diabetes (DM2/no diabetes) and odds ratios for each of the two levels of the main comorbidities (yes/no) were calculated.

Furthermore, several mediation analyses were conducted to assess the potential role of the presence of CAVDs as a mediator (intermediate factor) in the association between DM2 and death in people with COVID-19 and between glycaemic control and death and between diabetes duration and death in people with COVID-19 and DM2. The R package "medflex" and Stata's "paramed" command were used. The percentage mediated was calculated as (NDE*(NIE-1)) / (NDE*NIE −1), where NDE is a natural direct effect (the difference between the value of the counterfactual outcome if the individual had DM2 and the value of the counterfactual outcome if the same individual did not have DM2, with the mediator assuming whatever value it would have taken at the reference value when the exposure (DM2) was not present) and NIE is a natural indirect effect (the contrast, having set the exposure to having DM2, between the value of the counterfactual outcome if the mediator assumed whatever value it would have taken if having DM2 and the value of the counterfactual outcome if the mediator assumed whatever value it would have taken at a reference level of the exposure) [18,19].

Stata/IC 16.1 (Stata Corporation, College Station, Texas 77,845 USA) software and R software were used for all analyses.

3. Ethics

The study was approved by the "Area Vasta Emilia Nord" (AVEN)

Ethics Committee on 07/04/2020 n° 2020/0045199.

4. Patient consent

In accordance with the Italian privacy law, no patient or parental consent is required for large retrospective population-based studies approved by the competent Ethics Committee if data are published only in aggregated form.

5. Results

There were 449,440 inhabitants of the Reggio Emilia Province (people over 18 years of age) included in the study. Of them, 32,494 had a diagnosis of DM, out of whom 29,825 had DM2. In total, 158,563 (35.3 %) residents had at least one swab performed, 37,100 (8.2 %) had at least one positive test for SARS-CoV-2 and 1,163 (0.3 %) died with a diagnosis of COVID-19. Almost one third of deceased people had DM2 (27.3 %) or hypertension (26.4 %), while only 0.2 % had DM1 (Table 1). While testing and positivity rates were similar among patients with DM1 and DM2 (42.6 % vs 37.3 % and 8.3 % vs 8.6 %, respectively), mortality was higher among patients with DM2 (1.1 % vs 0.2 %).

In multivariable analysis, both DM1 and DM2 were associated with a higher risk of death (Table 2). The presence of comorbidities, all comorbidities separately (cardiovascular and cerebrovascular diseases, chronic obstructive pulmonary disease-COPD, cancer, kidney failure), and triglycerides (>156 mg/dL) were associated with death following SARS-CoV-2 positivity. These characteristics were also associated with being tested for and being positive for SARS-CoV-2 (Supplementary Table S1).

Neither comorbidities nor obesity and triglycerides showed significant interaction in predicting mortality in positive patients, i.e., once SARS-CoV-2 is contracted (Table 3). However, obese patients with DM2 had an almost three times higher risk of COVID-19-related death compared to non-obese patients with DM2 (OR 4.3 vs 1.6).

Mediation analysis showed that most of the effect that DM2 manifests on the death from COVID-19 is explained through the direct effect (OR 1.59 95 %CI 1.36–1.85), although there is some significant indirect effect through CAVDs (OR 1.02 95 %CI 1.018–1.02) (Table 4). Overall, 5.1 % of the total effect of DM2 on odds of dying from COVID-19 was mediated through CAVDs.

The effects of the DM2 duration, glycaemic control, DM treatment, and BMI on being tested for, contracting, and dying from COVID-19 were analysed in the subgroup of individuals with DM2. Description of this subgroup concerning clinical variables and primary outcomes are presented in Supplementary Table 2. Patients with HBA1c over 8 % were at a higher risk of all three outcomes (Supplementary Table S3). The duration of DM2 was also significantly associated with all three outcomes, although with a small point estimate.

The presence of all comorbidities separately and CCI were predictors of death among positive patients with DM type 2 (Table 5). Furthermore, triglycerides, BMI (≥32.9), insulin therapy, and HBA1c over 8 % were associated with death following SARS-CoV-2 positivity.

There was a negligible correlation between DM2 duration and DM2 control (Spearman's $\rho = 0.23$, $p < 0.001$) so they were considered as two distinct indicators of DM2 severity and two distinct exposures in the mediation analysis. CAVDs mediated 40 % of the association between DM2 duration and risk of death due to COVID-19, however with very small point estimates (NIE OR 1.002 95 %CI 0.999–1.004) (Supplementary table S4). Uncontrolled DM2 (defined by HBA1c over 8 %), although with little precision and possibly due to chance, conferred risk for death mainly through the indirect effect (NIE OR 1.01 95 %CI 0.952–1.072) (Supplementary Table S5).

6. Discussion

In this population-based study, including almost half a million

Table 1
Patients' pre-existing condition and clinical variables.

Variables	Population	Tested for the presence of SARS-CoV-2	Positive for the presence of SARS-CoV-2	Deaths
	N (%)	N (%)	N (%)	N (%)
	449,440	158,563 (35.28)	37,100 (8.25)	1,163 (0.26)
Age, mean (sd)	52 (18.9)	51 (19.4)	50 (19.1)	82 (10.3)
Female sex	230,006 (51.2)	84,602 (53.4)	19,160 (51.6)	527 (45.3)
Foreigners	57,319 (12.8)	16,454 (10.4)	3,961 (10.7)	19 (1.6)
Diabetes (no)	416,946 (92.8)	146,377 (92.3)	34,294 (92.4)	831 (71.5)
Type 1	1,191 (0.3)	508 (0.3)	100 (0.3)	2 (0.2)
Type 2	29,825 (6.6)	11,117 (7.0)	2,570 (6.9)	317 (27.3)
Other	208 (0.1)	81 (0.1)	15 (0.0)	1 (0.1)
Not defined	1,270 (0.3)	480 (0.3)	121 (0.3)	12 (1.0)
Charlson Comorbidity Index				
0	416,072 (92.6)	143,445 (90.5)	34,126 (91.9)	659 (56.7)
1	14,333 (3.2)	6,219 (3.9)	1,305 (3.5)	214 (18.4)
2	13,182 (2.9)	5,701 (3.6)	1,101 (3.0)	157 (13.5)
3	5,853 (1.3)	3,198 (2.0)	568 (1.5)	133 (11.4)
COPD	3,566 (0.8)	1,933 (1.2)	373 (1.0)	95 (8.2)
Ischemic cardiopathy	8,772 (2.0)	3,930 (2.5)	780 (2.1)	135 (11.6)
Dementia	2,078 (0.5)	1,288 (0.8)	414 (1.1)	110 (9.5)
Chronic kidney failure	2,680 (0.6)	1,570 (1.0)	270 (0.7)	83 (7.1)
Cancer	27,487 (6.1)	11,149 (7.0)	2,108 (5.7)	184 (15.8)
Hypertension	18,082 (4.0)	7,959 (5.0)	1,650 (4.5)	307 (26.4)
Obesity	2,580 (0.6)	1,224 (0.8)	292 (0.8)	27 (2.3)
Heart failure	5,782 (1.3)	3,021 (1.9)	595 (1.6)	161 (13.8)
Arrhythmias	8,493 (1.9)	3,941 (2.5)	799 (2.2)	172 (14.8)
Vascular diseases	3,146 (0.7)	1,499 (1.0)	271 (0.7)	59 (5.1)
Cerebrovascular disease	7,393 (1.6)	3,456 (2.2)	776 (2.1)	162 (13.9)
Max triglycerides (mg/dl), mean (sd)[a]	133 (106.8)	133 (108.9)	132 (105.8)	154 (95.3)

COPD, chronic obstructive pulmonary disease.

[a] 186,790 (41.6%) missing.

inhabitants of the Reggio Emilia Province, in Northern Italy, an almost twofold risk of death was observed among patients with DM2 compared to the general population, together with an increased risk of being tested and testing positive for COVID-19. COVID-19-related death was almost three times higher among obese vs non-obese patients with DM2. We found no interaction between DM2 and CAVDs. However, the presence of CAVDs accounted for a small indirect effect (5.1 %) of DM2 on COVID-19 death. In addition, CAVDs were responsible for a great part of effect of DM2 duration on COVID-19 death but did not mediate the association between glycaemic control and COVID-19 death.

Our results are in line with two large-scale national studies, in the UK and South Africa, which examined the risk of COVID-19 adverse outcomes among the general population rather than in a population infected with SARS-COV-2 [20,21]. They showed increased risks associated with obesity and most comorbidities, including DM (with a higher

Table 2

Multivariable logistic regression among positive cases, adjusted for sex and age.

Variables	Death	
	OR	95 % CI
Foreigners	0.847	0.524–1.370
Diabetes (no)	1	
Type 1	1.584	0.347–7.232
Type 2	1.699	1.460–1.976
Other	0.981	0.108–8.887
Not defined	0.971	0.510–1.847
Charlson Comorbidity Index (0)	1	
1	1.805	1.499–2.172
2	2.052	1.667–2.526
3	3.040	2.398–3.853
COPD	2.197	1.679–2.874
Ischemic cardiopathy	1.543	1.238–1.924
Dementia	1.329	1.039–1.698
Chronic kidney failure	2.985	2.203–4.045
Cancer	1.534	1.273–1.849
Hypertension	1.794	1.533–2.099
Obesity	3.472	2.212–5.449
Heart failure	1.909	1.544–2.361
Arrhythmias	1.646	1.348–2.010
Vascular diseases	2.018	1.447–2.812
Cerebrovascular disease	1.582	1.290–1.941
Max triglycerides [a] (≤78)	1	
79–109	1.19	0.92–1.55
110–156	1.32	1.03–1.70
≥157	1.80	1.41–2.31
missing	1.01	0.77–1.34
*trend**	1.22	1.13–1.30

*Trend is evaluated using continuous exposure variables, excluding missing values.

[a] Triglycerides were categorized based on quartiles.

COPD, chronic obstructive pulmonary disease.

Table 3

The odds ratio for each level of diabetes and of the main comorbidities among positive cases, logistic models are adjusted for sex and age (excluding diabetes type 1, other or not defined).

Variables	Deaths		
		OR	*95 % CI*
DM2#all cardiovascular diseases			
	OR all CAVDs at DM2 = 0	1.89	1.58–2.25
	OR DM2 at all CAVD = 0	1.73	1.43–2.09
	OR all CAVDs at DM2 = 1	1.49	1.14–1.94
	OR DM2 at all CAVDs = 1	1.37	1.06–1.76
DM2#ischemic cardiopathy			
	OR DM2 at ischemic cardiopathy = 1	1.54	1.00–2.36
DM2#vascular diseases			
	OR DM2 at vascular diseases = 1	0.93	0.46–1.87
DM2#cerebrovascular diseases			
	OR DM2 at CEVDs = 1	1.34	0.88–2.04
DM2#hypertension			
	OR DM2 at hypertension = 1	1.48	1.10–1.99
DM2#heart failure			
	OR DM2 at heart failure = 1	1.33	0.88–2.02
DM2#arrhythmias			
	OR DM2 at arrhythmias = 1	1.47	0.99–2.18
DM2#obesity			
	OR obesity at DM2 = 0	1.44	0.55–3.74
	OR DM2 at obesity = 0	1.60	1.37–1.87
	OR obesity at DM2 = 1	3.86	2.23–6.69
	OR DM2 at obesity = 1	4.30	1.44–12.81
DM2#trigliyceridies (quartiles)			
	OR triglycerides at DM2 = 0	1.21	1.02–1.44
	OR DM2 at triglycerides = 0	1.37	0.99–1.89
	OR triglycerides at DM2 = 1	1.52	1.09–2.11
	OR DM2 at triglycerides = 1	1.71	1.42–2.05

DM2: diabetes type 2.

CAVDs: all cardiovascular diseases.

CEVDs: cerebrovascular diseases.

Table 4

Total, direct and indirect (through CAVDs) effects of the DM2 on COVID-19 death among SARS-CoV-2 positive people.

	OR[a]	95 % CI	OR[b]	95 % CI
NDE	1.591	1.365–1.854	1.497	1.273–1.760
NIE	1.018	1.011–1.024	1.018	1.011–1.024
Total effect	1.619	1.390–1.886	1.523	1.295–1.790

NDE, natural direct effect; NIE, natural indirect effect.

[a] Model adjusted for sex and age (n = 36864).

[b] Model adjusted for sex, age, and triglycerides (n = 22257).

risk associated with elevated HbA1c). A Swedish study with complete population coverage identified DM2 and obesity as major determinants of mortality irrespective of age, sex, and kidney failure [22].

The effect of DM1 on COVID-19 prognosis is not consistent in the literature. While in some population cohort studies both DM1 and DM2 were associated with a higher risk of COVID-19 mortality [23], other populations, with a high prevalence of DM1, did not find a significant effect of DM1 on COVID-19 mortality [24]. Even though it may be due to chance, in our study DM1 was associated with being tested, testing positive and dying from COVID-19 when adjusted for age and sex. In-depth population-based analyses are needed to confirm the role of DM1 and its complications on the risk of severe COVID-19.

Results of our mediation analysis suggest that the presence of CAVDs only slightly mediates the effect of DM2 on COVID-19-related death. The presence of obesity, on the other hand, increased the risk of death in patients with DM2 compared to those without obesity. All this suggests that while obesity and DM2 might have an overlapping effect on death, the presence of CAVDs is more likely to be an additional independent predictor of death. This is the first study to our knowledge that explored possible pathways of this association, so there are no studies with which we could compare our results. However, the general knowledge is that the chronic low-grade inflammatory state ongoing in subjects with obesity and DM2 could intensify the inflammatory response to SARS-CoV-2 infection precipitating the cytokine storm that consequently leads to pneumonia, acute respiratory distress syndrome (ARDS), and multiorgan failure observed in severe COVID-19 cases [25]. Obesity, DM2, and CAVDs commonly coexist in the same individuals, and it is likely that they share the same mechanisms that cause damage and vascular remodelling, increasing the risk of COVID-19 death [26].

In our study, diabetes control (HBA1c over 8 %), DM2 duration, and treatment of DM2 with insulin were significantly associated with being tested for, contracting, and dying from COVID-19. Similarly, a population-based study from the Piedmont region in Italy reported a relative risk of 1.26 in patients with DM2 and HBA1c over 8 % [27]. A large population-based study of all patients diagnosed with DM1 and DM2 in the UK showed that patients with an HbA1c over 7.6 % had a 22 % higher risk of COVID-19-related mortality than patients with HbA1c below 6.5–7 % [28]. An Israeli cohort study found that lowering HbA1c from 8.0 % to 6.0 % was associated with a 29.0 % decreased risk of developing severe COVID-19 [29]. However, a recent *meta*-analysis of 22 studies found no association between HbA1c and risk of COVID-19-related death or severity of COVID-19 [10].

Mediation analysis, based on the suggested associations from the DAG, showed that in CAVDs did not mediate the effect of DM2 control on death, but it mediated a great part of the effect of DM2 duration on death, although it had a small point estimate. This is somewhat expected given that DM2 duration is strongly associated with the risk of macro-vascular events, microvascular events, and all-cause mortality [30]; on the one hand, poor glycaemic control is considered an important

Table 5
Multivariable logistic regression among patients with DM type 2 positive for SARS-CoV-2, adjusted for sex and age.

Variables	Deaths	
	OR	95 % CI
Foreigners	0.84	0.39–1.78
Charlson Comorbidity Index (0)	1	
1	1.47	1.02–2.10
2	2.07	1.44–2.98
3	2.52	1.67–3.80
COPD	1.73	1.07–2.82
Ischemic cardiopathy	1.43	1.00–2.04
Dementia	1.13	0.72–1.77
Chronic kidney failure	2.70	1.76–4.16
Cancer	1.65	1.16–2.34
Hypertension	1.63	1.23–2.15
Obesity[a]	3.29	1.91–5.66
Heart failure	1.63	1.15–2.33
Arrhythmias	1.55	1.09–2.19
Vascular diseases	1.37	0.77–2.44
Cerebrovascular disease	1.37	0.94–2.00
Max triglycerides[b] (⟨118)	1	
118–159	1.26	0.87–1.81
160–224	1.65	1.14–2.38
>224	1.66	1.12–2.46
missing	0.77	0.38–1.53
trend [c]	1.20	1.06–1.36
BMI [b,d] (≤25.9)	1	
25.9–29.1	1.25	0.76–2.05
29.11–32.9	1.03	0.61–1.74
≥ 32.9	2.38	1.42–3.99
Glycated haemoglobin (≤7%)	1	
7–8 %	1.23	0.90–1.69
> 8 %	1.40	0.97–2.02
Diabetic drugs (only diet)	1	
Insulin	2.37	1.56–3.59
Oral hypoglycemics	1.26	0.91–1.75
Insulin + oral hypoglycemics	1.41	0.94–2.13
Duration of diabetes (year)	1.01	0.99–1.02

COPD, chronic obstructive pulmonary disease.

[a] Data on obesity was collected from the hospital discharge database, i.e., among people hospitalized at least once with obesity as an underlying disease.

[b] BMI and triglycerides were categorized based on quartiles.

[c] Trend is evaluated using continuous exposure variables, excluding missing values.

[d] Data on the most recent BMI was retrieved from the diabetes registry.

independent risk factor for a severe course or death of COVID-19 [31]. In fact, poor DM2 control is known to increase the risk of common infections as well as some of the most serious types of infections, such as sepsis and endocarditis seen in patients with DM2. Glycometabolic distress, a result of chronic hyperglycaemic states, detected by raised HbA1c, reduces various protective functions, such as phagocytic functions of monocytes, inhibits effects of complement, and impairs cytokine release [32].

6.1. Strengths and limitations

We acknowledge that our study has limitations. Patients living with DM are more vigilant regarding their adherence to prescribed medications during the COVID-19 pandemic, keeping their glucose level controlled or even improving it [33,34]. They are probably more reserved in social contacts and more responsive to minimal signs of infection meaning that they might be less exposed to the virus and test more often compared to the non-diabetic population. However, they have generally increased predisposition to all infections due to compromised immune systems secondary to the metabolic derangements in obesity and DM and chronic low-grade inflammation [25]. Moreover, being positive for SARS-CoV-2 from PCR does not represent all positive people, especially in the general population [13]. The most recent HbA1c concentration, measured on a single occasion in

patients with prevalent DM2, may not be representative of an effect of longer-term hyperglycaemia. There might also be a misclassification due to placing undiagnosed DM into the non-diabetic population and underestimating the risk of infection if there is a real association. The data about obesity was recovered from the hospital discharge database, i.e., only among people who were hospitalized at least once with obesity as an underlying disease, and thus does not represent obesity of the entire population. Although a DAG was constructed and an attempt was made to disentangle the effect of DM2, CAVDs, and obesity by checking interaction and performing official mediation analysis, this is hardly sufficient to understand this complex interplay or draw conclusions about causal inference. There might also be some unmeasured confounders, such as smoking and other behaviours (Supplementary Figure).

The major strength of this study is the inclusion of the entire population, not only hospitalizations, thus diminishing selection bias present in most observational hospital-based studies. Furthermore, we had the opportunity to use data from a diabetes registry collecting data on duration and control of the disease.

7. Conclusion

We have confirmed the importance of DM2, obesity, and presence of CAVDs as clinical factors associated with COVID-19 infection and death in a large cohort study in the general population of one Italian province. A complex interplay was observed between these three comorbidities on their effects on COVID-19 death; the presence of CAVDs only slightly mediate the effect of DM2 on COVID-19-related death and the effect of DM2 is similar in the presence and absence of CAVDs while obesity amplifies the effect of DM2 on COVID-19-related death. Both DM2 control (expressed as HbA1c) and DM2 duration are important predictors of COVID-19 infection and death, however, only duration of DM2 evinces its effect on death through an increased risk of CAVDs.

Contributions statement

MV, VM and PGR designed the study. VM, MG and AP contributed to the collection and management of the data. MO curated, analysed and visualized the data. OD interpreted the results and wrote the manuscript. MV, VM and PGR supervised the study. AP, MG, MV, FV, VM and PGR reviewed and edited the manuscript. All authors revised the manuscript and approved the final version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data are available upon reasonable request. According to Italian law, anonymized data can only be made publicly available if there is no potential for the re-identification of individuals (https://www.garanteprivacy.it). Thus, the data underlying this study are available on request to researchers who meet the criteria for access to confidential data. In order to obtain data, approval must be obtained from the Area Vasta Emilia Nord (AVEN) Ethics Committee, who would then authorize us to provide aggregated or anonymized data. Data access requests

should be addressed to the Ethics Committee at CEReggioemilia@ausl.
re.it as well as to the authors at the Epidemiology unit of AUSL – IRCCS
of Reggio Emilia at info.*epi*@ausl.re.it, who are the data guardians.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.
org/10.1016/j.diabres.2022.110051.

References

[1] World Health Organization. Coronavirus disease (COVID-19) outbreak,
https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-
covid-19/news/news/2020/01/2019-ncov-outbreak-is-an-emergency-of-
international-concern; 2020 [accessed 02 February 2022].

[2] Centers for disease control and prevention. Underlying Medical Conditions
Associated with Higher Risk for Severe COVID-19: Information for Healthcare
Providers, https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underl
yingconditions.html; 2019 [accessed 02 February 2022].

[3] Kompaniyets L, Pennington AF, Goodman AB, Rosenblum HG, Belay B, Ko JY, et al.
Underlying Medical Conditions and Severe Illness Among 540,667 Adults
Hospitalized With COVID-19, March 2020–March 2021. Prev Chronic Dis 2021;18:
210123. https://doi.org/10.5888/pcd18.210123.

[4] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of
critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-
centered, retrospective, observational study. Lancet Respir Med 2020;8(5):475–81.

[5] Sonmez A, Demirci I, Haymana C, Tasci I, Dagdelen S, Salman S, et al. Clinical
characteristics and outcomes of COVID-19 in patients with type 2 diabetes in
Turkey: A nationwide study (TurCoviDia). J Diabetes 2021;13:585–95. https://doi.
org/10.1111/1753-0407.13171.

[6] Zádori N, Váncsa S, Farkas N, Hegyi P, Erőss B, Szakó L, et al. KETLAK Study
Group. The negative impact of comorbidities on the disease course of COVID-19.
Intensive Care Med 2020;46(9):1784–6.

[7] Corona G, Pizzocaro A, Vena W, Rastrelli G, Semeraro F, Isidori AM, et al. Diabetes
is a most important cause for mortality in COVID-19 hospitalized patients:
Systematic review and meta-analysis. Rev Endocr Metab Disord 2021;22:275–96.
https://doi.org/10.1007/s11154-021-09630-8.

[8] Mahamat-Saleh Y, Fiolet T, Rebeaud ME, Mulot M, Guihur A, El Fatouhi D, et al.
Diabetes, hypertension, body mass index, smoking and COVID-19-related
mortality: a systematic review and meta-analysis of observational studies. BMJ
Open 2021;11(10). https://doi.org/10.1136/bmjopen-2021-052777.

[9] Bradley SA, Banach M, Alvarado N, Smokovski I, Bhaskar SMM. Prevalence and
impact of diabetes in hospitalized COVID-19 patients: A systematic review and
meta-analysis. J Diabetes 2021;14:1–14. https://doi.org/10.1111/1753-
0407.13243.

[10] Schlesinger S, Neuenschwander M, Lang A, Pafili K, Kuss O, Herder C, et al. Risk
phenotypes of diabetes and association with COVID-19 severity and death: a living
systematic review and meta-analysis. Diabetologia 2021;64(7):1480–91.

[11] Zhou Y, Yang Q, Chi J, Dong B, Lv W, Shen L, et al. Comorbidities and the risk of
severe or fatal outcomes associated with coronavirus disease 2019: A systematic
review and meta-analysis. Int J Infect Dis 2020;99:47–56.

[12] Yang J, Zheng Ya, Gou Xi, Pu Ke, Chen Z, Guo Q, et al. Prevalence of comorbidities
and its effects in patients infected with SARS-CoV-2: a systematic review and meta-
analysis. Int J Infect Dis 2020;94:91–5.

[13] Griffith GJ, Morris TT, Tudball MJ, Herbert A, Mancano G, Pike L, et al. Collider
bias undermines our understanding of COVID-19 disease risk and severity. Nat
Commun 2020;11(1). https://doi.org/10.1038/s41467-020-19478-2.

[14] Gangopadhyay KK. Does having diabetes increase chances of contracting COVID-
19 infection? Diabetes Metab Syndr 2020;14:765–6. https://doi.org/10.1016/j.
dsx.2020.05.048.

[15] Mankovsky B, Halushko O. COVID-19 in diabetes patients in Ukraine: lessons for
doctors and patients. Georgian Med News 2020; 4: 105-112. PMID: 32535573.

[16] Ballotari P, Chiatamone Ranieri S, Vicentini M, Caroli S, Gardini A, Rodolfi R, et al.
Building a population-based diabetes register: an Italian experience. Diabetes Res
Clin Pract 2014;103(1):79–87.

[17] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying
prognostic comorbidity in longitudinal studies: development and validation.
J Chronic Dis 1987;40:373–83. https://doi.org/10.1016/0021-9681(87)90171-8.

[18] VanderWeele T. Explanation in Causal Inference. Methods for Mediation and
Interaction. New York: Oxford University Press; 2015.

[19] Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods,
interpretation and bias. Int J Epidemiol 2013;42:1511–9. https://doi.org/10.1093/
ije/dyt127.

[20] Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors
associated with COVID-19-related death using OpenSAFELY. Nature 2020;584
(7821):430–6.

[21] Western Cape Department of Health in collaboration with the National Institute for
Communicable Diseases, South Africa. Risk Factors for Coronavirus Disease 2019
(COVID-19) Death in a Population Cohort Study from the Western Cape Province,
South Africa. Clinical Infectious Diseases 2021; 73: e2005–e2015. https://doi.org/
10.1093/cid/ciab803.

[22] Hergens M-P, Bell M, Haglund P, Sundström J, Lampa E, Nederby-Öhd J, et al. Risk
factors for COVID-19-related death, hospitalization and intensive care: a
population-wide study of all inhabitants in Stockholm. Eur J Epidemiol 2022;37
(2):157–65.

[23] Vangoitsenhoven R, Martens P-J, van Nes F, Moyson C, Nobels F, Van
Crombrugge P, et al. No Evidence of Increased Hospitalization Rate for COVID-19
in Community-Dwelling Patients With Type 1 Diabetes. Diabetes Care 2020;43
(10):e118.

[24] Rawshani A, Kjölhede EA, Rawshani A, Sattar N, Eeg-Olofsson K, Adiels M, et al.
Severe COVID-19 in people with type 1 and type 2 diabetes in Sweden: A
nationwide retrospective cohort study. Lancet Reg Health Eur 2021;4:100105.

[25] Holly JMP, Biernacka K, Maskell N, Perks CM. Obesity, Diabetes and COVID-19: An
Infectious Disease Spreading From the East Collides With the Consequences of an
Unhealthy Western Lifestyle. Front Endocrinol (Lausanne) 2020;11:582870.
https://doi.org/10.3389/fendo.2020.582870.

[26] de Almeida-Pititto B, Dualib PM, Zajdenverg L, Dantas JR, de Souza FD, Rodacki M,
et al. Severity and mortality of COVID 19 in patients with diabetes, hypertension
and cardiovascular disease: a meta-analysis. Diabetol Metab Syndr 2020;12(1).
https://doi.org/10.1186/s13098-020-00586-4.

[27] Giorda CB, Picariello R, Tartaglino B, Nada E, Doglio M, Romeo F, et al. From swab
testing to health outcomes within the T2DM population: Impact of diabetes
background on COVID19 progression. Diabetes Res Clin Pract 2021;180:109021.

[28] Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, et al. Risk factors for
COVID-19-related mortality in people with type 1 and type 2 diabetes in England: A
population-based cohort study. Lancet Diabetes Endocrinol 2020;8(10):823–33.

[29] Hayek S, Ben-Shlomo Y, Balicer R, Byrne K, Katz M, Kepten E, et al. Preinfection
glycaemic control and disease severity among patients with type 2 diabetes and
COVID-19: A retrospective, cohort study. Diabetes Obes Metab 2021;23:
1995–2000. https://doi.org/10.1111/dom.14393.

[30] Zoungas S, Woodward M, Li Q, Cooper ME, Hamet P, Harrap S, et al. Impact of age,
age at diagnosis and duration of diabetes on the risk of macrovascular and
microvascular complications and death in type 2 diabetes. Diabetologia 2014;57
(12):2465–74.

[31] Landstra CP, de Koning EJP. COVID-19 and Diabetes: Understanding the
Interrelationship and Risks for a Severe Course. Front Endocrinol (Lausanne) 2021;
12:649525. https://doi.org/10.3389/fendo.2021.649525.

[32] Pearson-Stuttard J, Blundell S, Harris T, Cook DG, Critchley J. Diabetes and
infection: assessing the association with glycaemic control in population-based
studies. Lancet Diabetes Endocrinol 2016;4:148–58. https://doi.org/10.1016/
S2213-8587(15)00379-4.

[33] Falcetta P, Aragona M, Ciccarone A, Bertolotto A, Campi F, Coppelli A, et al. Impact
of COVID-19 lockdown on glucose control of elderly people with type 2 diabetes in
Italy. Diabetes Res Clin Pract 2021;174. https://doi.org/10.1016/j.
diabres.2021.108750.

[34] Eberle C, Stichling S. Impact of COVID-19 lockdown on glycemic control in
patients with type 1 and type 2 diabetes mellitus: a systematic review. Diabetol
Metab Syndr 2021;13:95. https://doi.org/10.1186/s13098-021-00705-9.