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From swab testing to health outcomes within the T2DM population: Impact of diabetes background on COVID19 progression

Carlo Bruno Giorda [a,*], Roberta Picariello [b], Barbara Tartaglino [c], Elisa Nada [a], Marella Doglio [a], Francesco Romeo [a], Giuseppe Costa [b,d], Roberto Gnavi [b]

[a] Metabolism and Diabetes Unit, ASL TO5, Regione Piemonte, Chieri, Italy
[b] Epidemiology Unit, ASL TO3, Regione Piemonte, Grugliasco, Italy
[c] Chaira Medica Association, Chieri, Italy
[d] Department of Public Health, University of Torino, Torino, Italy

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ABSTRACT

Background: We aimed to study the impact of diabetes background on COVID-19 progression from swab testing to health outcomes in type 2 diabetes (T2DM).
Methods: From the database of the diabetes units of Piedmont-Italy we extracted records of T2DM patients, which were linked with the swab-testing-database, and the database of hospital discharges. Five outcomes (PCR testing, PCR testing positivity, hospitalization, Intensive Care Unit (ICU), death) were evaluated using robust Poisson models.
Results: Among 125,021 T2DM patients, 1882 had a positive PCR test. Of these patients, 49.4% were hospitalized within 30 days, 11.8% were admitted to an ICU, and 27.1% died. Greater probability of death was associated with age, male sex, liver and renal impairment, Hba1c above 8%, and former smoking. Hospitalization and ICU admission were mainly affected by age, male sex, hypertension, and metabolic control. Notably, ICU admissions were reduced in very elderly people. No outcomes were associated with educational level.
Conclusions: Hospitalization and ICU admission are heavily affected by age and local triage policy. A key finding was that men who were > 75 years old and poorly compensated were highly vulnerable patients. Renal and/or hepatic impairment are additional factors. This information may be useful for addressing intervention priorities.

1. Introduction

To date, over 3.7 million cases of coronavirus disease 2019 (COVID-19) and over 114,000 related deaths have been reported in Italy [1]. Northern Italy was the first European area to be affected by the COVID-19 pandemic, and suffered the highest death toll during the so-called "first wave" [2,3].

Almost all studies have shown that poor prognosis is strongly predicted by older age and certain chronic medical conditions, with type 2 diabetes (T2DM), obesity, hypertension, and cardiovascular disease appearing to have the greatest impacts on COVID-19 progression [4,5]. Due to the syndromic nature of diabetes, it is likely that multiple factors affect the association between diabetes and worse prognosis.

* Corresponding author at: Diabetes and Endocrinology Unit, ASL TORINO 5, Via De Maria, 1, 10023 Chieri (To), Italy.
E-mail address: carlogiordaposta@gmail.com (C.B. Giorda).
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Frequent comorbidities and complications, organ damage, and a pro-inflammatory and pro-coagulative state all probably contribute to the risk of worse outcomes [5,6].

Current information has been extracted from in-hospital records and/or administrative data relating to type 2 subjects, but there is scarce information available regarding the history and characteristics of patients with diabetes during the period preceding the occurrence of SARS-CoV-2 infection.

Recent reports suggest the possibility that other factors, beside diabetes, may influence the course of COVID-19 infections starting from the first positive swab testing, including the type of treatment administered [7], the coexistence of chronic pulmonary disease [8], as well as the socioeconomic status of the patient [6]. These gaps in our knowledge warrant investigation on the grounds that physicians need a clear picture of how outcomes may be impacted by previous comorbidities, treatments, and quality of metabolic status [9].

To improve our knowledge of this matter, in the present study we linked the data from a large electronic medical record database (containing 14 years of clinical information from a regional diabetes unit network) with data from the regional hospital discharge database, and information derived from the regional PCR testing database. Our main objective was to analyse this population of T2DM patients, to determine the influence of diabetes background on COVID-19 progression from positive swab testing to several health outcomes.

2. Materials and methods

2.1. Study population and selection criteria

The study population was the cohort of patients cared for by the regional network of 19 diabetes care units in Piedmont (4,400,000 inhabitants in northwest Italy). This large diabetes database (Diabetes database) collects demographic and clinical data recorded by diabetologists during patients' medical examinations. From the Diabetes database, we extracted the data of all patients diagnosed with T2DM who were alive on 21 February 2020, when the first death from COVID-19 was recorded in Italy.

From the start of the COVID-19 epidemic, a surveillance system has been implemented to collect data from all residents undergoing reverse transcriptase-polymerase chain reaction (PCR testing) for SARS-CoV-2. This archive was also pseudo-anonymized and linked to the Diabetes database.

To comply with privacy law, personal patient data are pseudo-anonymized and all the databases are enriched with a unique anonymous identifier, encrypted to protect patient privacy. DBB and data from the COVID-19 surveillance system were thus linked together, and further linked with the regional hospital-discharge database (Hospital discharge database), as well as to the regional registry office. In this way, we were able to enrich the clinical characteristics of the patient records held in the Diabetes database, particularly with regards to comorbidities, and to follow-up each patient in terms of hospitalization and mortality.

Diabetes database

2.2. Outcomes

We considered five separate outcomes that summarize the patients' disease course during the first wave of the epidemic. We obtained information about testing for SARS-CoV-2 (outcome 1) and positive testing (outcome 2) from the surveillance system. To exclude hospital-acquired COVID-19, we excluded patients who tested positive more than three days after hospital admission. Hospitalization within 30 days after testing positive (outcome 3) was determined from record linkage with the Hospital discharge database. Among these patients, we identified those who were admitted to an intensive care unit (ICU) (outcome 4), based on whether the Hospital discharge database showed evidence of admission to an ICU or an ICD9-CM code referring to mechanical ventilation. Finally, we determined 30-day mortality after testing positive (outcome 5) by record linkage with the registry office.

2.3. Clinical characteristics and comorbidities

Based on the data contained in the Diabetes database, enriched with data from the HD, we categorized the patients according to the socio-demographics, clinical characteristics, and comorbidities that were present on 21 February 2021. Age was categorized into 10-year age intervals: <55, 55–64, 65–74, 75–84, and >84 years old. Individual educational level, obtained by record linkage with the last national census, was available for 97.7% of patients, and was classified as high (university/high school), medium (middle school), low (primary school/no formal education), or missing. Smoking history was only available for 60.4% patients, and was classified as current smoker, past smoker, never smoked, or missing. Body-mass index (BMI, weight in kg divided by height in meters squared) was stratified as follows: <25 (normal), 25–29.99 (overweight), ≥30 (obese), or missing. If more than one measurement had been recorded, we utilized the measurement closest to the date of PCR testing.

Patients were classified into four groups of hypoglycaemic treatment: innovative drugs (incretins and/or SGLT-2 inhibitors), insulin, oral antidiabetic drugs, and diet. Patients taking both insulin and oral antidiabetic drugs were assigned to the insulin group. Patients taking both innovative drugs and any other kind of antidiabetic drug were assigned to the "innovative drugs" group. The duration of diabetes was stratified as follows: <2, 2–3.9, 4–6.9, and ≥7 years. HbA1c level was only considered if recorded during 2018 or 2019 (available for 83.1% of patients), and was stratified into four categories: <7%, 7–7.9%, 8–8.9%, and ≥9%. If more than one measurement was recorded, we used the one closest to the date of PCR testing.

Information regarding comorbidities was retrieved either from the Diabetes database, or from hospitalizations that occurred between 2015–2019. Table 1 contains the ICD9-CM codes used to select comorbidities in the hospital-discharge database.

2.4. Statistical analysis

The proportions (i.e. the crude prevalences) of the variables, by each of the five outcomes, were calculated, and the differ-

Table 1 – Sources and criteria used for selecting comorbidity groups.

	From hospital discharge or diabetes database		From diabetes database only
	ICD IX CM code (diagnosis)	ICD IX CM (procedure)	
Cirrhosis/chronic hepatitis	5714–5719		
Neuropathy	2506, 337, 354, 355, 3572, 3574, 3581, 5363, 7135		
Retinopathy	362, 369, 2505	1435	
Coronary heart disease	410–414	0066, 3606, 3607, 361, 362	
Cerebrovascular disease	430–438		
Heart failure	39891, 402, 40401, 40403, 40411, 40413, 40491, 40493, 425, 428, 78,551	3751	
Hypertension	401–405		ATC C02 (antihypertensive treatment), or PAD > 90, PAS > 140
Cancer (in the last two years)	140–239		
Dialysis		3995, 5498	
Diabetic foot/limb amputation/PAD	2507, 4402, 4439, 44381, 44422, 6811, 6826, 6827, 7071, 7854, 73007–73017, 99,674	3925, 3950, 8411–8419, 8663–8666	
Nephropathy	2504, 58181, 58381, 585, 586, 6393		EGfr < 60, albumin excretion rate > 20, albumin/creatinine ratio > 2.5 and male, albumin/creatinine ratio > 3.5 and female, microalbuminuria > 30
COPD	main diagnosis at discharge 490–492, 494, 496 or main diagnosis 51881–51884, 7860, 7862, 7864 and secondary diagnosis 490–492, 494, 496		Exemption from co-payment due to COPD or drug prescriptions with the ATC codes: R03A, R03CC02–R03CC04, R03CK, R03BB01, R03BB02, R03BB04, R03DA01, R03DA04, R03DA05, R03DA08, R03DA11, R03DA49; at least four different prescriptions during 2018–2019 (excluding patients with asthma)

COPD: Chronic obstructive pulmonary disease.
PAD: Phriferal artery disease.

ences in baseline characteristics were evaluated using the X^2 test. To investigate the relationship between the outcomes and the explicative variables, we used robust Poisson models, and the results are presented as prevalence ratios (PRs), which are a better estimate of the relative risk when the prevalence of the outcome is high, with 95% confidence intervals [10]. All analyses were performed using SAS version 9.4.

3. Results

At the beginning of the COVID-19 epidemic, 150,392 T2DM patients were cared for by the network of diabetes clinics of Piedmont. Fig. 1 shows the paths that these patients followed from 21 February 2020 to 31 May 2020, with regards to their clinical history related to COVID-19. Among these patients, 7.5% received PCR testing, and 1.56% were positive for COVID-19 (20.9% of those tested). Within 30 days of a positive test, 49.4% of patients were hospitalized, 11.8% were admitted to an ICU, and 27.1% died. Of these deaths, 67.8% occurred in a hospital. Fig. 1 also shows the numbers and percentages of the population who had at least one HbA1c measurement recorded in 2018 or 2019, which represents the cohort analysed in the current study.

3.1. *Study population and PCR testing*

Table 2 presents the characteristics of the study population, the crude prevalence rates of patients tested for COVID-19 and those who tested positive for the virus. We identified 125,021 T2DM patients who were eligible for the study, of whom, over half were male, 73% were over 65 years old, and 42% had a low education level. Only 11% were current smokers, and 75% were overweight or obese. With regards to their history of diabetes, nearly half of the population had a disease duration exceeding 7 years, 44% were treated with oral hypoglycaemic drugs and a quarter with insulin. Half had normal HbA1c, while 21% had an HbA1c level of >8%. The most frequently reported comorbidity was hypertension (86%), half of the population had some renal impairment (including dialysis), and about 17% had some micro or macro vascular complication.

Testing for COVID-19 was more frequent among women, older people, less educated people, patients who did not take any hypoglycaemic drugs, patients with higher HbA1c levels, and patients of normal weight. Most patients with comorbidities exhibited above average use of PCR testing, ranging from 8% among those with retinopathy to 33% among patients on

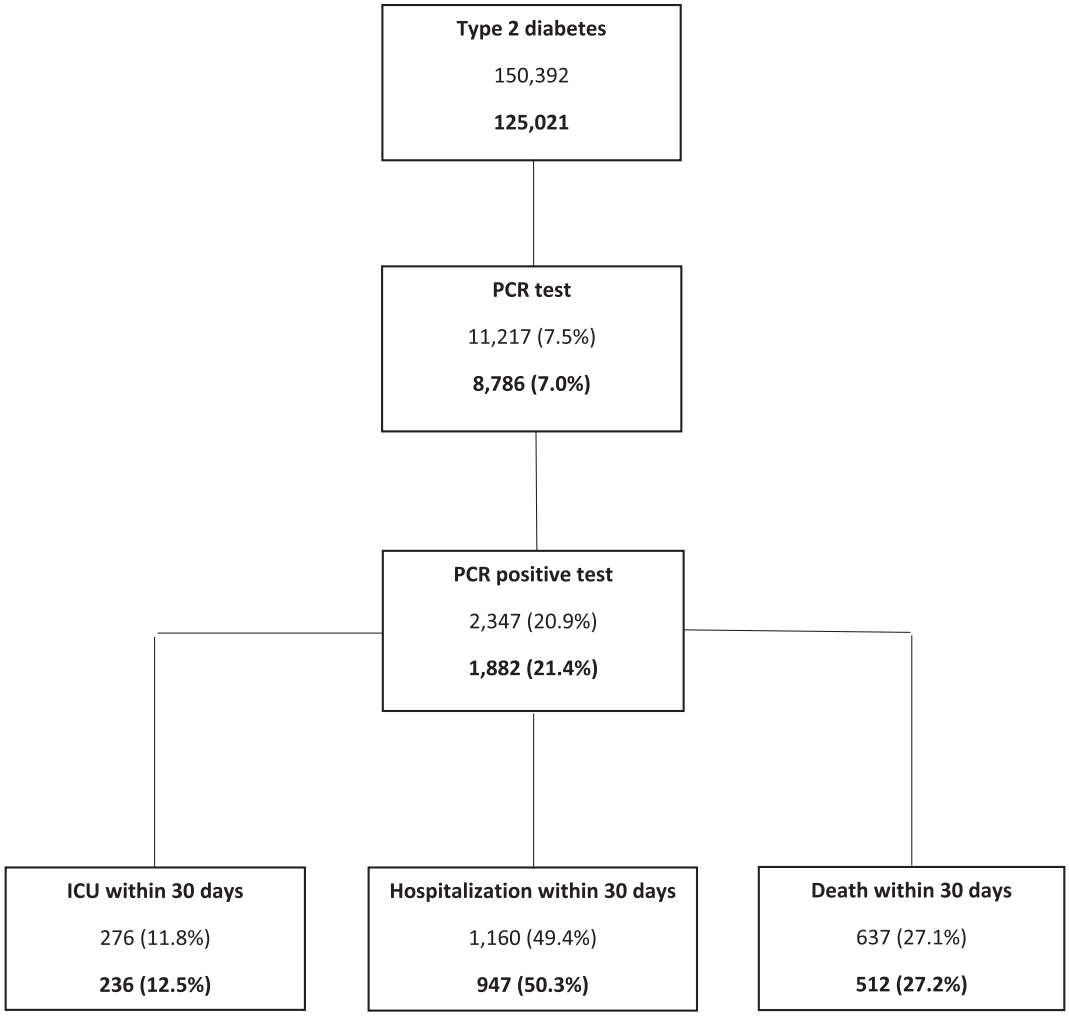


Fig. 1 – Study profile. Bold text indicates study population having at least one HbA1c measurement from 2018 or 2019.

Table 2 – Characteristics of the study population and of patients who received PCR testing.

	T2DM population		PCR tested			Positive (among tested patients)		
	n	%	n	%	p χ^2	n	%	p χ^2
Sex					<0.0001			0.0045
Men	68,760	55.0	4213	6.1		957	22.7	
Women	56,261	45.0	4573	8.1		925	20.2	
Age					<0.0001			<0.0001
<65 years	32,275	26.2	1856	5.7		300	16.2	
65–74 years	39,463	31.6	1842	4.7		404	21.9	
75–84 years	39,399	31.5	2954	7.5		702	23.8	
≥85 years	13,384	10.7	2134	15.9		476	22.3	
Educational level					<0.0001			0.1903
High	21,699	17.4	1356	6.3		285	21.0	
Medium	47,109	37.7	2790	5.9		565	20.3	
Low	53,355	42.7	4468	8.4		990	22.2	
Missing	2858	2.3	172	6.0		42	24.4	
Smoking habit					<0.0001			<0.0001
No	39,243	31.4	2603	6.6		578	22.2	
Yes	13,935	11.2	913	6.6		143	15.7	
Former	22,340	17.9	1372	6.1		329	24.0	
Missing	49,503	39.6	3898	7.9		832	21.3	
Duration of diabetes					0.2093			0.3501
<2 years	8113	6.5	528	6.5		100	18.9	
2–4 years	17,763	14.2	1262	7.1		276	21.9	
4–7 years	38,121	30.5	2727	7.2		605	22.2	
≥7 years	61,024	48.8	4269	7.0		901	21.1	
Antidiabetic therapy					<0.0001			0.8991
new hypoglycaemic drugs	26,175	20.9	1405	5.4		307	21.9	
Insulin	31,203	25.0	3046	9.8		656	21.5	
oral hypoglycaemic drugs	55,081	44.1	2792	5.1		585	21.0	
no drug therapy	12,562	10.1	1543	12.3		334	21.6	
BMI					<0.0001			0.5761
<25 (underweight/normal)	27,689	22.2	2236	8.1		460	20.6	
25–29.99 (overweight)	48,079	38.5	3006	6.3		650	21.6	
≥30 (obese)	46,060	36.8	3057	6.6		659	21.6	
Missing	3193	2.6	487	15.3		113	23.2	
HbA1c					<0.0001			0.7136
<7%	64,360	51.5	4513	7.0		989	21.9	
7–8%	34,613	27.7	2228	6.4		466	20.9	
8–9%	16,150	12.9	1196	7.4		251	21.0	
≥9%	9898	7.9	849	8.6		176	20.7	
Comorbidity groups								
cirrhosis/chronic hepatitis	5182	4.1	339	6.5	0.1623	66	19.5	0.3718
neuropathy	11,711	9.4	993	8.5	<0.0001	202	20.3	0.3793
retinopathy	21,290	17.0	1666	7.8	<0.0001	343	20.6	0.3577
coronary heart disease	22,143	17.7	1958	8.8	<0.0001	409	20.9	0.5153
cerebrovascular disease	20,467	16.4	1957	9.6	<0.0001	461	23.6	0.0090
heart failure	13,818	11.1	1697	12.3	<0.0001	353	20.8	0.4890
hypertension	108,477	86.8	7380	6.8	<0.0001	1588	21.5	0.6110
COPD	7563	6.1	835	11.0	<0.0001	175	21.0	0.7321
cancer (in the last 2 years)	6015	4.8	629	10.5	<0.0001	114	18.1	0.0365
diabetic foot/limb amputation/PAD	16,040	12.8	1628	10.2	<0.0001	337	20.7	0.4326
Dialysis	767	0.6	259	33.8	<0.0001	36	13.9	0.0027
nephropathy	61,603	49.3	5124	8.3	<0.0001	1132	22.1	0.0695
TOTAL	125,021	100	8786	7.0		1882	21.4	

COPD: Chronic obstructive pulmonary disease.
PAD: Peripheral artery disease.
χ^2: Chi-square.

dialysis. The multivariate model (Table 3) revealed that PCR testing was more common among women and people at higher risk of serious consequences in the event of COVID-19. Overall, PCR test positivity only slightly differed among the tested patient groups. Notably, the prevalence of infection increased with age, particularly in patients over 65 years old,

Table 3 – PCR testing: multivariate analysis.

		PCR tested				At least one positive test (among tested patients)			
		PR	95% CI		p value	PR	95% CI		p value
Sex									
	men	1				1			
	women	1.26	1.21	1.32	<0.0001	0.85	0.78	0.93	0.0004
Age									
	<65 years	1				1			
	65–74 years	0.76	0.72	0.82	<0.0001	1.34	1.17	1.55	<0.0001
	75–84 years	1.11	1.04	1.18	0.0017	1.45	1.26	1.67	<0.0001
	≥85 years	2.07	1.93	2.22	<0.0001	1.38	1.19	1.61	<0.0001
Educational level									
	high	1				1			
	medium	0.92	0.87	0.98	0.0121	0.96	0.85	1.09	0.5281
	low	0.98	0.93	1.05	0.6075	0.96	0.84	1.09	0.4927
	missing	0.96	0.82	1.11	0.5684	1.16	0.88	1.54	0.2927
Smoking habit									
	no	1				1			
	yes	1.22	1.13	1.31	<0.0001	0.74	0.62	0.87	0.0005
	former	1.05	0.99	1.12	0.1295	1.02	0.90	1.16	0.7590
	missing	1.18	1.12	1.24	<0.0001	0.94	0.85	1.03	0.1715
BMI									
	<25 (underweight/normal)	1				1			
	25–29.99 (overweight)	0.87	0.83	0.92	<0.0001	1.07	0.96	1.19	0.2312
	≥30 (obese)	0.94	0.89	0.99	0.0193	1.12	1.00	1.25	0.0431
	missing	1.48	1.35	1.63	<0.0001	1.13	0.93	1.38	0.2035
Duration of diabetes									
	<2 years	1				1			
	2–4 years	1.10	0.99	1.21	0.0668	1.14	0.93	1.41	0.2045
	4–7 years	1.12	1.02	1.22	0.0197	1.16	0.95	1.41	0.1434
	≥7 years	1.04	0.95	1.14	0.3708	1.09	0.89	1.33	0.3875
Antidiabetic therapy									
	new hypoglycaemic drugs	1				1			
	insulin	1.49	1.40	1.59	<0.0001	0.99	0.88	1.12	0.8888
	Oral hypoglycaemic drugs	0.98	0.92	1.05	0.6220	0.94	0.83	1.07	0.3563
	no drug therapy	2.00	1.86	2.15	<0.0001	0.95	0.83	1.10	0.5055
HbA1c									
	<7%	1				1			
	7–8%	0.95	0.90	1.00	0.0337	0.95	0.86	1.05	0.2827
	8–9%	0.99	0.93	1.06	0.8477	0.95	0.84	1.08	0.4352
	≥9%	1.11	1.03	1.20	0.0067	0.97	0.83	1.13	0.6813

Table 3 – (Continued)

	PCR tested				At least one positive test (among tested patients)			
	PR	95% CI		p value	PR	95% CI		p value
Comorbidity groups**								
cirrhosis/chronic hepatitis	1.04	0.94	1.16	0.4152	0.91	0.73	1.13	0.3999
neuropathy	0.99	0.92	1.06	0.7465	0.95	0.82	1.09	0.4711
retinopathy	1.01	0.95	1.06	0.8122	0.94	0.84	1.05	0.2598
coronary heart disease	1.07	1.01	1.13	0.0142	0.92	0.83	1.02	0.1264
cerebrovascular disease	1.27	1.21	1.33	<0.0001	1.11	1.01	1.22	0.0369
heart failure	1.37	1.29	1.44	<0.0001	0.94	0.85	1.05	0.3087
hypertension	0.78	0.74	0.83	<0.0001	1.01	0.89	1.14	0.9043
COPD	1.28	1.19	1.37	<0.0001	0.95	0.82	1.09	0.4488
cancer (in the last 2 years)	1.43	1.32	1.54	<0.0001	0.83	0.70	0.99	0.0355
diabetic foot/limb amputation/PAD	1.29	1.21	1.37	<0.0001	0.98	0.87	1.11	0.7603
dialysis	3.32	2.98	3.69	<0.0001	0.65	0.47	0.89	0.0069
nephropathy	1.16	1.11	1.21	<0.0001	1.05	0.96	1.15	0.2851

* Within 30 days after testing positive on PCR test.
** "without comorbidity" is the reference group.
COPD: *Chronic obstructive pulmonary disease*
PAD: *Peripheral artery disease*

and in former smokers or non-smokers. The multivariate model (Table 3) showed that age was the strongest determinant of COVID-19 infection, while positivity rates were lower among women, smokers, and patients on dialysis or with cancer.

3.2. *Hospitalization*

Among the PCR-positive patients, half were admitted to a hospital within 30 days from testing (Table 4). The hospitalization rate was higher among men, patients 65–74 years old, former smokers, overweight or obese patients, patients with high HbA1c levels, and patients treated with new hypoglycaemic drugs. Patients on dialysis had the highest risk of hospitalization. On the other hand, very elderly patients and patients with a low education level had much lower chances of hospital admission. The multivariate model largely confirmed the observations in the univariate analysis (Fig. 2) Age showed a U-shaped pattern, with people of 65–84 years old having a higher risk of hospitalization. Hospitalization risk was also higher for men, former smokers, and patients with poorly controlled glycemia. In the multivariate model, differences according to educational level disappeared, and dialysis was the only comorbidity that remained significantly associated with hospital admission.

3.3. *ICUxxx*

Among the hospitalized patients, one-quarter (12.5% of the positive patients) required ICU admission (Table 4). Similarly to hospitalization, the ICU admission rates were higher in men, former smokers, overweight and obese patients, and patients with high HbA1c levels. ICU admission rates declined sharply among patients over 75 years of age, and were almost negligible among very old patients. Multivariate analysis (Fig. 3) confirmed the increased risk of ICU admission for men, as well as the U-shaped pattern in terms of age, with the elderly, and especially very elderly, people almost excluded from ICU care. Women and insulin-treated patients were less likely to be admitted to an ICU, while former smokers and decompensated patients were at increased risk. As regards comorbidities, only hypertension showed a statistically significant association with ICU admission. Educational level was not associated with ICU admission.

3.4. *Mortality*

Finally, mortality rates were higher among men, elderly patients, poorly educated people, patients with longer disease duration, insulin-treated patients, and in all patients with comorbidity (particularly nephropathy, cancer, heart failure, or coronary artery disease) (Table 4). The multivariate model (Fig. 4) confirmed the causal role of age, while we no longer saw associations with conditions closely related to age, such as educational level, diabetes duration, high BMI, and insulin therapy. Mortality was also significantly increased among men, former smokers, and patients with poor metabolic control. Increased risk of death was also associated with liver disease, cancer, and dialysis or nephropathy.

Table 4 – Outcomes within 30 days after a positive PCR test.

	Hospitalization			ICU			Mortality		
	n	%	p value	n	%	p value	n	%	p value
Sex			<0.0001			<0.0001			<0.0001
Male	580	60.6		171	17.9		305	31.9	
Female	367	39.7		65	7.0		207	22.4	
Age			<0.0001			<0.0001			<0.0001
<65 years	144	48.0		55	18.3		22	7.3	
65–74 years	250	61.9		112	27.7		87	21.5	
75–84 years	368	52.4		62	8.8		225	32.1	
≥85 years	185	38.9		7	1.5		178	37.4	
Educational level			0.0139			<0.0001			0.0054
High	163	57.2		51	17.9		66	23.2	
Medium	297	52.6		85	15.0		135	23.9	
Low	468	47.3		92	9.3		303	30.6	
Missing	19	45.2		8	19.0		8	19.0	
Smoking habit			<0.0001			<0.0001			<0.0001
No	265	45.8		57	9.9		124	21.5	
yes	64	44.8		13	9.1		29	20.3	
Former	201	61.1		69	21.0		116	35.3	
Missing	417	50.1		97	11.7		243	29.2	
Duration of diabetes			0.4555			0.2827			0.1393
<2 years	47	47.0		14	14.0		20	20.0	
2–4 years	148	53.6		38	13.8		65	23.6	
4–7 years	311	51.4		85	14.0		171	28.3	
≥7 years	441	48.9		99	11.0		256	28.4	
Antidiabetic therapy			<0.0001			<0.0001			0.0013
new hypoglycaemic drugs	180	58.6		60	19.5		79	25.7	
Insulin	330	50.3		72	11.0		214	32.6	
oral hypoglycaemic drugs	302	51.6		81	13.8		143	24.4	
no drug therapy	135	40.4		23	6.9		76	22.8	
BMI			0.0283			<0.0001			0.4112
<25 (underweight/normal)	209	45.4		32	7.0		134	29.1	
25–29.99 (overweight)	332	51.1		89	13.7		169	26.0	
≥30 (obese)	355	53.9		108	16.4		173	26.3	
Missing	51	45.1		7	6.2		36	31.9	
HbA1c			0.0002			0.0091			0.1201
<7%	451	45.6		101	10.2		249	25.2	
7–8%	264	56.7		68	14.6		138	29.6	
8–9%	140	55.8		36	14.3		79	31.5	
≥9%	92	52.3		31	17.6		46	26.1	
Comorbidity groups									
cirrhosis/chronic hepatitis	31	47.0	0.5796	10	15.2	0.5143	23	34.8	0.1555
neuropathy	99	49.0	0.6937	25	12.4	0.9408	50	24.8	0.4071
retinopathy	173	50.4	0.9613	42	12.2	0.8553	104	30.3	0.1516
coronary heart disease	233	57.0	0.0024	53	13.0	0.7726	149	36.4	<0.0001
cerebrovascular disease	216	46.9	0.0869	41	8.9	0.0065	141	30.6	0.0605
heart failure	162	45.9	0.0650	36	10.2	0.1405	129	36.5	<0.0001
hypertension	812	51.1	0.1004	212	13.4	0.0136	448	28.2	0.0226
COPD	83	47.4	0.4220	18	10.3	0.3444	58	33.1	0.0638
cancer (in the last 2 years)	59	51.8	0.7518	14	12.3	0.9313	41	36.0	0.0301
diabetic foot/limb amputation/PAD	160	47.5	0.2496	43	12.8	0.8930	104	30.9	0.0961
Dialysis	23	63.9	0.1001	4	11.1	0.2017*	15	41.7	0.0490
Nephropathy	571	50.4	0.8958	130	11.5	0.0893	363	32.1	<0.0001
TOTAL	947	50.3		236	12.5		512	27.2	

* Fisher's exact test.

COPD: Chronic obstructive pulmonary disease.

PAD: Peripheral artery disease.

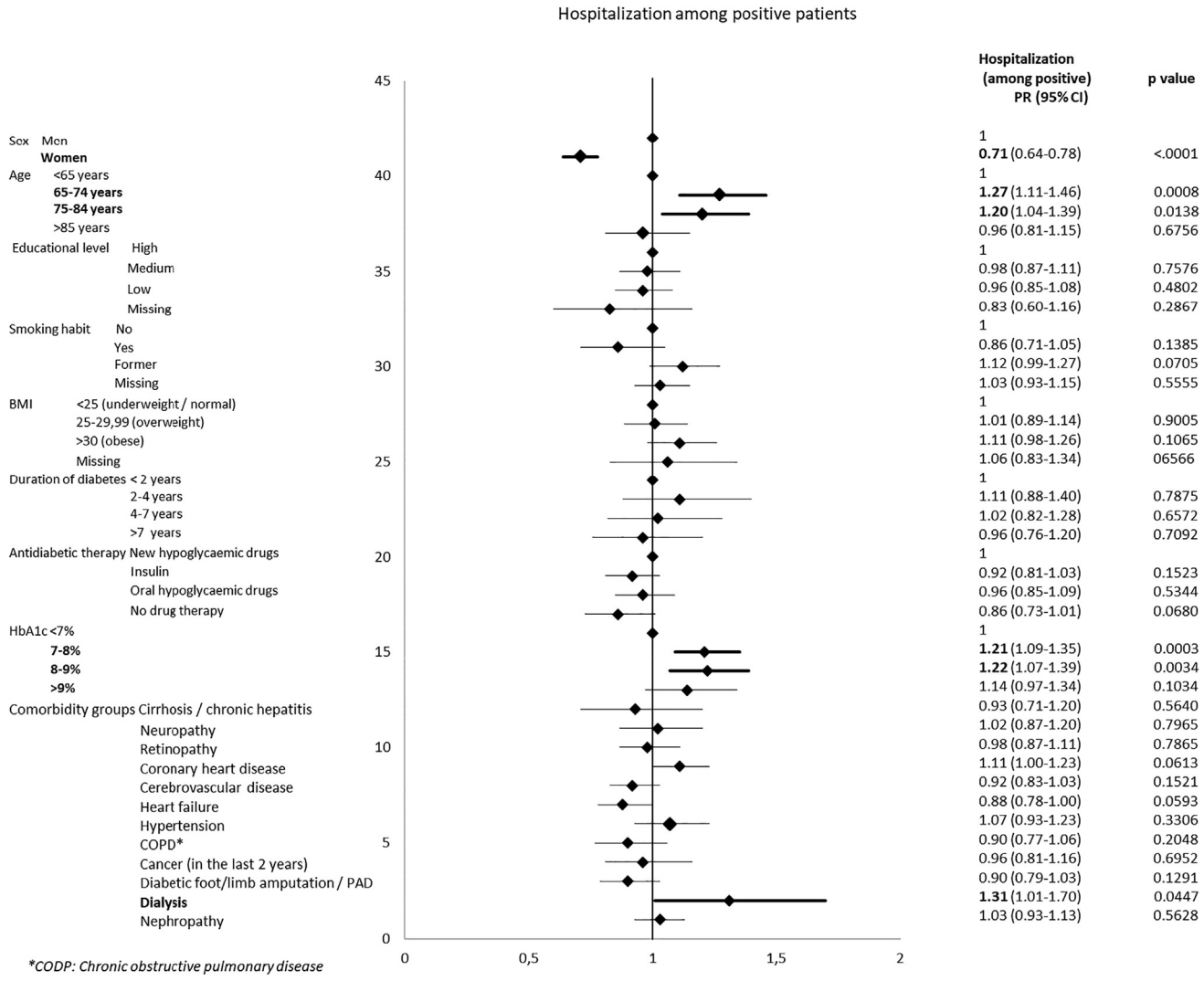


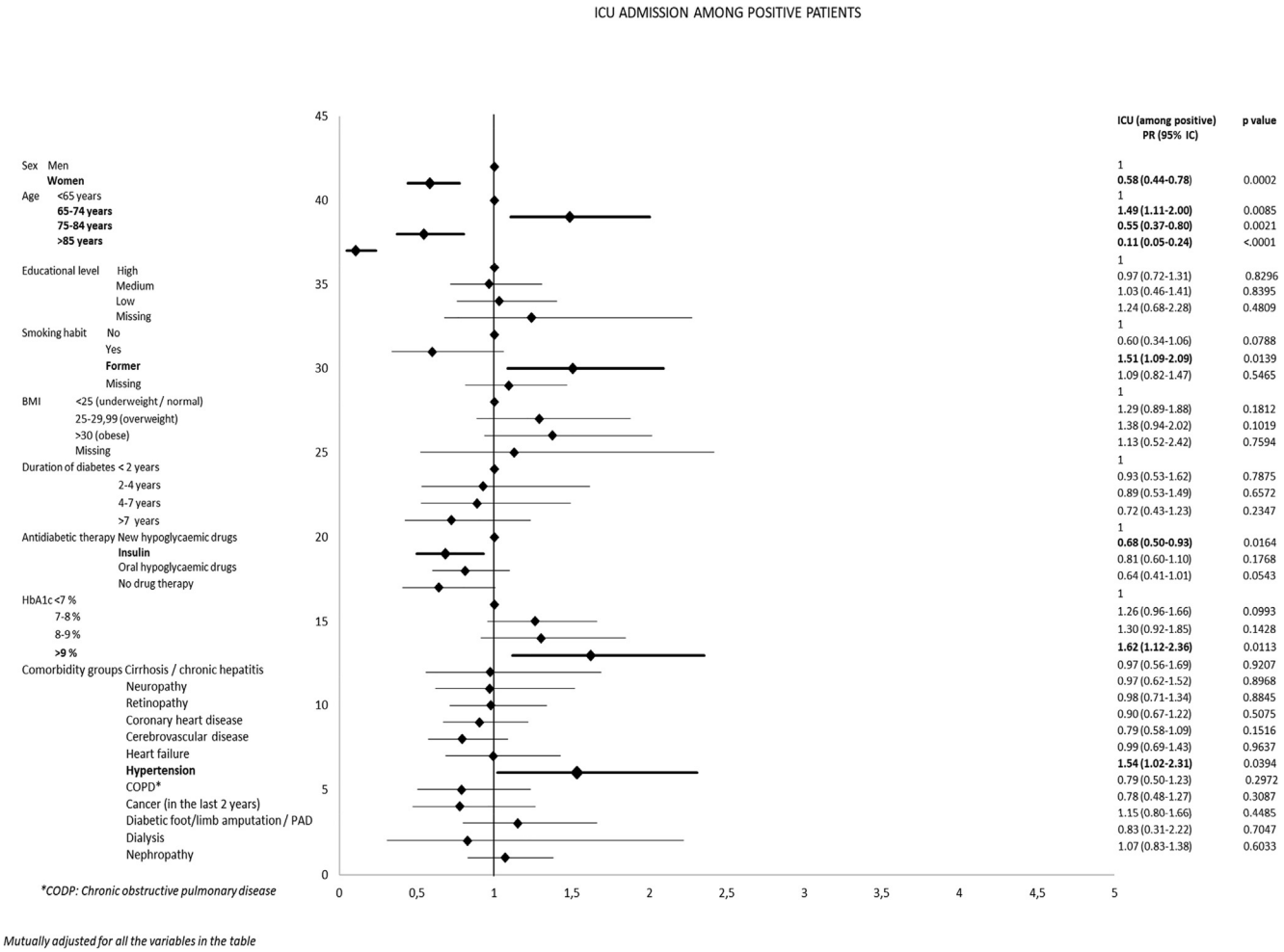
Fig. 2 – Forest plots showing adjusted prevalence ratios for Covid-19 related hospitalization in positive patients with type 2 diabetes in Piedmont (Italy).

4. Discussion

The Piedmont region of Italy was severely impacted by the first wave of the COVID-19 pandemic. Here we found that, compared to previously published data from the general population of this region, DMT2 patients exhibited a PCR positivity rate that was nearly three times higher, and that positive cases showed a very high hospital admission rate, and a doubled 30-day case-fatality rate, despite the fact that the median age of the general population died from COVID-19 in Piedmont was 83 years, the same of the DMT2 patients of the present study [3]. These rates are higher than those reported in other countries [11,12], and indicate that persons with COVID-19 and diabetes have more severe hospital stays, poorer outcomes, and higher resource utilisation [13]. The primary objective of our research was to further examine whether worse health outcomes of COVID-19 infection, starting from a positive swab test, may be associated with specific clinical, social, or anthropometric characteristics, related to the patients' diabetes history and to the extraordinary situation during the first months of the pandemic.

In our analyses, male gender emerged as being associated with everything that marks worse COVID-19 progress, confirming that the predisposition of males to this infection (as seen in the general population) holds true in cases of diabetes. On the other hand, PCR swab testing was more frequent among women, possibly reflecting the typical increased health awareness of women. Interestingly, women were less likely to be hospitalized or admitted to an ICU, and also had a lower probability of death. This may be considered an indirect confirmation of the finding that female sex confers increased protection against the most unfavourable outcomes of COVID-19 [14].

We also found that age was a powerful predictive factor in terms of mortality, with the highest PR found for patients over 75 years old. However elderly people showed the lowest PR for



Mutually adjusted for all the variables in the table

Fig. 3 – Forest plots showing adjusted prevalence ratios for Covid-19 related ICU admission in positive patients with type 2 diabetes in Piedmont (Italy).

admission to an ICU. Likely explanations for this finding are that age-based admission triage was performed during the overwhelming influx of patients with respiratory failure in March and April of 2020, along with the higher mortality prior to ICU admission among the elderly.

In contrast to reports from other countries, such as the UK [6], Sweden [15], or the USA [16], we did not find that educational level was associated with any of the evaluated outcomes in our study population. Additionally, we found that current smoking played a neutral role in outcomes, while previous smoking had a negative impact; similar findings have been previously reported [6,11], whereas other authors [17] have highlighted opposite conclusions. This unexpected finding should not be considered evidence that smoking is protective against COVID-19 infection in patients with diabetes, as some media have reported. It cannot be excluded that the designation "former smoker" acts as a proxy of advanced chronic obstructive lung disease [18].

As expected, the degree of metabolic control affected both hospital and ICU admission, as well as mortality. HbA1c levels of over 7% predisposed patients to more frequent hospital admissions, in agreement with the well-known association between poor glucose control and rate of hospital admissions for all causes beyond the context of COVID-19. It is basic rule of clinical diabetology that high blood glucose levels are a powerful antagonist of immune responses.

In studies that have compared patients with both type 1 and type 2 diabetes versus the general population, BMI is frequently reported as a predictor of SARS-CoV-2 infection and hospitalization [19,20]. Our present results indicated that BMI was somewhat correlated with greater ICU admissions and mortality in univariate analysis, but not in the multivariate models. Notably, our analysis was performed in a population with type 2 diabetes, and these patients are generally overweight, which may make it difficult to assess the specific contribution of BMI [21].

Our results indicated that cancer, cirrhosis, haemodialysis, and nephropathy—all well-defined conditions characterized by immunodeficiency and debilitation—were associated with higher mortality but not more frequent hospitalization or ICU admission. Since one-third of deaths occurred out of the hospital, it cannot be excluded that these patients were denied hospitalization in favour of patients with a higher life expectancy, given the shortage of hospital beds during the peak days of the epidemic. One novelty in our findings is that liver cirrhosis had a negative impact on mortality. From a clinical

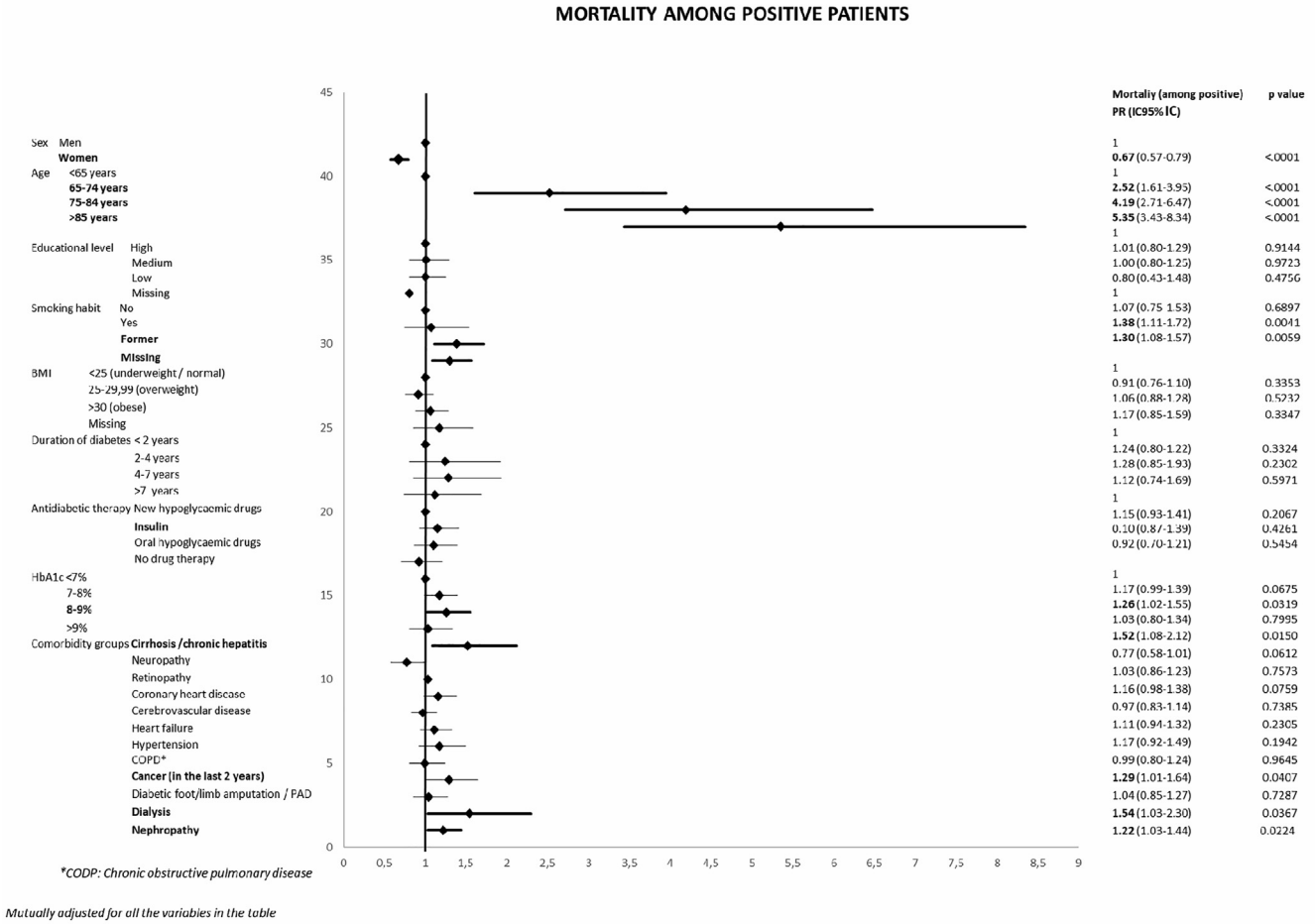


Fig. 4 – Forest plots showing adjusted prevalence ratios for Covid-19 related mortality in positive patients with type 2 diabetes in Piedmont (Italy).

perspective, this is a highly plausible result, given the general debilitation and immunodeficiency of these patients. To our knowledge, there is only one prior report of an association between liver disease and COVID-19 [11].

One strength of our study is that we did not limit the study population to hospitalized patients, which would be a potential source of bias [9], but we rather included people with type 2 diabetes who received care within the regional network of diabetes clinics, and who had a COVID-19 diagnosis confirmed by a positive PCR test. The separation of type 2 diabetes from type 1 diabetes may have provided more accurate results. Furthermore, collecting data from both clinical and administrative sources (Hospital Discharges, national census, and population register) enabled us to describe, and adjust for, some patient socio-demographic and clinical characteristics with a fair degree of accuracy. Likewise, we followed the patients' entire clinical history at the population level (i.e. including out-of-hospital deaths), from the time of PCR testing to the assessed health outcomes, with a rather long-term prognosis. Even if the cause of death was not available from the death certificates, the time window of 30 days from a positive test is commonly used to identify COVID-related deaths [3,22]. Notably, in Piedmont, 95% of deaths occurred within the first 30 days following diagnosis [3]. With regards to hospitalization, 98.7% had a main or secondary diagnosis at discharge, which was certainly related to COVID-19.

Some limitations of this study must also be acknowledged. First, we excluded 17% of patients due to a lack of a recent HbA1c determination. However, the two populations showed very small differences in the prevalence of outcomes (as shown in Fig. 1); thus, it is unlikely that a selection bias was introduced. Secondly, patients receiving care at diabetes clinics are not representative of the full population of diabetes patients. Notably, patients attending clinics are more likely to adhere to clinical guidelines and have more favourable outcomes [23]. This suggests that our results can likely be considered more favourable compared to the health outcomes in the total population with diabetes.

5. Conclusions

Within a population with diabetes, male sex, age of > 75 years, and poor glycemic compensation were factors associated with unfavourable outcomes in COVID-19 patients. Moreover, a patient's risk may be better characterized based on the presence of renal impairment and/or hepatic disease. Patients' educational level did not influence hospitalization or ICU

admission neither mortality. Our present study clearly demonstrated that among patients with type 2 diabetes, older age is a determinant of poor prognosis after infection, powerful enough to warrant special attention. Efforts should be made to direct vaccination priority and use of innovative treatments, such as monoclonal antibodies, towards this category of patients.

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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.

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CBG literature search, study design, data collection, data interpretation, writing.; RP data collection, data analysis; BT literature search, data collection; EN literature search, data collection; MD literature search, data collection, FR literature search, study design, data interpretation; GC data interpretation, writing; RG literature search, study design, data collection, data interpretation, writing.

All authors had full access to the data, approved the final version, and accept the responsibility to submit the study for publication.

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