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SARS-CoV-2 and COVID-19 in diabetes mellitus. Population-based study on ascertained infections, hospital admissions and mortality in an Italian region with ~5 million inhabitants and ~250,000 diabetic people

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Abstract *Background and aims:* Diabetes conveys an increased risk of infectious diseases and related mortality. We investigated risk of ascertained SARS-CoV-2 infection in diabetes subjects from the Veneto Region, Northeastern Italy, as well as the risk of being admitted to hospital or intensive care unit (ICU), or mortality for COVID-19.
Methods and results: Diabetic subjects were identified by linkage of multiple health archives. The rest of the population served as reference. Information on ascertained infection by SARS-CoV-2, admission to hospital, admission to ICU and mortality in the period from February 21 to July 31, 2020 were retrieved from the regional registry of COVID-19. Subjects with ascertained diabetes were 269,830 (55.2% men; median age 72 years). Reference subjects were 4,681,239 (men 48.6%, median age 46 years). Ratios of age- and gender-standardized rates (RR) [95% CI] for ascertained infection, admission to hospital, admission to ICU and disease-related death in diabetic subjects were 1.31 [1.19–1.45], 2.11 [1.83–2.44], 2.45 [1.96–3.07], 1.87 [1.68–2.09], all $p < 0.001$. The highest RR of ascertained infection was observed in diabetic men aged 20–39 years: 1.90 [1.04–3.21]. The highest RR of ICU admission and death were observed in diabetic men aged 40–59 years: 3.47 [2.00–5.70] and 5.54 [2.23–12.1], respectively.
Conclusions: These data, observed in a large population of ~5 million people of whom ~250,000 with diabetes, show that diabetes not only conveys a poorer outcome in COVID-19 but also confers an increased risk of ascertained infection from SARS-CoV-2. Men of young or mature age have the highest relative risks.

Abbreviations: ACG, Adjusted Clinical Group; BMI, Body Mass Index; CI, Confidence Intervals; CoV, Coronarovirus; COVID, Coronarovirus Disease; ICU, Intensive Care Unit; IQR, Interquartile Range; RR, Rate Ratio (or Relative Risk); SARS, Severe Acute Respiratory Syndrome.

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Introduction

The pandemic of COVID-19 is striking the world since early 2020 with more than 150 million people affected and more than 3 million deaths so far [1]. Almost 500 million people have diabetes in the world [2] and they are unfortunately expected to have an increased risk of contracting SARS-CoV-2 and to have a poorer outcome in case of COVID-19. In fact, diabetes conveys an increased risk of infectious diseases [3,4] and mortality for infectious diseases is increased in diabetic subjects [5,6].

Many studies focused on the association between diabetes and COVID-19 and comprehensive reviews were published on this topic [7–9]. Many original papers published so far were based on hospital series [10–16] whereas few were based upon data collected at population level [17–23]. The severity of the disease and related mortality were generally the focus of these papers. It is known from these studies and also from meta-analysis [24,25] that as many as 20–30% of subjects admitted to hospital for COVID-19 have diabetes and that outcomes are poorer when COVID-19 and diabetes coexist in patients admitted to hospital. Less is known as to whether diabetes actually increases the risk of contracting SARS-CoV-2 infection and what is the burden of COVID-19 in terms of hospitalization and death when the entire population is under study. In other words, it is still unknown how diabetes impacts on outcomes when all patients with COVID-19 are examined, not only those admitted to hospital.

In the present study we investigated the risk of ascertained SARS-CoV-2 infection in all subjects with ascertained diabetes living in the Veneto Region, Northeastern Italy, as well as their risk of being admitted to hospital and to intensive care unit (ICU), and their risk of mortality for COVID-19.

Methods

All subjects registered in the Veneto Health Care Population Registry have medical coverage from the Italian National Health System. All of them are allowed to be admitted to public hospitals free of charge, with costs covered by general taxation. After certification by a specialist, subjects with diabetes are exempted to pay a fee (co-payment) for specific medicines, exams and medical visits. Diabetic patients were identified through the Johns Hopkins University Adjusted Clinical Groups System (ACG® v.12.0.1) from multiple routinely available administrative databases, including hospital discharge diagnoses, chronic disease registry for copayment exemptions, antihyperglycemic drug prescriptions [26].

A regional COVID-19 registry was established since the onset of the outbreak where all cases of positivity for SARS-CoV-2 found in rhino-pharyngeal swab, and all admissions to hospital and to ICU for COVID-19 are registered. In this database also data on mortality attributed to the disease are recorded. Ascertainment of positive testing and outcomes is thought to be complete because notification of cases was mandatory in the Veneto Region.

Ascertained SARS-CoV-2 infection (positive testing) and COVID-19 outcomes were assessed in the diabetic and nondiabetic population by linkage of the above registries after an anonymization process that assigned a unique code to personal data of each subjects (e.g., national fiscal code) allowing record-linkage, without any possibility of retrieving the identities of patients. The procedure is standardized and was routinely applied in the Veneto Region for more than 10 years. The risk of mismatching is expected to be minimal and due to possible inconsistencies between personal data in the various health databases and the regional COVID registry. The observational period was from February 21 (first case registered in Veneto) to July 31, 2020. No approval from Ethics Committee was necessary because the study has a retrospective design and is based upon routinely collected anonymized data.

No clinical information was available in the linked databases and therefore no additional covariates (e.g., type of diabetes, HbA1c, etc.) could be added in analyses.

Age and gender-specific rates of COVID-19 related events (SARS-CoV-2 infection, hospitalization, ICU admission and death) were computed separately in diabetic and nondiabetic subjects; the corresponding rate ratios (RR) with 95% exact confidence intervals (95% CI) were calculated for each age and gender stratum by means of the STATA 16 software. To contrast the overall diabetic vs. non-diabetic population, age and gender standardized rates of study outcomes (direct standardization, reference = overall regional population) were obtained; the corresponding rate ratios were computed with approximate 95% CI [27].

Results

In January 2020 the residents of the Veneto Region were 4,951,069. Those with ascertained diabetes were 269,830 (55.2% men; median age 72 years, IQR 17). Subjects without ascertained diabetes were therefore 4,681,239 (men 48.6%, median age 46 years, IQR 35). During the 22 weeks of observation, cases of ascertained SARS-CoV-2 infection, admission to hospital and admission to ICU for COVID-19 and disease-related death were 2107 (0.78%), 1112 (0.41%), 182 (0.07%) and 549 (0.20%), respectively, in subjects with diabetes. The corresponding figures in subjects without diabetes were 17,051 (0.36%), 4389 (0.09%), 621 (0.01%), and 1494 (0.03%), respectively, all $p < 0.001$. Gender- and age-adjusted rate ratios [95% CI] for ascertained infection, admission to hospital, admission to ICU and COVID-19 related death were 1.31 [1.19–1.45], 2.11 [1.83–2.44], 2.45 [1.96–3.07], and 1.87 [1.68–2.09], respectively, in diabetic vs. nondiabetic subjects, all $p < 0.001$ (Table 1).

The highest rate ratio (or relative risk) of ascertained infection was observed in diabetic men aged 20–39 years (+90%), followed by diabetic women aged 70–79 years (+65%). Relative risk was only moderately increased (~20%) in very old diabetic subjects (Table 2).

We observed the highest relative risk of hospital admission for COVID-19 in diabetic men and women aged

Table 1 Cases and rates of SARS-CoV-2 ascertained infections (positive tests) and major outcomes in subjects without and with diabetes in the Veneto Region from February 21 to July 31, 2020. Age = median [IQR]. RR = Ratio of age- and gender standardized rates [95% CI].

Outcome	No diabetes Cases (n) Men (%) Age (yrs)	Crude rate (per 10,000)	Diabetes Cases (n) Men (%) Age (yrs)	Crude rate (per 10,000)	RR
SARS-CoV-2 positive tests	17,051 42 56 [33]	36.4	2107 50 79 [18]	78.1	1.31 [1.19−1.45] p < 0.001
Admission to hospital	4389 55 72 [26]	9.4	1112 60 78 [16]	41.2	2.11 [1.83−2.44] p < 0.001
Admission to ICU	621 76 67 [17]	1.3	182 75 72 [12]	6.7	2.45 [1.96−3.07] p < 0.001
Death	1494 49 85 [12]	3.2	549 56 83 [11]	20.3	1.87 [1.68−2.09] p < 0.001

20−39 years (6-fold higher risk), although with wide confidence intervals. Relative risk in diabetic subjects of mature age was 2 to 3-fold higher, and it was ∼50% higher in very old diabetic subjects (Table 2).

A ∼3-fold increase in relative risk of admission to ICU for COVID-19 was observed in diabetic men and women aged 40−59 years and in diabetic women aged 70−79 and ≥ 80 years. The relative risk was slightly lower in diabetic men and women aged 60−69 years, and definitely lower in diabetic men older than 70 years (Table 3).

The highest relative risks of death for COVID-19 were observed in diabetic men aged 40−59 years (more than 5-fold higher) and in diabetic men and women aged 60−69 years (∼4 fold higher). Relative risk was only ∼50% higher in very old diabetic subjects (Table 3).

Fig. 1 illustrates ascertained infections, admissions to hospital and ICU, and mortality in diabetic subjects stratified according to 3 age groups (<60, 60−79 and ≥ 80 years). Ascertained infections and admissions to hospital were represented with similar proportions (∼45% each) in subjects aged 60−79 and ≥ 80 years, and less frequently (∼10%) in younger individuals. Admissions to ICU were most represented (∼75%) among subjects aged 60−79 years, whereas deaths were more represented (∼65%) in oldest subjects. Nevertheless, ∼35% of deaths occurred in diabetic subjects aged less than 80 yrs.

Discussion

Our results show that diabetes not only conveys a poorer outcome in COVID-19 but also confers an increased risk of ascertained infection from SARS-CoV-2 (positive testing). The latter finding is rather unique in the bulk of literature reporting the association of COVID-19 with diabetes (several hundreds of specific papers available in PubMed).

Information on risk of ascertained SARS-CoV-2 infection and COVID-19 in diabetes, indeed, was generally indirectly inferred from studies comparing the prevalence of diabetes in the general population and in subjects hospitalized for COVID-19 [28−31]. According to these studies, diabetes would not increase the risk of an ascertained infection. Some more direct information was achieved from a registry of ∼20,000 subjects tested for SARS-CoV-2 in Texas, USA, showing that the presence of diabetes without complications (∼5000 subjects tested) increased the risk of nasopharyngeal swab positivity by 40% [20]. On the other hand, in a study carried out in Sicily on ∼2500 subjects undergoing swab testing for suspect disease or strict contact with a person with COVID-19, the presence of diabetes did not increase the risk of positivity [32].

As to hospitalizations and mortality, very few studies are population-based. In the UK Biobank Prospective Study, risk of hospitalization for COVID-19 was investigated in

Table 2 SARS-CoV-2 positivity in rhino-pharyngeal swab and hospital admission in diabetic and nondiabetic subjects by gender and age class, with corresponding rate ratios (RR). *p < 0.05; **p < 0.001.

Classes of age (years)	Population		SARS-CoV-2 Positivity		RR	Hospital admissions		RR
	No diabetes	Diabetes	No diabetes	Diabetes		No diabetes	Diabetes	
Women								
0−19	423,750	770	338	1	1.63 [0.04−9.13]	12	1	45.9 [1.07−310]*
20−39	502,751	5208	1647	15	0.88 [0.49−1.45]	80	5	6.03 [1.91−14.7]*
40−59	763,191	17,726	3583	88	1.06 [0.85−1.31]	385	26	2.91 [1.88−4.33]**
60−69	291,555	22,137	861	96	1.47 [1.18−1.81]**	255	45	2.32 [1.65−3.20]**
70−79	231,259	36,611	822	215	1.65 [1.42−1.92]**	361	111	1.94 [1.56−2.41]**
≥80	192,849	38,537	2599	638	1.23 [1.12−1.34]**	864	254	1.47 [1.27−1.69]**
Men								
0−19	449,919	815	321	1	1.72 [0.04−9.65]	6	0	–
20−39	521,306	2887	1328	14	1.90 [1.04−3.21]*	88	3	6.16 [1.25−18.6]*
40−59	756,376	29,501	2549	143	1.44 [1.21−1.70]**	683	63	2.36 [1.80−3.06]**
60−69	257,673	39,074	1081	226	1.38 [1.19−1.59]**	531	145	1.80 [1.49−2.17]**
70−79	183,379	47,645	857	330	1.48 [1.30−1.68]**	497	224	1.73 [1.47−2.04]**
≥80	107,231	28,919	1065	340	1.18 [1.04−1.34]*	627	235	1.39 [1.19−1.62]**

Table 3 - Admissions in intensive care unit (ICU) and deaths for COVID-19 in diabetic and nondiabetic subjects by gender and age class, with corresponding rate ratios (RR). *p < 0.05; **p < 0.001.

Classes of age (years)	Population		Admissions in ICU		RR	Deaths		RR
	No diabetes	No diabetes	No Diabetes	Diabetes		No Diabetes	Diabetes	
Women								
0–19	423,750	770	0	0	–	0	0	–
20–39	502,751	5208	6	1	16.1 [0.35–133]	1	0	–
40–59	763,191	17,726	45	3	2.87 [0.57–8.94]	22	2	3.91 [0.45–15.92]
60–69	291,555	22,137	38	7	2.43 [0.91–5.50]	21	7	4.39 [1.58–10.72]*
70–79	231,259	36,611	44	23	3.30 [1.90–5.59]**	84	43	3.23 [2.19–4.72]**
≥80	192,849	38,537	18	12	3.34 [1.47–7.32]*	631	191	1.51 [1.28–1.78]**
Men								
0–19	449,919	815	0	0	–	0	0	–
20–39	521,306	2887	9	0	–	0	0	–
40–59	756,376	29,501	133	18	3.47 [2.00–5.70]**	37	8	5.54 [2.23–12.1]*
60–69	257,673	39,074	128	47	2.42 [1.70–3.41] **	68	41	3.98 [2.63–5.94]**
70–79	183,379	47,645	149	53	1.37 [0.98–1.88]	183	93	1.96 [1.51–2.52]**
≥80	107,231	28,919	51	18	1.31 [0.72–2.28]	447	164	1.36 [1.13–1.63]**

~340,000 subjects, 649 cases were registered of which 114 in people with diabetes. In this relatively small study the risk was increased ~2.5-fold in those who were undiagnosed and ~2-fold in those in very poor glycemic control but was not increased in those in good or fair control [22], making intriguing these findings. In a study based upon data collected in 137 service locations in Eastern USA ~300 subjects with diabetes and COVID-19 were compared to ~6000 subjects with COVID-19 but no diabetes. The former had a 4-fold increase in the risk of more severe illness [21]. Figures, however, were relatively small. In a nationwide study carried out in England deaths due to COVID-19 were compared in ~3 million subjects with diabetes and ~58 million subjects without diabetes. The former had a 2 to 3-fold increase in the risk of death for COVID-19 [17]. When this nationwide study more specifically focused on mortality among subjects with diabetes, it was documented an increased risk of death in men vs. women, an increased risk in elderly subjects and a decreased risk in younger diabetic subjects vs. those aged 60–69 years [18]. Another population-based study from England examining data from ~1,5 million diabetic people vs. ~17 million nondiabetic subjects yielded consistent results on COVID-19 mortality [19]. A more recent study carried out on all residents of Scotland reported an increased risk of a combined endpoint of ICU and death in people with diabetes [23]. These four monumental studies, however, did not report any information on hospitalization rates, and did not report risk of death in diabetic vs. nondiabetic persons stratified according to gender in classes of age.

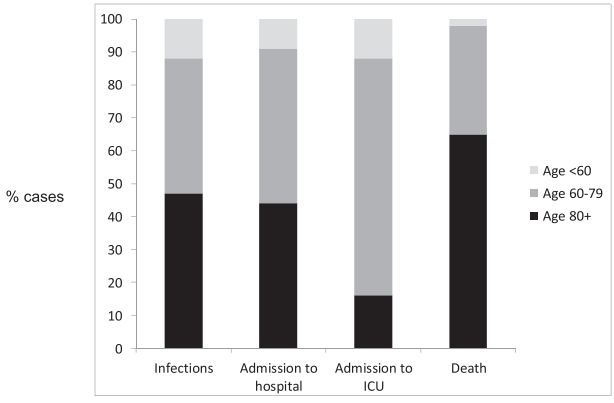

Figure 1 Ascertained SARS-CoV-2 infections, admissions to hospital and intensive care unit (ICU) and mortality in diabetic subjects stratified in age classes.

Overall, there is a paucity of true population-based studies on the association of diabetes with ascertained SARS-CoV-2 infection and hospital admission and death from COVID-19. Our very large population-based study comprehensively reports data on ascertained infections, admission to hospital and mortality. In ~5 million people of whom ~250,000 with diabetes observed for 22 weeks in the early period of pandemic, we registered ~20,000 cases of SARS-CoV-2, ~5000 hospital admissions and ~2000 deaths for COVID-19. Our results point out the need of effective strategies to prevent the disease in diabetes, a goal of particular importance due to the presumed and likely higher risk of contracting SARS-CoV-2 infection and the poorer outcome in subjects with diabetes developing COVID-19. The latter concept is consistent with findings from other studies [7–25,28–31] but our present paper extends the current knowledge, providing gender-specific risks in different age classes. In particular, our findings emphasize the high relative risk of poorer outcome in mature age subjects.

It is a well consolidated notion that most of deaths due to COVID-19 occur in elderly subjects [33]. This is confirmed by our present data, showing that among subjects with diabetes as many as 88% of deaths occurred in those aged ≥70 years. However, it cannot be neglected that 12% of deaths occurred in diabetic subjects younger than 70 years and 1 out of 6 of them occurred in subjects aged 40–59 years. Fortunately, no death occurred in diabetic subjects younger than 40 years. Nevertheless, 42% of admissions to ICU occurred in diabetic subjects younger than 70 years and 1 out of 4 of these admissions due to severe illness occurred in subjects aged 40–59 years. As to overall hospital admissions, it is interesting to remark that

those occurring in people with diabetes represented ~20% of total. This proportion is consistent with those reported by others in hospital series [10–16]. The relative risk of admission to hospital was modestly increased in diabetic men and women aged ≥80 years. The relative risk of admission to ICU was modestly and not significantly increased in men aged ≥70 years. These findings probably reflect the stringent policy of admissions to hospital and ICU in a period of dramatic and overwhelming pressure on emergency rooms and shortage of hospital beds, mainly in ICUs. In this respect, it is impressive the 4 to 5-fold higher relative risk of death for COVID-19 observed in diabetic men aged 40–59 and in diabetic men and women aged 60–69 years.

Strengths of the present study are its population-based approach, the very large number of subjects included in analyses, the evaluation of hospitalized as well as not hospitalized subjects, the completeness of data concerning ascertained SARS-CoV-2 infections and admission to hospital and ICU and deaths due to COVID-19. In fact, all positive nasopharyngeal swabs, all hospital admissions and all deaths were registered since the outbreak of the disease.

Weakness of the study is the identification of diabetic patients through linked electronic health archives, possibly leading to the exclusion of subjects treated with diet only, no exemption from co-payment and no inclusion of diabetes in discharge records. However, previous publications revealed that these misunderstood diabetic subjects are a very small percentage of Italian diabetic population [34]. Moreover, the inclusion of undetected cases of diabetes in the nondiabetic population might slightly reduce rather than amplify the observed differences between subjects with and without diabetes.

Hypothetical greater surveillance and more frequent access to healthcare services, including SARS-CoV-2 search with nasopharyngeal swabs in diabetic subjects, might widen differences between them and subjects without diabetes when assessing ascertained infection rates. However, the search of Coronavirus infection is expected to be carried out in suspected cases independently of pre-existing diseases. As to swabs in strict contacts of confirmed positive subjects, there is no reason to believe they are planned more frequently in diabetic people. Nonetheless, we cannot exclude that in the presence of diabetes this search could be pursued with greater attention and decision. Unfortunately, we don't have information on this aspect. In the Friuli Region, Northeastern Italy, a ~30% greater likelihood of being tested in the presence of diabetes was observed [35]. In this study, swab positivity was higher in diabetic vs. nondiabetic subjects but the difference was not statistically significant, although consistent with our observation in the Veneto Region. On the other hand, personal shielding (e.g., careful use of mask, more frequent hand washing, etc.) might have been more stringent in people with diabetes and this might have somewhat blunted rather inflated the differences between those with and without diabetes. Overall, it is highly improbable that a strong diabetes-related selection bias occurred when comparing positive testing in diabetic and nondiabetic subjects. Nevertheless, many cases of SARS-CoV-2 infection remain undiagnosed because they are asymptomatic. Therefore, the present study is unable to provide data on true infection rates. No bias is expected to occur in searching hospital admissions and deaths because they are mandatory in the Veneto Region.

Availability of molecular testing and completeness of contact tracing increased over time in Italy as in the rest of the world. Since the present data were collected during the first wave of the pandemic in 2020, the higher ascertained infection rate in diabetic persons might reflect a higher risk of developing a symptomatic vs. asymptomatic infection in diabetes and therefore a higher probability to be tested. Studies collecting data during phases of pandemic with more extensive testing might more accurately address the question on whether diabetes increases or not the risk of SARS-CoV-2 infection. In this regard, however, it should be pointed out that in the Veneto Region testing and tracing procedures were implemented soon after the beginning of the outbreak [36]. Accordingly, in the period February–July 2020, as many as 1,228,000 rhino-pharyngeal swabs were examined, with an average of 10,000 per day from middle April to end of July 2020. This figure was not substantially different from that observed during the second wave of pandemic.

The nature of the study, with analysis carried out on administrative databases, does not allow any evaluation of clinical data such as type of diabetes, time since diagnosis, degree of glycemic control, BMI, hypertension, serum lipids, other biomarkers or comorbidities, etc. Nonetheless, in our opinion the main messages from the study, i.e. more ascertained infections, more severe illnesses, more fatalities in people with diabetes, are well supported by available data and therefore conclusions are reliable.

The study was conducted in the Veneto Region of Northeastern Italy, where the National Health System allows each general practitioner to assist ~1500 citizens, the network of public hospitals is quite tight and approximately 30 Diabetes Clinics are operating. Generalizability of data to Countries where healthcare systems are less funded or, on the contrary, are more provided with human and material resources is not possible. Nonetheless, our data, are reasonably well representative of the scenario in affluent Western Countries.

In conclusion, to the best of our knowledge, this is the first large population-based study focusing on incidence of ascertained SARS-CoV-2 infection and not solely on outcome during COVID-19 in diabetes. Although with the limitations intrinsically implicit in a study where SARS-CoV-2 was not searched in a random sample from the population, our data show that the presence of diabetes conveys an increased risk of ascertained infection. The present study, which included also not hospitalized subjects, points out that the outcome during COVID-19 is poorer in subjects with diabetes, emphasizing that the relative risk of death compared to age- and gender-matched subjects is particularly high in patients of mature age (less than 70 years). Therefore, effective strategies

aimed to prevent SARS-CoV-2 infection should be implemented in people with diabetes. Yet, a greater attention should be paid when COVID-19 occurs in nonelderly individuals with diabetes. In these subjects a more precocious hospitalization might prevent the progression of the disease to an irreversible and fatal condition.

Access to data

UF, ES have full access to all regional registries and their data.
EB has the final responsibility for the decision to submit for publication.

Contribution from authors

EB conceived the study and the analyses plan. GZ, UF and ES reviewed the analyses plan. UF and ES searched the data and made statistical analyses. EB drafted the manuscript. All authors contributed to interpretation of data and revision of the manuscript. All authors approved the final version of the manuscript.

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Declaration of competing interest

None of the authors have any interest to disclose pertaining to this study.

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