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Outcome of COVID-19 infection in people with diabetes mellitus or obesity in the primary care setting in Catalonia, Spain: A retrospective cohort study of the initial three waves

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ABSTRACT

Aim: We estimate the incidence and risk factors for fatal and non-fatal events among the COVID-19 infected subjects based on the presence of obesity or diabetes during the initial three epidemiological waves in our region.
Methods: This was a retrospective cohort study. A primary care database was used to identify persons with COVID-19. We stratified for subjects who either had diabetes mellitus or obesity. The follow-up period for study events was up to 90 days from inclusion.
Results: In total, 1238,710 subjects were analysed. Subjects with diabetes mellitus or obesity were older and had a worse comorbidity profile compared with groups without these conditions. Fatal events were more frequent among people with diabetes and during the first wave. In the second and third waves, the number of study events decreased. Diabetes was a risk factor for fatal events in all models, while obesity was only in the model adjusted for age, sex, diabetes and COVID-19 waves. HIV, cancer, or autoimmune diseases were risk factors for mortality among subjects with COVID-19 in the fully-adjusted model.
Conclusions: Diabetes was an independent risk factor for mortality among people with COVID-19. The number of fatal events decreased during the second and third waves in our region, both in those with diabetes or obesity.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has evolved into a world pandemic in the last few years, accumulating over six million deaths to date [1,2]. During this pandemic, preliminary data indicated that obesity and diabetes mellitus may contribute independently and proportionally to a higher incidence of complications and a worse COVID-19 prognosis. These conditions were observed to be the most common comorbidities and predictors of critical illness in hospitalised patients [3]. Diabetes and obesity are complex chronic diseases that generate high morbidity and mortality in general. They are also predisposing factors for other cardiovascular and renal diseases

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and/or the reason for worse health evolution and prognosis.

When it comes to diabetes, it is a frequent major comorbidity and risk factor for poor prognosis in COVID-19 patients [4,5]. The risk of intensive care unit (ICU) admission and the poor short-term outcome were higher in COVID-19 patients with diabetes [6], with twice the risk of COVID-19 mortality as non-diabetics [7]. Furthermore, patients with diabetes may experience prolonged symptoms or develop post-discharge complications such as post-COVID-19 syndrome [8]. This relationship between diabetes mellitus and COVID-19 infection may be bidirectional, as some studies have observed that diabetes may not only be a cause of poor COVID-19 prognosis, but COVID-19 may induce worsening hyperglycaemia and insulin resistance in return [8].

Similarly, body mass index (BMI) and obesity have been independently associated with the COVID-19 severity in different studies [4], and many reports to date have associated obesity with a higher COVID-19 mortality rate [9]. Obese diabetic patients have also been reported to have a worse outcome after COVID-19 infection [3,4,10].

Several mechanisms could explain the association between COVID-19 and diabetes or obesity, one of them being the chronic low-grade pro-inflammatory status present in diabetic and obese patients [5]. These conditions, in addition to the SARS-CoV-2 infection, could lead to an over-production of pro-inflammatory cytokines (TNFα, IL-6, IL-1β, and CXC-chemokine ligand) [10] that would result in a worse cytokine storm, mediating a progression toward a catastrophic inflammatory response and organ failure [11–15]. In addition, diabetic patients suffering from COVID-19 infection have been observed to be more susceptible to the destructive effect of this cytokine storm than non-diabetic subjects [16]. All in all, diabetes and obesity have been seen to entail cardiovascular, respiratory, metabolic and immune dysfunctions that induce a pro-inflammatory, prothrombotic state and reduced respiratory capacity. This, in turn, may contribute to developing severe COVID-19 infection in these patients [17].

Previously, we published findings on the high burden associated with diabetes mellitus (DM) in patients hospitalised with COVID-19 infection, particularly among men, the elderly, and those with impaired kidney function [18]. However, the study was limited to in-hospital subjects admitted for COVID-19 and DM during the first wave. In the current study, we used a large population primary healthcare database to estimate the incidence and risk factors for fatal and non-fatal events among the COVID-19 infected subjects based on the presence of obesity or diabetes during the initial three epidemiological waves in our region.

2. Methods

2.1. Settings

We used the SIDIAP (Sistema de Información para el desarrollo de la Investigación en Atención Primaria) primary care database to perform a retrospective cohort analysis from February 1st 2020 until June 30th 2021. This population database is a well-validated secondary data source for performing epidemiological and pharmacoepidemiological studies from primary care settings in Catalonia (Spain). Besides standard datasets of variables related to different clinical variables (health problems, explorations, laboratory parameters, medication prescription/dispensations) collected routinely from pseudo-anonymised patients' electronic records, the database was especially updated with specific variables related to the COVID-19 pandemic (diagnostic tests, procedures) in order to help investigators perform specific epidemiological studies related to this topic [19].

2.2. Selection criteria

During the observational period, we included all individuals in the database with a positive COVID-19 diagnostic test or diagnostic code (ICD-10: B34.2; B97.2; B97.21; B97.29; J12.81; J12.89; U07.1; Z20.828; J12.89; J20.8; J22; J40; J80; J98.8). Only the first infection with COVID-19 was considered for inclusion. Subjects with less than one year of medical history records in the database, those with diagnostic codes for COVID-19 before the observational period starting date, and those under 18 years of age were excluded from the analysis.

2.3. Study variables

At inclusion, subjects with DM were identified in the database using an algorithm as a diagnostic code for type 2 diabetes or type 1 diabetes (ICD-10: E10, E11 and subcodes) and/or the presence of antidiabetic treatment and/or previous registry of glycosylated haemoglobin (HbA1c) value $\geq$ 6.5% (48 mmol/mol). Subjects with obesity were identified by diagnostic code (ICD-10:E66 and sub-codes) and presence of body mass index (BMI) registry $>$ 30 kg/m^2. The relevant comorbidities such as hypertension and hyperlipidaemia were identified by the ICD-10 diagnostic code and treatment, while other comorbidities such as cardiovascular diseases, heart failure, cerebrovascular diseases, ischemic heart disease, peripheral artery disease, chronic obstructive pulmonary disease-COPD, human immunodeficiency virus-HIV, autoimmune disease, and cancer were only identified by the diagnostic code. Chronic kidney disease was defined by the diagnostic code and/or estimated glomerular filtration rate (eGFR) $<$ 60 ml/min / 1.73 m^2 calculated using the CKD-EPI equation and/or a ratio of albumin/creatinine (CAC) in urine $\geq$ 30 mg/g. We also collected data related to laboratory parameters (glycaemic, renal, lipid, hepatic profile), physical exploratory data (systolic/diastolic blood pressure, BMI), and relevant concomitant drugs.

During the 90-day follow-up period after inclusion, we collected data on fatal (mortality) and non-fatal events (mechanical ventilation, cardiovascular complications, neurological complications, respiratory complications, thrombotic complications, and days of hospitalization). These events were defined by diagnostic codes and hospital discharge information.

2.4. Statistical methods

Descriptive analyses were performed on all clinically important variables at the time of inclusion and for study events during the observational period. The qualitative variables were described by numbers and percentages, while mean values and standard deviation described the quantitative variables. We calculated the incidence of study events during the 90-day follow-up period from inclusion. The events were calculated for three different COVID-19 epidemiologic waves defined as the first wave (01/02/2020–30/06/2020), second wave (01/7/2020–31/12/2020) and third wave (01/01/2021–31/03/2021). Different multivariable logistic models were performed for the clinically relevant variables. The occurrence of death was defined as the dependent variable in the fatal events model. In contrast, in the non-fatal events model, the dependent variable was defined as a combination of cardiovascular and/or respiratory and/or neurological complications during the 90-day follow-up period. On the other hand, we considered the presence of different clinical characteristics at inclusion as independent variables (age, sex, comorbidities, laboratory parameters, clinical variables, and COVID-19 waves). The statistical analyses were performed using R3.6.1 software (https://www.r-project.org/).

2.5. Ethics committee approval

The IDIAP Jordi Gol Ethics Committee approved the study, protocol approval number 20/077-PCV, on 13/04/2020.

3. Results

From the initial population of 1,450,335 people with a positive COVID-19 diagnostic test or diagnostic code in the database, a total of 1,238,710 participants met all study selection criteria and were included

in the study. Fig. 1 shows the study flowchart.

3.1. Subjects' characteristics

Table 1 summarises the baseline characteristics of subjects in the cohort and different groups. Mean age of the overall cohort was 47.3 (± 18.5) years, the majority females (54.8%), and 15.0% of users came from high deprivation areas. The subgroup of subjects with diabetes was much older (on average 19.6 years older) than those without diabetes. People with diabetes had a poorer comorbidity profile, especially for the higher frequency of hypertension, hyperlipidaemia, obesity, cardiovascular disease, chronic kidney disease, and the presence of any autoimmune disease, compared with the non-DM group. Regarding laboratory parameters, non-DM subjects had a worse lipid profile (LDL cholesterol and total cholesterol); however, mean triglyceride levels were higher in the DM group. Also, glomerular filtration was lower in the DM group.

The analysis by obesity status showed that obese subjects were 10.3 years older and were more frequently female than those without obesity. Of the obese subjects, 18.6% came from high deprivation areas, the highest percentage compared with the other groups. Regarding comorbidities, subjects with obesity had a poorer comorbidity profile than those without. Hypertension was the most prevalent comorbidity (48.0%), followed by hyperlipidaemia (31.2%) and diabetes (23.3%). Twelve percent had a cardiovascular disease, and 8.2% had some type of cancer.

3.2. Fatal and non-fatal events

During the 90-day follow-up period, we observed the highest percentages of mortality events among people with DM and obesity during the first wave (7.0% and 3.6%, respectively). Fatal events decreased drastically during the second and third COVID-19 waves. A decrease was also observed for non-fatal events during the three waves. Of the DM subjects, 10.6% were hospitalised during the first wave, while this percentage was only 1.7% during the third wave. Among the DM subjects, cardiovascular and neurological complications were mostly present as events during the follow-up periods in all three COVID-19 waves. A higher incidence of thrombotic complications was observed among obese subjects during the first and third waves compared with other groups. Table 2 summarises events among the different groups' participants and waves during the 90-day follow-up period.

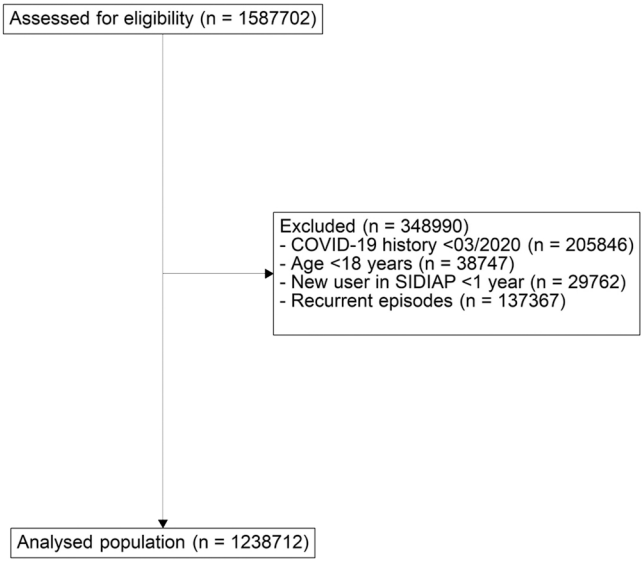

Fig. 1. Study flowchart.

3.3. Factors associated with fatal and non-fatal events

Table 3 shows different model associations between risk factors and mortality events during the 90 days. In the unadjusted analysis, positive associations (OR>1) were observed for most variables and mortality events. The only negative association was observed for being male, and subjects from the second and third COVID-19 waves compared with the first wave. In the multivariable analyses, diabetes mellitus remained a risk factor for death in all models, while obesity was a risk factor associated with this fatal event only in the model adjusted for age, sex, and COVID-19 waves. Subjects with HIV had a four-fold probability of mortality during the 90-day follow-up period in the fully adjusted model.

Regarding the risk factors related to non-fatal events, male sex was negatively associated with these events in both adjusted and unadjusted models. Compared with the fatal events model, hyperlipidemia at inclusion was positively associated with non-fatal events in both unadjusted and fully adjusted models. The presence of diabetes or obesity remained as risks factors for cardiovascular and/or respiratory and/or neurological complications during the 90-day follow-up period in all models. Table 4 summarizes the odds ratios for non-fatal events at a 90-day follow-up period.

4. Discussion

This retrospective cohort study of the primary healthcare database from Catalonia (Spain) revealed a high incidence of a fatal outcome among people with diabetes and obesity during the first wave in our region. Mortality decreased during the second and third waves. The same decreasing trend was observed for non-fatal events (cardiovascular, neurological, thrombotic, or respiratory complications) at short-term follow-up (90 days) during the three COVID-19 waves.

Globally, a total of 6318,093 people are estimated to have died from COVID-19 since the pandemic's beginning [20]. The prevalence of diabetes varies among studies; in previously published meta-analyses, DM prevalence ranged from 8% to 21% of cases with COVID-19 [21, 22]. Regarding the prevalence of obesity observed in other international studies, depending on the country and type of registry, these percentages ranged from 15.4% in France [23] to 48.3% in the North American COVID-NET registry [24]. Comparing our data with those of other studies using the same database, for the period between 15 March and 24 April 2020, the prevalence of diabetes and obesity was similar to our study [25]. Another published study using the same database, which included a total of 311,542 participants with COVID-19 between March 2020 and 30 June 2020, found a slightly higher prevalence of diabetes (10.0%) and obesity (50.5%) compared with our study [26]. These differences could be due to the definition of obesity, the differences in the study population, and the different timeframes for considering the obesity cases. We included obese subjects defined as those with obesity diagnostic codes or recent BMI measures over 30 kg/m^2 at any time and closest to the index date.

The current study cohort had clinical characteristics similar to previously reported analyses with the same database for age, BMI, socioeconomic index (deprivation index), and comorbidities [25,26]. The worst comorbidity profile among DM subjects observed in our cohort is in line with previously reported studies [27]. On the other hand, for subjects with obesity, numerous comorbidities were present, such as hypertension, dyslipidaemia, type 2 diabetes, and chronic kidney or liver disease, which are risk factors for COVID-19 [28]. At inclusion, 22.2% of DM subjects and 18.7% of subjects with obesity had a concomitant active diagnosis of autoimmune disease.

Since the beginning of the pandemic, different meta-analyses on risk factors for COVID-19 outcomes were reported. Advanced age, male sex, and having pre-existing cardiovascular diseases were associated with worse COVID-19 outcomes [29–32]. Pre-existing diabetes and obesity are risk factors for the severity outcomes associated with coronavirus. In

Table 1
Baseline characteristics.

	All N = 1238,710	Diabetes		Obesity	
		Without N = 1120,711	With N = 117,999	Without N = 968,156	With N = 270,554
Age, mean, SD	47.3 (18.5)	45.4 (17.7)	65.0 (17.0)	45.0 (17.7)	55.3 (19.0)
Sex (female), n (%)	678,338 (54.8)	613,593 (54.8)	64,745 (54.9)	516,917 (53.4)	161,421 (59.7)
MEDEA, n (%)					
Lowest living area deprivation	182,993 (14.8)	169,378 (15.1)	13,615 (11.5)	154,354 (15.9)	28,639 (10.6)
Highest living area deprivation	185,473 (15.0)	164,983 (14.7)	20,490 (17.4)	135,148 (14.0)	50,325 (18.6)
Clinical variables (mean, SD)					
BMI	28.4 (5.65)	27.8 (5.54)	30.2 (5.61)	24.7 (3.06)	32.9 (4.76)
Systolic blood pressure	76.4 (10.6)	76.5 (10.6)	75.9 (10.5)	126 (15.9)	131 (15.6)
Diastolic blood pressure	128 (16.0)	127 (15.9)	132 (15.8)	75.6 (10.5)	77.9 (10.6)
Total cholesterol	195 (42.7)	198 (42.1)	183 (43.3)	195 (42.6)	194 (42.8)
LDL cholesterol	119 (36.9)	123 (36.2)	104 (35.5)	121 (37.0)	116 (36.6)
Triglycerides	133 (89.1)	124 (77.4)	162 (115)	123 (81.9)	150 (97.7)
Glomerular filtration	80.8 (15.5)	82.5 (13.6)	73.5 (20.1)	82.2 (14.2)	77.8 (17.5)
HbA1c	6.49 (1.37)	5.55 (0.40)	7.15 (1.41)	6.31 (1.32)	6.66 (1.39)
ALT	22.7 (24.4)	22.4 (23.3)	24.3 (28.7)	26.1 (29.6)	27.2 (30.2)
AST	26.5 (29.8)	26.2 (27.8)	27.5 (36.4)	21.8 (23.7)	24.7 (25.8)
GGT	36.6 (67.0)	33.7 (58.7)	49.1 (93.4)	33.3 (63.4)	43.3 (73.4)
Comorbidities, n (%)					
Hypertension	254,769 (20.6)	180,118 (16.1)	74,651 (63.3)	149,321 (15.4)	129,938 (48.0)
Hyperlipidaemia	209,477 (16.9)	148,494 (13.2)	60,983 (51.7)	125,039 (12.9)	84,438 (31.2)
Obesity	270,554 (21.8)	207,536 (18.5)	63,018 (53.4)	0 (0.00)	270,554 (100)
Diabetes mellitus	117,999 (9.53)	0 (0.00)	117,999 (100)	54,981 (5.68)	63,018 (23.3)
Cardiovascular diseases	74,466 (6.01)	46,282 (4.13)	28,184 (23.9)	42,112 (4.35)	32,354 (12.0)
Heart failure	30,794 (2.49)	17,316 (1.55)	13,478 (11.4)	13,872 (1.43)	16,922 (6.25)
Cerebrovascular diseases	37,819 (3.05)	24,571 (2.19)	13,248 (11.2)	22,422 (2.32)	15,397 (5.69)
Ischemic heart disease	35,282 (2.85)	20,207 (1.80)	15,075 (12.8)	18,507 (1.91)	16,775 (6.20)
Peripheral artery disease	14,645 (1.18)	7460 (0.67)	7185 (6.09)	8359 (0.86)	6286 (2.32)
Chronic kidney disease	63,180 (5.10)	50,490 (4.51)	33,602 (28.5)	45,106 (4.66)	38,986 (14.4)
COPD	39,531 (3.19)	26,913 (2.40)	12,618 (10.7)	72,701 (7.51)	29,763 (11.0)
HIV	2561 (0.21)	2287 (0.20)	274 (0.23)	2171 (0.22)	390 (0.14)
Autoimmune disease	158,101 (12.8)	131,280 (11.7)	26,821 (22.7)	107,415 (11.1)	50,686 (18.7)
Cancer	64,584 (5.21)	49,261 (4.40)	15,323 (13.0)	42,325 (4.37)	22,259 (8.23)

ALT: Alanine transaminase AST: Aspartate transaminase; BMI: body mass index; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease, GGT: Gamma-glutamyl transferase; HIV: human immunodeficiency virus; HbA1c: glycosylated haemoglobin; LDL: Low-density lipoprotein; SD: standard deviation

Table 2
Events at 90-day follow-up period during the three waves.

	First wave			Second wave			Third wave		
Events, n (%)	All N = 244,165	DM N = 29,935	Obesity N = 61,336	All N = 704,080	DM N = 61,411	Obesity N = 148,294	All N = 288,060	DM N = 26,414	Obesity N = 60,410
Overall mortality	6032 (2.47)	2107 (7.04)	2220 (3.62)	3665 (0.52)	1338 (2.18)	1445 (0.97)	449 (0.16)	165 (0.62)	171 (0.28)
Hospital mortality	1382 (0.57)	543 (1.81)	578 (0.94)	918 (0.13)	353 (0.57)	405 (0.27)	111 (0.04)	37 (0.14)	46 (0.08)
Hospital admission	11,397 (4.67)	3169 (10.6)	4920 (8.02)	12,537 (1.78)	3625 (5.90)	5686 (3.83)	1487 (0.52)	467 (1.77)	663 (1.10)
Mechanical ventilation	541 (0.22)	210 (0.70)	283 (0.46)	588 (0.08)	222 (0.36)	314 (0.21)	43 (0.01)	11 (0.04)	22 (0.04)
ICU	865 (0.35)	265 (0.89)	414 (0.67)	1078 (0.15)	351 (0.57)	489 (0.33)	109 (0.04)	30 (0.11)	44 (0.07)
Cardiovascular complications	10,120 (4.14)	3245 (10.8)	4705 (7.67)	11,066 (1.57)	3444 (5.61)	5179 (3.49)	1475 (0.51)	483 (1.83)	680 (1.13)
Neurological complications	9467 (3.88)	1916 (6.40)	3043 (4.96)	11,237 (1.60)	1782 (2.90)	3282 (2.21)	1339 (0.46)	255 (0.97)	413 (0.68)
Thrombotic complications,	296 (0.12)	61 (0.20)	129 (0.21)	311 (0.04)	65 (0.11)	131 (0.09)	50 (0.02)	11 (0.04)	28 (0.05)
Respiratory complications	10,475 (4.29)	2360 (7.88)	4100 (6.68)	11,112 (1.58)	2241 (3.65)	4307 (2.90)	1266 (0.44)	240 (0.91)	493 (0.82)

DM: diabetes mellitus; ICU: intensive care unit

our study, considering all-cause mortality during the 90-day follow-up period, having been hospitalised or not, we found a positive association between diabetes and mortality. This is in line with a recent meta-analysis of observational studies, evaluating a total of 198,491 deaths among 1165,897 subjects with COVID-19; the summary relative risk was 1.54 (95% CI: 1.44; 1.64) [33]. However, a recent meta-analysis with 7244 hospital patients from 11 different countries, evaluating only mortality as an outcome, showed that obesity and diabetes were associated with severity (mechanical ventilation) but not in-hospital death [29]. One of the limitations of this meta-analysis was that it only considered in-hospital mortality. In our multivariable analyses, testing different risk factors in different models, the obesity odds ratios decreased and remained positively associated with mortality after adjusting for age, sex, diabetes, and COVID-19 waves. However, in the fully adjusted model, obesity was not associated with mortality. On the other hand, diabetes remained an independent mortality risk factor in all models. In our analysis, we observed that a previous history of HIV was associated with a four-fold increase in COVID-19 mortality. This is in line with a recent meta-analysis of 22 studies that included a total of 20,982,498 subjects. Subjects with HIV had a pooled mortality rate of

Table 3
Unadjusted and adjusted odds ratios for fatal event at 90-day follow-up period.

	Fatal events during 90 days period			
Risk Factor	Unadjusted OR 95CI [Li; Ui]	Model 1 Adjusted OR 95CI [Li; Ui]	Model 2 Adjusted OR 95CI [Li; Ui]	Model 3 Adjusted OR 95CI [Li; Ui]
Age	1.12 [1.12; 1.12]	1.11 [1.11; 1.11]	1.10 [1.10 – 1.10]	1.10 [1.10; 1.10]
Male, ref: Female	0.95 [0.91; 0.99]	1.60 [1.54; 1.67]	1.51 [1.44; 1.58]	1.32 [1.26; 1.38]
Obesity, (ref: No-obese subjects)	2.19 [2.11; 2.28]	1.07 [1.03; 1.12]	1.01 [0.97; 1.06]	0.98 [0.94; 1.03]
Diabetes mellitus, (ref: No-diabetic subjects)	5.38 [5.16; 5.60]	1.43 [1.37; 1.50]	1.31 [1.25; 1.37]	1.29 [1.23; 1.35]
Wave 2, ref: wave 1	0.21 [0.20; 0.22]	0.38 [0.36; 0.40]	0.39 [0.37; 0.41]	0.39 [0.37; 0.41]
Wave 3, ref: wave 1	0.06 [0.06; 0.07]	0.10 [0.09; 0.11]	0.11 [0.10; 0.12]	0.11 [0.10; 0.12]
Hypertension, ref: No hypertension	17.9 [17.0; 18.8]		1.30 [1.22; 1.39]	1.26 [1.19; 1.35]
Hyperlipidaemia, ref: No hyperlipidaemia	3.71 [3.56; 3.86]		0.83 [0.80; 0.87]	0.82 [0.78; 0.85]
CVD, ref: No CVD	10.9 [10.5; 11.4]		1.45 [1.38; 1.52]	1.41 [1.34; 1.40]
CKD, ref: No CKD	16.1 [15.4; 16.7]		1.42 [1.36; 1.49]	1.37 [1.31; 1.43]
COPD, ref: No COPD	8.04 [7.65; 8.45]			1.47 [1.39; 1.55]
Autoimmune disease, ref: No AI disease	2.59 [2.48; 2.71]			1.09 [1.04; 1.14]
HIV, ref: No HIV	1.98 [1.43; 2.66]			4.09 [2.91; 5.59]
Cancer, (ref: No cancer)	6.89 [6.58; 7.20]			1.74 [1.66; 1.82]
number	1,238,712			
R2	–	0.096	0.099	0.102

CKD: Chronic kidney disease; CI: Confidence intervals; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease, HIV: human immunodeficiency virus; Li: lower limit, Ui: upper limit,
Fatal events: mortality
Model 1 adjusted for age, sex, diabetes, obesity, COVID-19 waves,
Model 2 adjusted for: Model 1 variables adding common comorbidities: hypertension, hyperlipidaemia, CVD, and CKD
Model 3 adjusted for: Model 1 and Model 2 variables, adding additional comorbidities: COPD, Autoimmune disease, HIV and cancer

Table 4
Unadjusted and adjusted odds ratios for non-fatal events at 90-day follow-up period.

	Non-fatal events during 90 days period			
Risk Factor	Unadjusted OR 95CI [Li; Ui]	Model 1 Adjusted OR 95CI [Li; Ui]	Model 2 Adjusted OR 95CI [Li; Ui]	Model 3 Adjusted OR 95CI [Li; Ui]
Age	1.03 [1.03;1.03]	1.02 [1.02; 1.03]	1.01[1.01; 1.02]	1.01 [1.01; 1.01]
Male, ref: Female	0.84 [0.83;0.86]	0.94 [0.92; 0.96]	0.89 [0.87; 0.90]	0.86 [0.85; 0.88]
Obesity, (ref: No-obese subjects)	2.16 [2.12;2.20]	1.53 [1.50; 1.56]	1.39 [1.36; 1.42]	1.15 [1.12; 1.18]
Diabetes mellitus, (ref: No-diabetic subjects)	2.57 [2.52;2.63]	1.36 [1.33; 1.40]	1.17 [1.14; 1.20]	1.29 [1.23; 1.35]
Wave 2, ref: wave 1	0.42 [0.41;0.43]	0.50 [0.49; 0.51]	0.50 [0.49; 0.51]	0.50 [0.50; 0.51]
Wave 3, ref: wave 1	0.13 [0.12;0.13]	0.14 [0.14; 0.15]	0.14 [0.14; 0.15]	0.15 [0.14; 0.15]
Hypertension, ref: No hypertension	3.33 [3.27;3.39]		1.54 [1.50; 1.58]	1.52 [1.48; 1.56]
Hyperlipidaemia, ref: No hyperlipidaemia	2.49 [2.45;2.54]		1.19 [1.16; 1.22]	1.17 [1.15; 1.20]
CVD, ref: No CVD	3.54 [3.45;3.62]		1.38 [1.34; 1.42]	1.32 [1.28; 1.36]
CKD, ref: No CKD	3.27 [3.20;3.35]		1.08 [1.05; 1.11]	1.04 [1.01; 1.07]
COPD, ref: No COPD	3.83 [3.72;3.95]			1.71 [1.65; 1.76]
Autoimmune disease, ref: No AI disease	1.80 [1.77;1.84]			1.18 [1.16; 1.21]
HIV, ref: No HIV	2.01 [1.74;2.30]			1.83 [1.58; 2.11]
Cancer, (ref: No cancer)	2.27 [2.20;2.33]			1.15 [1.11; 1.18]
number	1238712			
R2	–	0.037	0.041	0.043

CKD: Chronic kidney disease; CI: Confidence intervals; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease, HIV: human immunodeficiency virus; Li: lower limit, Ui: upper limit,
Non-fatal events: cardiovascular and/or respiratory and/or neurological complications
Model 1 adjusted for age, sex, diabetes, obesity, COVID-19 waves,
Model 2 adjusted for: Model 1 variables adding common comorbidities: hypertension, hyperlipidaemia, CVD, and CKD
Model 3 adjusted for: Model 1 and Model 2 variables, adding additional comorbidities: COPD, Autoimmune disease, HIV and cancer

12.65% (95% CI 6.81;22.31%, I 2 =74%; $p < 0.01$ [34]. Regarding cancer and COVID-19, our results align with those reported in a recently published meta-analysis of 17 retrospective cohort studies evaluating the in-hospital mortality risk among persons with cancer; this study reported a pooled mortality risk for cancer subjects of 14.1% (95%CI: 9.1%;19.8%) [35]. Another meta-analysis of 37 studies, reported higher odds ratios for risk of death compared with our study (OR = 2.97, 95% CI:1.48; 5.96]; P = 0.002) among those with cancer and COVID-19 [36]. The presence of hyperlipidaemia in our fully adjusted model was negatively associated with COVID-19 mortality but remained an independent risk factor (positively associated) for non-fatal events in all models. The negative association in the mortality model could be due to various reasons, like the variable collinearity or the effect of lipid-lowering drugs. In our study, hyperlipidaemia was defined as a combination of diagnostic code and/or lipid-lowering treatment. So far, previously published observational studies have observed that the use of statin therapy prior to admission was associated with reduced COVID-19 severity or mortality [37–39]. Concerning the decrease in mortality rates observed in our study during the first three COVID-19 waves, similar results were reported using only hospitalised subjects with COVID-19, identified from the central electronic hospital record of our region [40]. The latter evaluated morality events during a 30-day period and reported higher mortality rates for hospitalised subjects during the first wave. Afterwards, mortality decreased and remained stable during the second and third waves. Our study observed decreases in overall and in-hospital deaths between the second and third COVID-19 wave. The authors also reported that age, sex, diabetes, cancer, and chronic kidney disease were risk factors for COVID-19 death.

This study has some limitations that should be considered. This was an observational study with real-world data from a primary healthcare database. The presence of missing values for some clinical variables is an intrinsic limitation of this type of study. Not all subjects had registers of BMI or obesity diagnostic codes in the database. Moreover, not all subjects had BMI registers at the time of inclusion in the study. This is why we used a proxy algorithm to estimate the cases of obesity, as the presence of BMI or diagnostic code at any time near the inclusion date. Possible misclassifications or infra-registration of diagnostic codes of diabetes are also possible. For this reason, we used diagnostic codes, HbA1c values and/or register of antidiabetic treatment to identify as many cases of diabetes as possible in our database. We only considered mortality 90 days after inclusion. It is possible that the current analysis did not cover the long-term effect of COVID-19 and its complications.

However, our analysis has some strengths, such as the large number of participants included in the study from primary healthcare, representing a global view of the impact of COVID-19 on our users and healthcare system.

In conclusion, the results of our study show that diabetes was an independent risk factor for mortality among people with COVID-19 during the initial three waves. The number of fatal events decreased during the second and third waves among subjects with diabetes or obesity. It is important to continue the surveillance of the impact of COVID-19 and its variants in order to identify risk factors and improve the control of the pandemic.

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CRediT authorship contribution statement

Conceptualisation, E.O, J.F-N, M.M-C, B.V, D.M; methodology, E.O, J.F-N, M.M-C, B.V, D.M; formal analysis, J.R; resources and data curation, J.R and B.V; writing—original draft preparation, B.V and B.F-C; writing—review and editing, E.O, J.F-N, M.M-C, FX.C, B.V, B.F-C and D.M; supervision: D.M, and J.F-N.; project administration: B.V. All authors approved the current version of the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: E. O has received advisory and or speaking fees from Astra-Zeneca, Boehringer Ingelheim, Lilly, MSD, Novo Nordisk, Sanofi, and Amgen; they received research grants for the institution from MSD and Amgen. M. M-C. has received an advisory honorarium from Astra-Zeneca, Bayer, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; they received speaker honoraria from Astra-Zeneca, Bayer, Boehringer Ingelheim, GSK, Lilly, Menarini, MSD, Novartis, Novo Nordisk, and Sanofi; he received research grants for the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi. J. F-N has received advisory and or speaking fees from Astra-Zeneca, Ascensia, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; he received research grants for the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi, and Boehringer. D. M. has received advisory and/or speaking fees from Almirall, Esteve, Ferrer, Lilly, Janssen, Menarini, Lilly, MSD, Novo Nordisk, and Sanofi. B. V, FX.C-C, J.R, and BF-C have no conflict of interest to declare.

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Conflict of interest

The funders had no role in the design of the study, in the collection, analysis, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

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