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Relationship between obesity and severe COVID-19 outcomes in patients with type 2 diabetes: Results from the CORONADO study

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Abstract

Aim: To assess the relationship between body mass index (BMI) classes and early COVID-19 prognosis in inpatients with type 2 diabetes (T2D).

Methods: From the CORONAvirus-SARS-CoV-2 and Diabetes Outcomes (CORONADO) study, we conducted an analysis in patients with T2D categorized by four BMI subgroups according to the World Health Organization classification. Clinical characteristics and COVID-19–related outcomes (i.e. intubation for mechanical ventilation [IMV], death and discharge by day 7 [D7]) were analysed according to BMI status.

Results: Among 1965 patients with T2D, 434 (22.1%) normal weight (18.5-24.9 kg/m^2, reference group), 726 (36.9%) overweight (25-29.9 kg/m^2) and 805 (41.0%) obese subjects were analysed, including 491 (25.0%) with class I obesity (30-34.9 kg/m^2) and 314 (16.0%) with class II/III obesity (≥35 kg/m^2). In a multivariable-adjusted model, the primary outcome (i.e. IMV and/or death by D7) was significantly associated with overweight (OR 1.65 [1.05-2.59]), class I (OR 1.93 [1.19-3.14]) and class II/III obesity (OR 1.98 [1.11-3.52]). After multivariable adjustment, primary outcome by D7 was significantly associated with obesity in patients aged younger than 75 years, while such an association was no longer found in those aged older than 75 years.

Conclusions: Overweight and obesity are associated with poor early prognosis in patients with T2D hospitalized for COVID-19. Importantly, the deleterious impact of obesity on COVID-19 prognosis was no longer observed in the elderly, highlighting the need for specific management in this population.

KEYWORDS
COVID-19, elderly, mechanical ventilation, obesity, prognosis, type 2 diabetes

1 | INTRODUCTION

Since December 2019, the new coronavirus, Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2), which causes coronavirus disease-2019 (COVID-19), has spread throughout the world, leading the World Health Organization (WHO) to issue a pandemic alert on 11 March 2020. In addition to the urgent need to develop efficient therapeutic strategies, identifying those who are most at risk of severe disease has quickly emerged as a major factor in facing this worldwide challenge.

From the first epidemiological reports, obesity and diabetes have both been identified as co-morbidities frequently associated with severe forms of COVID-19,[1,2] in accordance with previous reports from epidemic outbreaks due to the H1N1 influenza in 2009 or MERS-CoV in 2012.[3–5] For instance, the prevalence of obesity and diabetes, respectively, reached 41.7% and 33.8% among 5700 patients admitted for COVID-19 in 12 hospitals in the New York City area.[6] In patients admitted to intensive care units (ICUs) in the UK, 73.3% were reported to be overweight or obese.[7] Moreover, a French study recently reported that obesity is more prevalent in patients with critical COVID-19 compared with those with either non-critical forms of the disease or those admitted to ICUs for diagnoses other than COVID-19.[8]

In addition to its high prevalence in patients with COVID-19, obesity has also been identified as an independent risk factor for the severity of the disease.[9] A recent study in the United States showed that people with a body mass index (BMI) of 35 kg/m^2 or higher displayed a 3.5-fold increased risk of COVID-19–related death compared with those with a BMI of 25-34 kg/m^2.[10] Severe COVID-19 was recently reported to affect younger people in US populations with a high prevalence of obesity.[11] Similarly, diabetes was recently recognized as an independent predictor of poor prognosis in patients with COVID-19 with a greater than 2-fold risk of ICU admission and a higher than 3-fold risk of death.[12]

Obesity and diabetes, especially type 2 diabetes (T2D), are two commonly associated conditions that are supported by epidemiological as well as genetic studies. Their combination could therefore confer a particularly high risk of severe COVID-19. Accordingly, in an interim analysis of the CORONAvirus-SARS-CoV-2 and Diabetes Outcomes (CORONADO) study, we recently showed that BMI was positively and independently associated with severe COVID-19-related outcomes (i.e. intubation for mechanical ventilation [IMV] or death within 7 days of hospital admission) in patients with diabetes hospitalized for COVID-19.[13]

In the present analysis of the entire CORONADO population, we aimed at further deciphering the relationship between obesity and COVID-19 severity in patients with T2D hospitalized for this infectious disease. To this end, clinical characteristics and COVID-19-related outcomes were assessed according to patient BMI status, ranging from normal weight to class II/III obesity. Finally, as the elderly are particularly prone to severe forms of the disease, we specifically addressed the question of the influence of age on the relationship between BMI and COVID-19 prognosis.

2 | METHODS

2.1 | Study design and patients

The French multicentre, nationwide CORONADO study (ClinicalTrials.gov NCT04324736) was a retrospective study designed to describe the phenotypic characteristics and prognosis of patients with diabetes admitted to hospitals for COVID-19 from 10 March to 10 April 2020. The study was conducted in accordance with the declaration of Helsinki and French legislation, and obtained approval from the local ethics committee (IRB/IEC - GNEDS; ref. CORONADOV2), the CEREES (no. INDS: 1544730) and the CNIL (DR-2020-155/920129). Inclusion criteria were: hospitalization in a dedicated COVID-19 unit with COVID-19 diagnosis confirmed biologically (by SARS-CoV-2 PCR test) and/or clinically/radiologically (i.e. as ground-glass opacity and/or crazy paving on chest computed tomography scan); and a personal history of diabetes or newly diagnosed diabetes upon admission (i.e. HbA1c ≥48 mmol/mol [6.5%] during hospitalization). The full study design is provided in the supporting information.

Focusing on the relationship between obesity and COVID-19 severity in T2D, the present analysis excluded individuals with type 1 diabetes, other types of diabetes and those with newly diagnosed diabetes upon admission (n = 406), as well underweight patients (BMI < 18.5 kg/m^2) to avoid interference caused by concomitant severe co-morbidities (n = 40) (Figure 1). Finally, 1965 CORONADO patients with a medical history of T2D and available data for age, sex and BMI were included in the analysis. Subjects were categorized by four subgroups according to the WHO classification: (a) normal weight (18.5-24.9 kg/m^2), (b) overweight (25-29.9 kg/m^2), (c) class I obesity (30-34.9 kg/m^2) and (d) class II/III obesity (≥35 kg/m^2). Subjects in the normal weight range were considered to be the reference group.

2.2 | Data collection

Data collection was performed by clinical research associates and physicians in each participating centre. They were instructed to systematically review the medical files of all COVID-19 inpatients, select those with diabetes, extract data from their medical files and, if necessary, contact the patient's general and/or specialist practitioners, regular pharmacist or biomedical laboratory. Collected data included clinical characteristics (age, sex, ethnicity and BMI), classification of diabetes as noted in the medical file by the physician in charge of the patient, duration of diabetes, recent glycaemic control (i.e. the two most recent HbA1c levels determined before admission), microvascular and macrovascular complications and co-morbidities. Full details of data collection are provided in the supporting information. Classification of diabetes, body weight and height (and/or BMI value) were collected as noted in the medical file by the physician in charge of the patient. HbA1c considered in the analysis was determined locally in the 7 days following admission or, if not available, was the result of a routine determination in the previous 6 months. Diabetic microvascular and macrovascular complications, as well as co-morbidities and

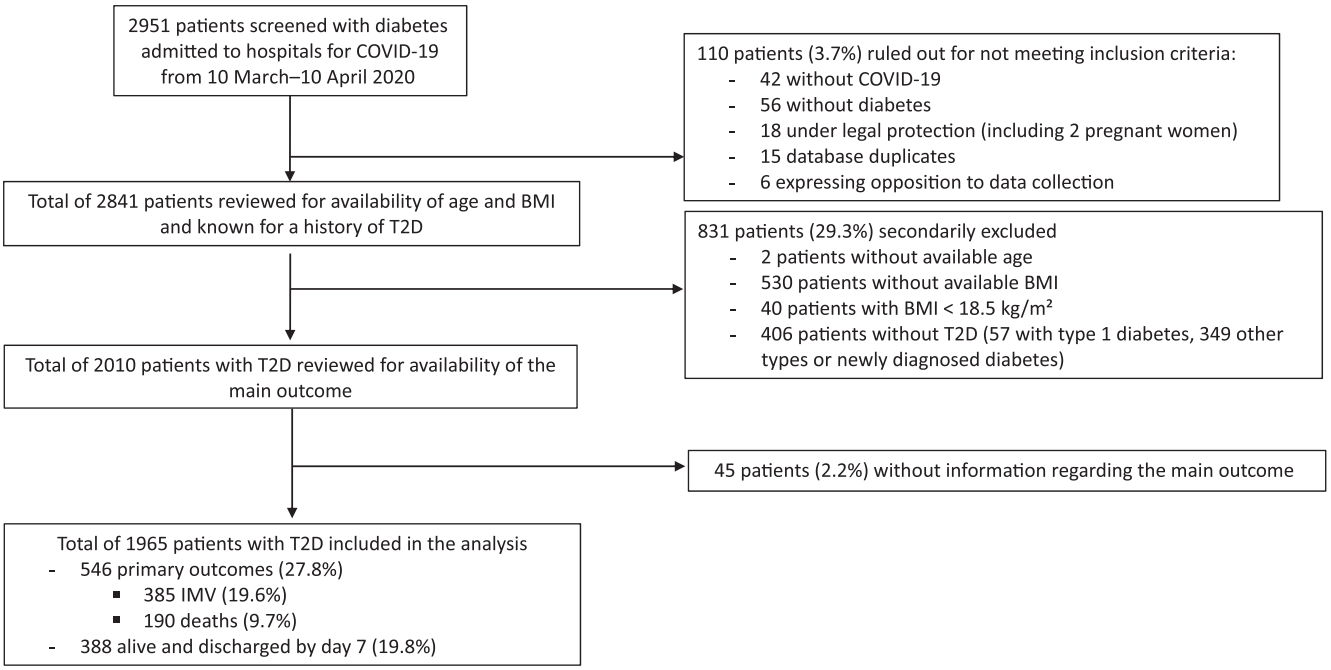

FIGURE 1 Flowchart. BMI, body mass index; IMV, intubation for mechanical ventilation; T2D, type 2 diabetes

routine treatment, were noted as reported in the medical file. Moreover, COVID-19-related clinical, radiological and biological characteristics were collected upon admission as well as the clinical evolution during hospital stays.

2.3 | Outcomes

The composite primary endpoint combined IMV and/or death by day 7 (D7). Secondary outcomes included death, IMV and hospital discharge, all considered by D7. Patients discharged before D7 were systematically contacted to check for the non-occurrence of these events by D7.

2.4 | Statistical methods

The study population was distributed according to the BMI categories. Quantitative variables were expressed as mean ± standard deviation (SD) or median [25th-75th percentile] and categorical variables as number (%) of patients. The statistical association between categorical variables was tested using Fisher's exact test. The statistical association between binary and quantitative variables was tested using unpaired t-test (Mann–Whitney U-test in case of skewed distribution) and, for variables with more than two categories, we used ANOVA (Kruskal–Wallis in case of skewed distribution). If necessary, confidence intervals for proportions were calculated using the Clopper–Pearson estimate.

Unconditional logistic regression models were used to calculate the OR associated with the different outcomes by D7. For quantitative variables, in case of skewed distribution, natural-log transformation was considered, and if applied, OR were expressed for an increase of 1 SD of the given variable. Multiple logistic regression analyses were performed focusing on the OR associated with BMI, considering covariates identified either as clinically relevant and/or significantly associated with obesity status in univariable analysis.

All statistical tests were two-sided with a type 1 error set at 5%. All analyses were performed on available data, without imputation, using statistical software R version 4.0.0.

3 | RESULTS

3.1 | Clinical and biological characteristics of patients according to BMI status

The present analysis included 1965 patients with T2D and confirmed COVID-19 admitted to 68 French hospitals from 10 March to 10 April 2020 (Figure 1). It should be noted that 45 patients with T2D and a BMI of 18.5 kg/m^2 or higher were excluded from the present analysis because of missing outcome data. However, their characteristics were similar to those of the analysed population (data not shown). Based on BMI status, the population distribution was as follows: 434 individuals with normal weight (22.1%), 726 with overweight (36.9%) and 805 with obesity (41.0%), including 491 with class I obesity (25.0%) and 314 with class II/III obesity (16.0%).

The patients' clinical characteristics before admission (i.e. medical history and routine treatment) and upon admission (clinical symptoms, radiological and biological findings) are detailed in Table 1 and Table S1, respectively. In contrast to a strong male predominance in the normal weight group, women were more represented in patients

TABLE 1 Clinical characteristics prior to admission of CORONADO participants according to BMI subgroups

	All	BMI 18.5-24.9 kg/m^2	BMI 25-29.9 kg/m^2	BMI 30-34.9 kg/m^2	BMI ≥35 kg/m^2	*P*-value
Clinical features	N = 1965	N = 434	N = 726	N = 491	N = 314	
BMI (kg/m^2)	28.7 [25.5; 32.8]	23.5 [22.3; 24.3]	27.6 [26.3; 28.7]	32.0 [30.9; 33.4]	38.5 [36.7; 42.0]	**<.0001**
Sex (female)	698/1965 (35.5%)	127/434 (29.3%)	202/726 (27.8%)	200/491 (40.7%)	169/314 (53.8%)	**<.0001**
Age (y)	70.1 ± 12.5	73.9 ± 12.3	70.9 ± 11.7	68.7 ± 12.6	64.9 ± 12.4	**<.0001**
Age categories (y)	N = 1965					**<.0001**
<55	224/1965 (11.4%)	35/434 (8.1%)	65/726 (9.0%)	66/491 (13.4%)	58/314 (18.5%)	
55-64	417/1965 (21.2%)	61/434 (14.1%)	147/726 (20.2%)	118/491 (24.0%)	91/314 (29.0%)	
65-74	577/1965 (29.4%)	114/434 (26.3%)	230/726 (31.7%)	139/491 (28.3%)	94/314 (29.9%)	
>75	747/1965 (38.0%)	224/434 (51.6%)	284/726 (39.1%)	168/491 (34.2%)	71/314 (22.6%)	
Ethnicity	N = 1562					**.0136**
EU	927/1562 (59.3%)	188/331 (56.8%)	334/581 (57.5%)	244/401 (60.8%)	161/249 (64.7%)	
MENA	322/1562 (20.6%)	74/331 (22.4%)	129/581 (22.2%)	80/401 (20.0%)	39/249 (15.7%)	
AC	254/1562 (16.3%)	46/331 (13.9%)	98/581 (16.9%)	65/401 (16.2%)	45/249 (18.1%)	
AS	59/1562 (3.8%)	23/331 (6.9%)	20/581 (3.4%)	12/401 (3.0%)	4/249 (1.6%)	
Diabetes duration (y)	12 [6; 20]	13 [7; 20]	11 [6; 20]	12 [7; 20]	13 [5; 20]	.4152
HbA1c (mmol/mol)	60.7 [50.8; 73.8]	58.5 [48.6; 75.4]	61.1 [50.8; 73.8]	60.1 [50.8; 70.5]	62.8 [53.0; 73.8]	.3931
HbA1c (%)	7.7 [6.8; 8.9]	7.5 [6.6; 9.1]	7.7 [6.8; 8.9]	7.7 [6.8; 8.6]	7.9 [7.0; 8.9]	.3931
Tobacco use	N = 1605					**.0155**
Never	949/1605 (59.1%)	198/345 (57.4%)	340/599 (56.8%)	238/400 (59.5%)	173/261 (66.3%)	
Former	567/1605 (35.3%)	118/345 (34.2%)	225/599 (37.6%)	148/400 (37.0%)	76/261 (29.1%)	
Current	89/1605 (5.5%)	29/345 (8.4%)	34/599 (5.7%)	14/400 (3.5%)	12/261 (4.6%)	
Microvascular complications	607/1338 (45.4%)	150/298 (50.3%)	220/475 (46.3%)	145/355 (40.8%)	92/210 (43.8%)	.0992
Macrovascular complications	717/1742 (41.2%)	186/388 (47.9%)	254/638 (39.8%)	169/440 (38.4%)	108/276 (39.1%)	**.0224**
Co-morbidities						
Hypertension	1556/1944 (80%)	321/425 (75.5%)	564/721 (78.2%)	401/486 (82.5%)	270/312 (86.5%)	**.0006**
Dyslipidaemia	977/1890 (51.7%)	203/415 (48.9%)	353/698 (50.6%)	260/474 (54.9%)	161/303 (53.1%)	.2866
Heart failure	214/1755 (12.2%)	58/387 (15.0%)	69/649 (10.6%)	50/447 (11.2%)	37/272 (13.6%)	.1563
NAFLD	133/1619 (8.2%)	18/370 (4.9%)	40/600 (6.7%)	39/405 (9.6%)	36/244 (14.8%)	**.0001**
Liver cirrhosis	55/1762 (3.1%)	11/395 (2.8%)	22/643 (3.4%)	13/451 (2.9%)	9/273 (3.3%)	.9378
Active cancer	195/1845 (10.6%)	49/408 (12%)	76/684 (11.1%)	43/465 (9.2%)	27/288 (9.4%)	.5015
COPD	194/1843 (10.5%)	38/413 (9.2%)	54/677 (8.0%)	56/467 (12.0%)	46/286 (16.1%)	**.0016**
Treated OSA	213/1741 (12.2%)	12/395 (3.0%)	49/637 (7.7%)	68/439 (15.5%)	84/270 (31.1%)	**<.0001**
Bariatric surgery	15/1866 (0.8%)	1/417 (0.2%)	3/686 (0.4%)	4/469 (0.9%)	7/294 (2.4%)	**.0147**
Routine treatment before admission						

(Continues)

TABLE 1 (Continued)

	All	BMI 18.5-24.9 kg/m^2	BMI 25-29.9 kg/m^2	BMI 30-34.9 kg/m^2	BMI ≥35 kg/m^2	*P*-value
Metformin	1163/1955 (59.5%)	239/432 (55.3%)	448/724 (61.9%)	293/486 (60.3%)	183/313 (58.5%)	.1659
Sulphonylurea/glinides	585/1955 (29.9%)	131/432 (30.3%)	224/724 (30.9%)	148/486 (30.5%)	82/313 (26.2%)	.4683
DPP4 inhibitors	480/1955 (24.6%)	121/432 (28.0%)	196/724 (27.1%)	115/486 (23.7%)	48/313 (15.3%)	**.0001**
GLP1-RA	213/1955 (10.9%)	18/432 (4.2%)	65/724 (9.0%)	64/486 (13.2%)	66/313 (21.1%)	**<.0001**
Insulin	762/1965 (38.8%)	163/434 (37.6%)	265/726 (36.5%)	188/491 (38.3%)	146/314 (46.5%)	**.0216**
Daily insulin dose (IU)	32 [20; 58]	24 [15; 37.5]	30 [20; 51.5]	42 [24; 64]	50 [30; 88]	**<.0001**
Thiazide diuretics	393/1955 (20.1%)	66/432 (15.3%)	146/724 (20.2%)	100/486 (20.6%)	81/313 (25.9%)	**.0049**
Beta blockers	729/1955 (37.3%)	153/432 (35.4%)	277/724 (38.3%)	181/486 (37.2%)	118/313 (37.7%)	.8115
ACE inhibitors	583/1955 (29.8%)	136/432 (31.5%)	206/724 (28.5%)	149/486 (30.7%)	92/313 (29.4%)	.7014
ARBs	581/1955 (29.7%)	106/432 (24.5%)	214/724 (29.6%)	155/486 (31.9%)	106/313 (33.9%)	**.0247**
ARBs and/or ACE inhibitors	1145/1955 (58.6%)	239/432 (55.3%)	412/724 (56.9%)	297/486 (61.1%)	197/313 (62.9%)	.0915
Statins	975/1955 (49.9%)	201/432 (46.5%)	361/724 (49.9%)	258/486 (53.1%)	155/313 (49.5%)	.2664

Abbreviations: AC, African or Caribbean; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin-2 receptor blocker; AS, Asian; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DPP4, dipeptidyl peptidase-4; EU, Europid; GLP-1RA, glucagon-like peptide-1 receptor agonist; MENA, Middle East North Africa; NAFLD, non-alcoholic fatty liver disease; OSA, obstructive sleep apnea. Data are presented as numbers (%) and mean ± SD, or median [25th; 75th percentile] if not normally distributed. Associated *P*-values are given using Fisher's exact test or, if not calculable, Pearson's chi-squared test (categorical variables), ANOVA or Kruskal-Wallis tests, respectively. Bold values denote statistical significance at the $P < 0.05$ level. HbA1c corresponds to the HbA1c value determined in the first 7 days following admission or the most recent value available in the 6 months prior to admission; microvascular complications correspond to severe diabetic retinopathy, diabetic kidney disease, history of diabetic foot ulcer; and macrovascular complications correspond to ischaemic heart disease, cerebrovascular disease and peripheral artery disease.

with obesity, especially in those with class II/III obesity (53.8% vs. 27.8%-40.7% in other groups). Patients with obesity were also younger than individuals with normal weight. Accordingly, the number of people aged 75 years or older decreased from 51.6% in the normal weight group to 34.2% and 22.6% in patients with class I and class II/III obesity, respectively. Diabetes duration was similar in all groups, as was HbA1c level. Patients with class II/III obesity were also more often treated with glucagon-like peptide-1 receptor agonists (21.1% vs. 4.2%-13.2% in other groups) and insulin (46.5% vs. 36.5%-38.3%). As expected, the prevalence of co-morbidities such as arterial hypertension, non-alcoholic liver fatty disease (NAFLD), chronic obstructive pulmonary disease (COPD) and treated obstructive sleep apnea (OSA) increased with the grading of obesity. Regarding the features of COVID-19 upon admission (Table S1), almost all of the patients were symptomatic without any influence of BMI status on the median duration of symptoms before admission (5 [2-9] days). Some COVID-19 symptoms were more frequently observed with obesity, including cephalalgia, dyspnoea, rhinitis and pharyngeal signs, ageusia and anosmia. Of note, it appears that some blood markers of inflammation, such as white cell count, C-reactive protein (CRP) or fibrinogen were lower in patients with obesity, particularly in those with a BMI of 35 kg/m^2 or higher, while creatine phosphokinase plasma concentration was higher in these groups.

3.2 | COVID-19–related outcomes according to BMI status

In the entire population, 546 (27.8%) individuals met the primary outcome by D7, 385 (19.6%) required IMV and 190 (9.7%) were deceased by D7. Conversely, 388 (19.8%) patients were discharged by D7. The influence of BMI status on these different outcomes is shown in Table 2. Multivariable analysis showed a significant association between the primary outcome and overweight (OR 1.65 [1.05-2.59]), class I (OR 1.93 [1.19-3.14]) and class II/III obesity (OR 1.98 [1.11-3.52]) (P = .0373) (Table 2). Regarding IMV, an association was also found from overweight to class II/III obesity. By contrast, death was not associated with BMI status (P = .9634). Altogether, these data indicate that BMI status is gradually associated with early severity of COVID-19 in patients with T2D, from overweight to class II/III obesity.

3.3 | Influence of age on the relationship between BMI and COVID-19 prognosis

To better understand the influence of age on the relationship between BMI status and COVID-19 prognosis, we studied the distribution of COVID-19-related outcomes according to BMI status in three age subgroups (<65, 65-74 and ≥75 years) (Figure 2). As shown in Figure 2, an increased rate of early death as well as a decreased rate of IMV and discharge by D7 was observed in patients aged 75 years or older compared with younger people, irrespective of BMI status. Given the specificity of BMI distribution in the elderly (Table 1) and considering the shift in the occurrence of clinical outcomes above 75 years (Figure 2), we then separately assessed the influence of overweight and obesity on clinical characteristics and COVID-19-related outcomes in patients with T2D younger than and older than 75 years of age. As shown in Table 3, the primary outcome was significantly associated with obesity in individuals younger than 75 years (P = .0077), whereas such an association was no longer found in the older patients (P = .1507).

To assess the effect of age on the clinical consequences of obesity, we compared the clinical features of patients with and without obesity (BMI ≥30 vs. <30 kg/m^2) separately within populations aged younger than and older than 75 years (Tables S2 and S3). Briefly, diabetes complications were more frequent in the elderly, irrespective of obesity. COPD and OSA were more prevalent in obese groups regardless of age, while an increase in NAFLD prevalence with obesity was only observed in individuals younger than 75 years. In insulin users, daily insulin dose was significantly higher in obese patients younger than 75 years whereas no difference was observed according to obesity status in those older than 75 years, suggesting less marked insulin resistance in older than in younger obese patients. Upon admission, an increased frequency of COVID-19 symptoms, such as cough and dyspnoea, was observed with obesity in older people, but obesity was not concomitant with higher biological inflammation, whatever the age.

4 | DISCUSSION

The interim analysis of the CORONADO study recently identified BMI as an independent predictor of poor early prognosis in patients with diabetes hospitalized for COVID-19.[13] In the present study, we took advantage of the whole CORONADO population with T2D to specifically address the relationship between BMI classes and severity of COVID-19, taking into account the influence of age. The main conclusion is that obesity is significantly and increasingly associated with the severity of COVID-19 in this population. Indeed, the primary outcome (IMV and/or death by D7) was gradually associated with overweight and obesity in patients with T2D. The second key message is that the relationship between obesity status and the primary outcome was no longer found in elderly patients with T2D aged 75 years or older.

Our present results therefore confirm in inpatients with T2D the close relationship between obesity and disease severity previously reported in COVID-19 patients with and without diabetes. In France, two monocentre studies of COVID-19 patients admitted to ICUs underlined a positive and significant association between the need for IMV and severe obesity (BMI ≥35 kg/m^2).[14,15] In line with these studies, data from 265 patients admitted to ICUs in five medical centres in the United States have suggested that obesity could shift severe COVID-19 to younger ages.[11] Another study conducted in 200 patients in the Bronx, New York, showed that in addition to increasing age and male sex, a BMI of 35 kg/m^2 or higher was independently associated with COVID-19-related mortality compared with individuals with a BMI of 25-34 kg/m^2.[10] More recently, among

TABLE 2 Association of BMI subgroups with COVID-19-related outcomes by day 7, using multiple logistic regression

	Primary outcome by D7			IMV by D7			Death by D7			Discharge by D7		
	Events/total number of participants (%)	Odds ratio (95% CI)		Events/total number of participants (%)	Odds ratio (95% CI)		Events/total number of participants (%)	Odds ratio (95% CI)		Events/total number of participants (%)	Odds ratio (95% CI)	
All	**546/1965 (27.8%)**	**Unadjusted**	**Adjusted**	**385/1964 (19.6%)**	**Unadjusted**	**Adjusted**	**190/1964 (9.7%)**	**Unadjusted**	**Adjusted**	**388/1955 (19.8%)**	**Unadjusted**	**Adjusted**
BMI subgroups, kg/m^2												
18.5-24.9	99/434 (22.8%)	**Ref.**	**Ref.**	55/433 (12.7%)	**Ref.**	**Ref.**	51/434 (11.8%)	**Ref.**	**Ref.**	80/431 (18.6%)	**Ref.**	**Ref.**
25-29.9	191/726 (26.3%)	1.21 (0.91-1.60) *P* = .1834	**1.65 (1.05-2.59) *P* = .0317**	135/726 (18.6%)	**1.57 (1.12-2.20) *P* = .0091**	**1.81 (1.02-3.22) *P* = .0436**	61/726 (8.4%)	0.69 (0.47-1.02) *P* = .0628	1.23 (0.62-2.44) *P* = .5493	148/723 (20.5%)	1.13 (0.83-1.53) *P* = .431	1.08 (0.70-1.67) *P* = .7326
30-34.9	148/491 (30.1%)	**1.46 (1.09-1.96), *P* = .0121**	**1.93 (1.19-3.14), *P* = .0078**	108/491 (22.0%)	**1.94 (1.36-2.76), *P* = .0003**	**2.31 (1.27-4.23), *P* = .0064**	49/490 (10.0%)	0.83 (0.55-1.26), *P* = .3929	1.26 (0.60-2.66), *P* = .5369	98/489 (20.0%)	1.10 (0.79-1.53), *P* = .5709	0.76 (0.46-1.24), *P* = .2673
≥35	108/314 (34.4%)	**1.77 (1.28-2.45), *P* = .0005**	**1.98 (1.11-3.52), *P* = .0208**	87/314 (27.7%)	**2.63 (1.81-3.83), *P* < .0001**	**2.29 (1.15-4.56), *P* = .019**	29/314 (9.2%)	0.76 (0.47-1.24), *P* = .273	1.56 (0.60-4.03), *P* = .3602	62/312 (19.9%)	1.09 (0.75-1.57), *P* = .6540	0.83 (0.46-1.48), *P* = .5213
P value[a]	-	**.0024**	**.0373**	-	**<.0001**	**.002**	-	.3065	.9634	-	.8884	.5987

Abbreviations: BMI, body mass index; D7, day 7; GLP-1RA, glucagon-like peptide-1 receptor agonist; IMV, intubation for mechanical ventilation; Ref., reference group.
The primary outcome is defined as IMV and/or death by D7. Therefore, by design, some patients met the two events, and the sum of both groups is greater than the number of primary outcomes.
Multiple logistic regression model unadjusted and adjusted for sex, age, tobacco use, microvascular complications, macrovascular complications, hypertension, non-alcoholic fatty liver disease, chronic obstructive pulmonary disease, treated obstructive sleep apnea and routine treatment with insulin and GLP1-RA.
[a]*P*-value: test for homogeneity for BMI as a nominal variable. Bold values denote statistical significance at the *P* <.05 level.

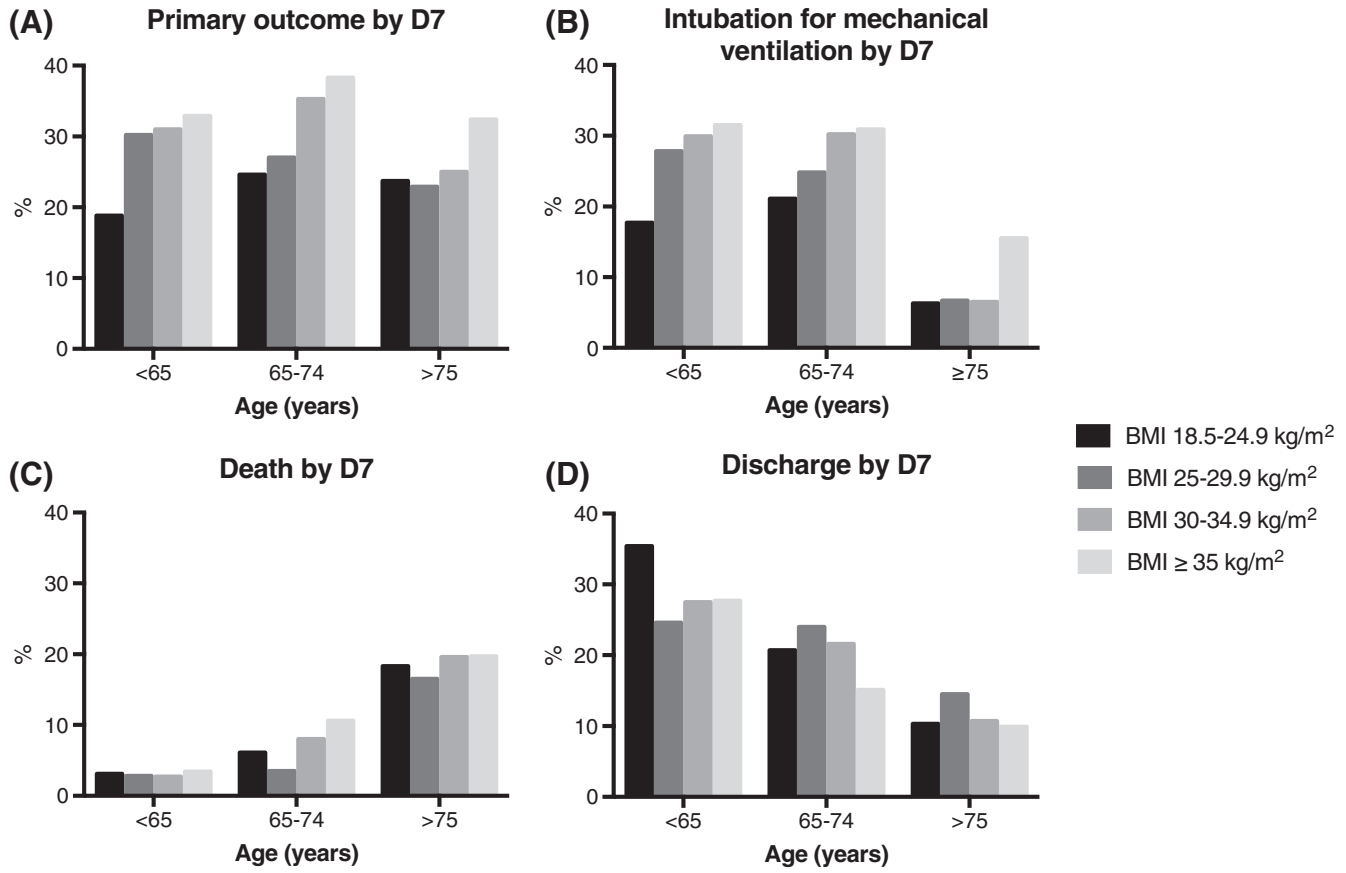

FIGURE 2 Distribution of COVID-19-related outcomes by day 7 per age and body mass index (BMI) subgroups: A) Primary outcome; B) IMV; C) Death; D) Hospital discharge

6916 patients with COVID-19, Tartof et al. described a gradually positive association between BMI and risk of death, even after adjustment for obesity-related co-morbidities.[16] The strength of the CORONADO study relies on a large and well-phenotyped population of COVID-19 patients with T2D admitted to medical units or ICUs. Hence, our data further indicate that an association between IMV and BMI already appeared from overweight, while no association was found for death occurring within 7 days.

The combined prevalence of overweight and obesity reached 77.8% in our study population, in agreement with the French epidemiological ENTRED-2 study, in which 80% of people living with T2D were overweight or obese.[17] As expected, the prevalence of obesity decreased with advancing age, as previously reported in the French population of elderly people with T2D.[18] Sex also impacted BMI distribution, with a clear male predominance in the normal weight group, whereas women were more represented in patients with obesity, especially in those with a BMI of 35 kg/m^2 or higher. Sex-dependent BMI distribution and a similarly higher prevalence of obesity in women than in men have already been described in the general population, such as in people with T2D.[19] Moreover, women have been reported to exhibit higher BMI values than men upon diagnosis of T2D.[20] Age and sex are therefore potential confounding factors when assessing the relationship between obesity and severe COVID-19 outcomes.

Considering the lower prevalence of elderly people among participants with obesity as well as the association with severe COVID-19 in this population, we further investigated the relationship between BMI status and COVID-19 prognosis according to age. Because our analyses revealed a shift in the occurrence of IMV and death by D7 above the age of 75 years, we decided to compare patients aged younger and older than 75 years, a cut-off used by numerous studies to capture an elderly population.[21,22] To balance the size of subgroups, we considered three BMI categories (<25, 25-29.9 and ≥30 kg/m^2), thus bringing together all obese patients, instead of the previous four-BMI-subgroups distribution applied to the whole population. We favoured a stratification approach where patients with normal BMI aged younger than 75 years were considered to be the reference group. While the association of obesity with the primary outcome was confirmed in patients younger than 75 years of age, this was no longer the case in those aged older than 75 years. Interestingly, similar findings were observed in a retrospective series of COVID-19 patients in New York City, with a positive association between obesity (BMI ≥35 kg/m^2) and ICU admissions in patients younger than 60 years (OR: 3.6 [95% CI: 2.5-5.3], $P < .0001$), but not in those who were older than 60 years (OR: 1.5 [95% CI: 0.9-2.3], $P = .10$).[23] While this article was being prepared, Anderson et al. also showed that a gradual association between obesity and IMV or death is observed in adults younger than 65 years who were hospitalized for COVID-19, but not in patients who were

TABLE 3 Association of BMI subgroups with the different outcomes by day 7 according to age (< or ≥75 years) using multiple logistic regression with multivariable adjustment

	Primary outcome by D7			
	Events/total number of participants (%)		Odds ratio (95% CI)	
All	<75 y	≥75 y	<75 y	≥75 y
BMI, kg/m^2				
18.5-24.9	46/210 (21.9%)	53/224 (23.7%)	1	1.15 (0.54-2.44), *P* = .7251
25-29.9	126/442 (28.5%)	65/284 (22.9%)	1.73 (0.92-3.24), *P* = .0897	1.85 (0.95-3.64), *P* = .0726
≥30	191/566 (33.7%)	65/239 (27.2%)	**2.32 (1.25-4.30), *P* = .0077**	1.68 (0.83-3.43), *P* = .1507
P-value			.0733	
P-value for interaction			.4767	

Abbreviations: BMI, body mass index; D7, day 7; GLP-1RA, glucagon-like peptide-1 receptor agonist; IMV, intubation for mechanical ventilation; Ref., reference group.

The primary outcome combines IMV and/or death by D7.

Multiple logistic regression model adjusted with sex, tobacco use, microvascular complications, macrovascular complications, hypertension, non-alcoholic fatty liver disease, chronic obstructive pulmonary disease, treated obstructive sleep apnea and routine treatment with insulin and GLP1-RA. Bold values denote statistical significance at the *P* <0.05 level.

older than 65 years.[24] Altogether, this reinforces the need for specific clinical management and dedicated trials in elderly people affected by COVID-19.

In a very different context to the COVID-19 pandemic, obesity has been reported to be deleterious in younger people (aged <65 years) with T2D but associated with better survival in older individuals (aged ≥65 years).[25] Accordingly, although obesity is a well-recognized risk factor for numerous cardiovascular and respiratory diseases in epidemiological studies, some protective role has already been linked with obesity status in the literature, a phenomenon known as the 'obesity paradox'.[26] Indeed, several studies have reported that patients with elevated BMI are characterized by lower all-cause and cardiovascular mortality than people in the normal weight range.[27,28] Importantly, the obesity paradox has mainly been reported in the elderly,[26] where excess weight is associated with preserved lean mass, and can limit the risk of undernutrition and frailty. Nevertheless, the concept of the obesity paradox has recently been challenged by the Fremantle diabetes study, which highlights the limitation of solely using BMI for a precise phenotyping of obesity.[29] Unfortunately, the specific COVID-19 context and the retrospective design of our study did not enable us to include measurements of waist and hip circumferences.

The observational design of the CORONADO study also did not allow us to identify clear mechanistic explanations for this differential impact of BMI according to age. This difference might be related to a power issue, even if the number of primary outcomes was substantial in elderly patients. However, we tried to identify some differences in the clinical and biological characteristics associated with obesity (BMI >30 kg/m^2) in elderly versus non-elderly patients. First, macrovascular complications were more prevalent in the elderly, irrespective of BMI status, which may have masked the deleterious effect of obesity. Second, in this population of patients with T2D, certain metabolic features associated with obesity and insulin resistance were less frequent in the elderly. Notably, obesity no longer influenced the prevalence of NAFLD, recently recognized as associated with severe COVID-19,[30,31] or the plasma level of liver enzymes in people aged 75 years or older.

Adipose tissue repartition should also be questioned, because visceral obesity is known to correlate with metabolic disorders, low-grade inflammation and higher mortality rates.[32] Ageing has already been reported to induce significant changes in body composition and adipose tissue distribution. Unfortunately, in the emergency context of COVID-19, we were unable to collect additional anthropometric and imaging variables to further characterize fat mass distribution. Among the multiple pathways by which obesity may worsen COVID-19 prognosis, the deleterious role of adipose tissue as a reservoir for more extensive viral spread and inflammatory response amplification has recently been suggested.[33,34] However, inflammatory markers such as CRP or fibrinogen did not vary with BMI status in either group of patients (aged < and ≥75 years) and this hypothesis should therefore be further investigated in patients with diabetes. In addition, people with obesity have displayed meta-inflammation and immune dysfunction, a condition similar to ageing. This immune dysregulation is characterized by cytotoxic lymphocyte T exhaustion and reduced natural killer cell cytotoxic function secondary to immune checkpoint pathway (PD1) activation.[35] Hence, such dysfunctions impair anti-tumour or anti-infectious immunity and could be accentuated by immune challenges like viral infections. Thus, the immunocompromised profile associated with obesity may contribute to the vulnerability to COVID-19 infection.

Our study has some limitations that must be acknowledged. CORONADO only included hospitalized COVID-19 cases and our results cannot be generalized to all COVID-19 patients with diabetes, especially those with a less severe form of the disease. We only focused on patients with T2D and our findings cannot be extrapolated in patients without diabetes. In addition, our primary combined

outcome was mainly driven by IMV, which depends on many equivocal factors such as clinical deterioration, refusal to be intubated, or a medical decision not to intubate, which can vary according to the frailty of the patient. Concerning the follow-up, our choice of D7 can be questioned. Of note, our primary objective was to identify phenotypic characteristics associated with severe COVID-19. The CORONADO scientific committee (which includes specialists in infectious diseases and in intensive care) proposed a primary endpoint combining death or IMV within the first 7 days following admission to assess the early severity of COVID-19. Indeed, providing data on 5700 persons hospitalized for COVID-19 in the New York City area, Richardson et al. recently observed that approximately three out of four participants died or were discharged within 7 days.[6] Furthermore, in 355 patients with COVID-19 hospitalized in metropolitan Detroit, the median time between hospital admission and IMV was only 1 day (IQR 0-3 days).[36] Thus, we strongly believe that COVID-19 severity is adequately captured by our primary composite endpoint by D7 in the vast majority of patients. Nevertheless, the short follow-up period is a limitation and caution is necessary when interpreting the results, especially in terms of causal relationships. Finally, the results reported in this paper originated from a post hoc analysis conducted on observatory data from a retrospective cohort study and they must therefore be confirmed by observations from large cohorts.

In conclusion, overweight and obesity are associated with poor early prognosis in patients with T2D hospitalized for COVID-19, supporting the need for reinforced prevention measures in these populations. The deleterious impact of obesity on COVID-19 prognosis appears to be much less pronounced in the elderly and advanced age by itself must be considered as a major risk for severe COVID-19 outcomes in all people with T2D, irrespective of BMI status.

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CONFLICT OF INTEREST

C.C. reports personal fees from Novo Nordisk, Gilead, MSD, Eli Lilly and Astra Zeneca and grant support from Gilead. L.P. reports personal fees and non-financial support from Sanofi, personal fees and non-financial support from Eli Lilly, personal fees and non-financial support from Novo Nordisk and personal fees and non-financial support from MSD. B.F. reports personal fees and non-financial support from Sanofi, Orkyn, Isis, MSD, NHC, Pfizer, Vitalair, Eli Lilly, Novo Nordisk, Merck and Servier. J.-F.G. reports personal fees and non-financial support from Eli Lilly, personal fees and non-financial support from Novo Nordisk, personal fees and non-financial support from Gilead and personal fees and non-financial support from Astra Zeneca. A.M. reports personal fees support from Novo Nordisk. D.S.-B. reports non-financial support from Novo Nordisk, Sanofi, MSD and Lilly. M.P. reports personal fees and non-financial support from Novo Nordisk, non-financial support from Sanofi and non-financial support from Amgen. S.H. reports personal fees and non-financial support from Astra Zeneca, grants and personal fees from Bayer, personal fees from Boehringer Ingelheim, grants from Dinno Santé, personal fees from Eli Lilly, non-financial support from LVL, personal fees and non-financial support from Merck Sharpe Dome, personal fees from Novartis, grants from Pierre Fabre Santé, personal fees and non-financial support from Sanofi, personal fees and non-financial support from Servier and personal fees from Valbiotis. B.C. reports grants and personal fees from Amgen, personal fees from Astra-Zeneca, personal fees from Akcea, personal fees from Genfit, personal fees from Gilead, personal fees from Eli Lilly, personal fees from Novo Nordisk, personal fees from Merck (MSD), grants and personal fees from Sanofi and grants and personal fees from Regeneron. P.G. reports personal fees from Abbott, personal fees from Amgen, personal fees from Astra-Zeneca, personal fees from Boehringer Ingelheim, personal fees from Eli Lilly, personal fees from Merck Sharp and Dohme, personal fees from Mundipharma, grants and personal fees from Novo Nordisk, personal fees from Sanofi and personal fees from Servier. All of the other authors declare no competing interests.

AUTHOR CONTRIBUTIONS

B.C., P.G. and M.W. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. S.S. and B.T. contributed to the work equally and should be regarded as co-first authors. B.C. and P.G. contributed to the work equally and should be regarded as co-last authors. Concept and design: B.C., P.G., S.H., S.S., B.T. and M.W. Acquisition, analysis or interpretation of data: S.S., B.T., B.C., P.G., S.H., M.P. and M.W. Critical revision of the manuscript for important intellectual content: all co-authors. Statistical analysis: M.W. Patient recruitment: B.T., C.C., B.G., C.V., B.V., D.A., C.A., L.A.B., O.B., C.C.-B., B.D., A.D.,

B.F., J.-F.G., N.G., E.L., S.L.-R., L.M., A.M., I.M., L.P., N.S., D.S.-B. and P.W. Fundraising: B.C., P.G., S.H. and M.P. B.C. and P.G. had final responsibility for the decision to submit for publication.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

No sharing of participant data is allowed by our regulatory authorities. So far, French regulations have not validated deidentified data or avatar for data sharing. Our statement might be modified in case French law changes. Whether additional, related documents will be available (eg, study protocol, statistical analysis plan, informed consent form) We will be happy to share study protocol, SAP and information document. • When these data will be available (beginning and end date, or "with publication", as applicable) Study protocol, SAP and information document will be made available with publication. Data dictionary will be made available Summer 2020 (JULY 15th). • Where the data will be made available (including complete URLs or email addresses if relevant); The CORONADO website is not active yet but we will give access to the scientific committee through our website, as soon as it is launched. Direct requests can be directed to PI (bertrand.cariou@univ-nantes.fr) or Chairman of the scientific committee (samy.hadjadj@univ-nantes.fr) • By what access criteria data will be shared (including with whom, for what types of analyses, by what mechanism - eg, with or without investigator support, after approval of a proposal, with a signed data access agreement - or any additional restrictions). Our data-base is open for any collaborative work with priority to academic partnership. Any proposal for collaboration requires examination by the scientific committee and the sponsor (CHU Nantes). A structured application proposal for collaboration will be available on request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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