**Obesity is a strong independent risk factor for short-term mortality and
adverse outcomes in Mexican patients with COVID-19: A national
observational study**

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1 **Abstract (199 words):**

2 We aimed to study obesity alone or in combination with other comorbidities as a risk
3 factor for short-term all-cause mortality and other adverse outcomes in Mexican
4 patients evaluated for suspected COVID-19.

5 We performed a retrospective observational analysis in a national cohort of 71,103
6 patients. Multivariate logistic regression models were applied to determine risk of
7 death, hospitalisation, invasive mechanical ventilation, pneumonia, and admission
8 to an intensive care unit, conferred by obesity and other comorbidities

9 From February 24 to April 26, 2020, 71,103 patients were evaluated for suspected
10 COVID-19; 15,529 (21.8%) had a positive test for SARS-CoV-2; 46,960 (66.1%),
11 negative, and 8,614 (12.1%), pending results. Obesity alone increased adjusted
12 mortality risk in positive patients (HR=2.37, 95%CI:1.96-2.86), but not in negative
13 and pending-result patients.

14 In conclusion, obesity is a strong independent risk factor for short-term mortality and
15 critical illness in Mexican patients with COVID-19; risk increases when obesity is
16 present with other comorbidities.

17
18 **Key words:** Obesity; comorbidities; COVID-19; SARS-CoV-2; mortality;
19 coronavirus.

20
21 **Key Findings**

- 22 • Obesity alone increased mortality risk in SARS-CoV-2-positive, but not in
23 negative or pending-result patients.

- After multivariable adjustment and sensitivity analysis, obesity persisted as a strong risk factor for death.
- Obesity combined with DM, hypertension, and immunosuppression further increased mortality risk.
- Risk of adverse events was increased in patients with obesity alone or combined with other comorbidities.
- Obesity is a strong independent risk factor for short-term mortality and critical illness in Mexican patients with COVID-19

1 Introduction

2
3 The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes an
4 acute respiratory and systemic disease known as coronavirus disease (COVID-19).
5 Systemic adiposity at all levels (subcutaneous, visceral, and ectopic) may complicate
6 the management of acute lung and systemic diseases like COVID-19 through
7 mechanical and inflammatory complications that commonly occur in the “chronic
8 diseases associated with adiposity” [1].

9 Mechanical consequences derive from the accumulation of adipose tissue in soft
10 tissues of the pharynx, which may compromise ventilation, and the visceral
11 compartment at the mesenteric and omental levels, causing renal compression that
12 favours systemic arterial hypertension and other dysregulations [2]. Inflammatory
13 mechanisms are promoted when adipocytes saturate their storage capacity and
14 undergo apoptosis, leading to a local inflammatory response that favours
15 remodelling of adipose tissue with a phenotypic switch of regulatory M2
16 macrophages to pro-inflammatory M1 macrophages which release pro-inflammatory
17 cytokines (i.e. IL-1 b, TNF a, IL-6) at the systemic level [3]. The chronic pro-
18 inflammatory state that characterises obesity could contribute to disease
19 progression in COVID-19 due to a strong, uncontrolled, and sustained systemic
20 inflammatory response.

21 The Mexican population is metabolically different from people of Asian and European
22 descent, having a higher prevalence of early-onset overweight and obesity [4].
23 Chronic overfeeding in quantity and frequency of highly processed foods has
24 unleashed an epidemic of obesity in recent decades [5]. Currently, 75.2% of the

1 Mexican population over 20 years of age is overweight (39.1%) or obese (36.1%)
2 [6]; thus, the toll of COVID-19 could be higher in Mexico by affecting younger people
3 compared to populations with a lesser burden of disease among young adults.

4 Increased age, chronic obstructive pulmonary disease (COPD), cardiovascular
5 disease (CVD), diabetes mellitus (DM), obesity, chronic kidney disease (CKD), and
6 immunocompromise have been established as the main risk factors for severe
7 disease in Mexican patients with COVID-19 [7–9]. Obesity is the comorbidity with
8 the strongest association with a positive test for SARS-CoV-2 in Mexican patients
9 with predominantly symptomatic COVID-19 [10]. However, the role of obesity as a
10 risk factor in COVID-19 remains controversial since one systematic review found that
11 obesity was not a strong predictor for COVID-19 severity and was not associated
12 with increased mortality risk [11], whereas another systematic review found that
13 obesity was associated with increased mortality only in studies with fewer chronic
14 and critical patients [12], suggesting that failure to include patients within the whole
15 spectrum of COVID-19 severity and with fewer comorbidities could mask the risk
16 attributable to obesity.

17 The impact of obesity as a contributing risk factor has been assessed in studies
18 including predominantly old multimorbid individuals, but not when obesity is the sole
19 or only concomitant comorbidity. This is problematic since estimated risks in
20 multimorbid patients with COVID-19 could be attributable to complex interactions
21 between distinct concomitant diseases and increased age. Therefore, it is important
22 to elucidate if individual comorbidities present in predominantly young patients act
23 as significant risk factors for adverse COVID-19-related outcomes and to explore the
24 effect of their combination with other individual comorbidities.

In this study, we aimed to elucidate if obesity is an independent risk factor for short-term mortality and other adverse outcomes in patients with obesity as their only comorbidity and patients with obesity plus one other comorbidity who were evaluated for suspected COVID-19 in both ambulatory units and hospitals in Mexico.

Methods

We carried out a retrospective observational study in a national cohort of individuals included in Mexico's COVID-19 National Epidemiologic Surveillance Study. To limit variations in testing, mortality rates, changes in standards of care, and to avoid the effect of saturation of hospitals, we contemplated 71,103 patients evaluated for suspected COVID-19 in the first 2-month period of the pandemic in Mexico between February 24 and April 26, 2020. We used an open dataset made available through the Directorate General of Epidemiology of Mexico's Secretariat of Health [13], in their Historical Dataset Repository [14]. Patients were grouped according to SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) result into positive, negative, or pending.

Criteria for suspected COVID-19 case were at least two of three signs/symptoms (cough, fever, or headache) plus at least one other (dyspnea, arthralgias, myalgias, sore throat, rhinorrhea, conjunctivitis, or chest pain) in the last 7 days.

Clinicians and epidemiologists collect baseline demographic and clinical variables, as well as follow-up variables daily for at least 7 days in ambulatory patients who are considered recovered after 14 days from symptom onset if alive and not hospitalised. For hospitalised patients, follow-up occurs daily until discharge. In order to upload

testing results, laboratories are required to have accredited SARS-CoV-2 RT-PCR procedures by the Mexican Institute of Diagnostics and Epidemiological Reference. Clinical, demographic, and follow-up data collected and publicly released were: age, origin, sex, nationality, pregnancy, smoker status, symptom onset date, date of medical attention, contact with another confirmed case, comorbidities (DM, COPD, asthma, immunosuppression, hypertension, CVD, obesity [defined as a body mass index ≥ 30], and CKD), clinical diagnosis of pneumonia, invasive mechanical ventilation (IMV), and admission to an intensive care unit (ICU). Age was categorized into 6 groups: ≤ 20 years, 21-30 years, 31-40 years, 41-50 years, 51-60 years, and >60 years. Days elapsed from symptom onset to initial care, and days from symptom onset to death were calculated. Comorbidities were determined by anamnesis and classified as dummy variables (present or absent). Patients with the same individual comorbidity were grouped to evaluate impact of isolated comorbidities; those with obesity and only one other comorbidity were also grouped and compared to patients with no comorbidities. The primary endpoint was all-cause mortality. Secondary endpoints were the hospitalisation, pneumonia, IMV, and ICU admission.

Statistical analysis

Categorical variables are presented as frequencies and percentages; quantitative variables, as mean and standard deviation (SD) or median with interquartile range (IQR). Comparisons between categorical variables were made with Chi-square. For

quantitative variables, with Student's t-Test, Mann Whitney U ore one-way ANOVA with post-hoc analysis by Tukey's test.

Multivariate regression analyses were done through Cox proportional-hazards regression models to predict mortality risk in patients with obesity and other comorbidities, according to test result: positive, negative, or pending. Logistic regression models were performed to determine the risk of other adverse events accordingly. Variables with a p value <0.1 were considered for inclusion in the multivariate regression model by the Enter method. Models for each group were adjusted for sex, age, smoker, and time from symptom onset to medical care. To corroborate robustness of the association between obesity and other comorbidities and mortality in SARS-CoV-2-positive patients, sensitivity analyses were performed; multivariate-adjusted Cox regression models were repeated in 3 subgroups after excluding hospitalised, intubated, and ICU-admitted patients. A $p < 0.05$ was used to define statistical significance. All analyses were performed in SPSS v.21 and GraphPad Prism v.8.0.1.

Results

71,103 patients evaluated for suspected COVID-19 were included for analysis, of which 15,529 (21.8%) tested positive for SARS-CoV-2, 46,960 (66.1%) were negative, and 8,614 (12.1%) had pending results. There was a higher proportion of men in positive-test and pending-result groups, whereas more women had a negative test. Patients in the positive-test group were older than negative-test and pending-result patients. Proportions of hospitalised patients, clinical diagnosis of

pneumonia, IMV, and ICU admission were greater in the positive-test group (Table 1).

The case-fatality rate in positive patients (9.2%) was higher than negative (1.9%) and pending-result (1.6%) patients. Of hospitalised patients, 21% of positive-test cases died, while only 8.3% and 4.6% in negative and pending-result groups died, respectively ($p<0.0001$).

Comorbidities of non-survivors in the positive-test, negative-test, and pending-result groups were, respectively: DM (38.8%, 40.9, and 38.8%), COPD (7.5%, 14.9%, and 8.8%), asthma (3.1%, 2.4%, and 5.1%), immunosuppression (4.7%, 10.3%, and 4.4%), hypertension (43%, 43.1%, and 38.7%), CVD (6.3%, 13.4%, and 10.2%), obesity (30.5%, 18%, and 23.4%), and CKD (6.6%, 13.4%, and 12.4%). Ages of non-survivors were similar ($p=0.9$) in the positive (59.3 years, SD:14.2), negative (57.9, SD:22.4), and pending-result (57.2, SD:17.5) groups. Non-survivors were older than survivors ($p<0.0001$): positive-test (59.3, SD:14.2 vs. 45.3, SD:15.04), negative-test (57.9, SD:22.4 vs. 39.2, SD:17.6) and pending-result (57.2, SD:17.5 vs. 42.9, SD:17.2). Median time from symptom onset to medical care was similar between survivors and non-survivors in positive cases (4 days, IQR:2-6 vs. 4 days, IQR:1-6, $p=0.4$), but not in negative (2 days, IQR:0-4.5 vs. 3 days, IQR:1-5, $p<0.0001$) and pending-result (4 days, IQR:1.5-7 vs. 3 days, IQR:1-5, $p=0.002$) groups.

After grouping patients with only one comorbidity and those with obesity plus only one other comorbidity (Supplementary Tables S1-S3), obesity was found to be the leading risk factor for death in positive-test patients. In all mortality risk models (Table 2) for individual comorbidities compared with no comorbidities, patients with obesity

1 had higher adjusted mortality risk than those with DM, COPD, asthma,
2 immunosuppression, hypertension, and CVD. When obesity was present with
3 another comorbidity, the risk has higher.

4 No changes in the findings of primary models resulted from sensitivity analyses for
5 obesity, but risks for other comorbidities did change (Table 3). Increased risk of
6 death in patients with obesity alone persisted after excluding hospitalised patients,
7 those requiring IMV, or admitted to ICU.

8 Obesity alone and in combination with other comorbidities was a significant risk
9 factor for secondary outcomes (pneumonia, hospitalisation, IMC, and ICU
10 admission) in patients positive for SARS-CoV-2 (Figure 1). However, it was not a
11 determining risk factor for all these endpoints in the negative and pending-result
12 groups (Figure 2 and Figure 3).

14 **Discussion**

15 The role of obesity as a risk factor for COVID-19-related adverse outcomes is
16 controversial since most studies including largely old, multimorbid, and severe-to-
17 critical patients often fail to detect differences in risks [11], but not when including
18 younger patients with lesser COVID-19 severity and burden of disease [12]. In this
19 retrospective national cohort study, we sought to study the impact of obesity alone
20 and in combination with other comorbidities as an independent risk factor for death
21 and other adverse outcomes (hospitalisation, pneumonia, IMV, and admission to
22 ICU) in patients evaluated for suspected COVID-19 in ambulatory units and hospitals
23 during the early stage of the pandemic in Mexico.

1 We observed that obesity was the leading independent risk factor for mortality and
2 other COVID-19-related adverse outcomes when present alone or in combination
3 with other individual comorbidities. Increased risk for short-term all-cause mortality
4 and adverse outcomes was greater in patients with a positive test for SARS-CoV-2
5 with obesity alone or in combination with one accompanying disease. Importantly, in
6 patients with a negative test for SARS-CoV-2 and patients without a definitive result,
7 obesity was not a risk factor for all these outcomes or had a lower increase in risk
8 than patients with a positive test.

9 Our study included both ambulatory and hospitalised patients, with a large
10 representation of COVID-19 patients who did not require hospitalisation (61.1%).
11 SARS-CoV-2-positive patients in our study were younger (46.6, SD:15.5 years) than
12 the majority of studies included in one systematic review to determine mortality risk
13 attributable to comorbidities in patients with COVID-19 [12]; 47.8% of cases in our
14 cohort were between 41 and 60 years old, reflecting that the pandemic affected
15 younger patients in Mexico during its early period. Like most other studies, men
16 (57.8%) comprised a greater proportion of confirmed COVID-19 cases [12].
17 Hypertension (21.7%), obesity (20.7%) and DM (18.2%) were the most prevalent
18 comorbidities in SARS-CoV-2-positive patients, being higher in non-survivors (43%,
19 30.5%, and 38.8%, respectively). The prevalence of hypertension (18.4%) in people
20 20 years and older reported in the 2018 National Health and Nutrition Survey is
21 similar to that in our study, whereas numbers for obesity (36.1%) and DM (10.3%)
22 were reported to be higher and lower, respectively, in the Mexican population [6].
23 Despite being younger, patients in our cohort had a higher prevalence of obesity

1 than both survivors (14.2%) and non-survivors (17.1%) included in a systematic
2 review [12].

3 After multivariable adjustment, obesity alone was a strong independent risk factor
4 for short-term all-cause mortality in patients with a positive test for SARS-CoV-2
5 (HR=2.37, 95%CI:1.96-2.86), but not in patients with a negative test (HR=1.09,
6 95%CI:0.74-1.59) or with unreleased results (HR=1.73, 95%CI:0.86-3.49). In the
7 sensitivity analyses, obesity persisted as a strong and significant risk factor for death
8 after excluding patients requiring hospitalisation, IMV, or ICU. Obesity alone was
9 also associated with increased risk of secondary adverse outcomes (pneumonia,
10 hospitalisation, IMV, and ICU admission). This is consistent with a recent
11 metanalysis which found that obesity was a significant risk factor for having a positive
12 test for SARS-CoV-2, COVID-19 severity, hospitalisation, IMV, ICU admission, and
13 mortality [15].

14 Other individual comorbidities associated with increased mortality after multivariable
15 adjustment were DM, COPD, immunosuppression, hypertension, and CVD, which
16 have also been found as risk factors in other studies [12,16]. However, obesity alone
17 had larger increases in mortality risk than all these diseases alone. After sensitivity
18 analyses, hypertension, DM, and immunosuppression, remained as significant risk
19 factors; COPD and CVD alone were not risk factors for death in these analyses,
20 which could be due to loss of statistical power after the exclusion of patients,
21 although this could reflect that rather than favouring disease progression, COPD and
22 CVD could complicate in-hospital management of patients [17,18]. Furthermore,
23 distinguishing between current and former smoker status is important to adequately
24 assess risks of adverse outcomes in patients with COPD [19]. Similar to other

1 studies, asthma was not a significant risk factor for COVID-19-related adverse
2 outcomes [16,20]; the combination of asthma and obesity increased mortality risk,
3 but this association was lost after sensitivity analyses. We were not able to assess the
4 effect of recent use of systemic corticosteroids in asthmatic patients, which has been
5 shown to be a significant risk factor for adverse outcomes in patients with COVID-
6 19 rather than history of asthma alone [16,20]. CKD alone did not increase mortality
7 risk, which could be due to the low number of patients included in our study since
8 CKD has been found to be a risk factor in others [16,21]. However, the role of CKD
9 as an individual risk factor for adverse outcomes in COVID-19 should be explored
10 since CKD is often present in combination with DM and hypertension [22], which
11 were individual risk factors in our study.

12 Obesity combined with DM, asthma, immunosuppression, and hypertension, had
13 higher increases in mortality risk than in patients with these comorbidities but without
14 obesity. For COPD, CVD, or CKD combined with obesity, mortality risks were not
15 statistically significantly increased, possibly due to the low number of patients
16 presenting these comorbidities combined (n=24, n=20, and n=11, respectively),
17 which reflects that these comorbidities are often present with more than one
18 concomitant disease in the general population [22–24].

19 Regarding secondary endpoints (pneumonia, hospitalisation, IMC, and ICU
20 admission), obesity alone and in combination with other individual comorbidities was
21 a significant risk factor in patients with a positive test for SARS-CoV-2, but not in
22 those with a negative or pending result.

23 The main limitation of our study is that obesity was classified as a dichotomous
24 variable in this dataset. Therefore, we were not able to assess if the magnitude of

1 obesity significantly modifies risks. One study found that higher obesity classes
2 gradually increase short-term mortality risk [16]. However, one metanalysis found
3 that obesity increases the risk of mortality, COVID-19 severity, and other adverse
4 outcomes in an non-body mass index dependent fashion [15]. Other limitations
5 include the retrospective observational limitation of our study, and the unavailability
6 of treatments in the dataset to evaluate their potential impact on mortality risks.

7 The strengths of our study are its high representativity and generalisability since we
8 included a large sample size from representative COVID-19 ambulatory units and all
9 hospitals in Mexico. Furthermore, we limited potential confounding by highly
10 delimiting the study period and through multivariable adjustment. Lastly, this is the
11 first study, to the best of our knowledge, to evaluate risk of death and other adverse
12 outcomes in predominantly young patients who have obesity as their sole
13 comorbidity or in combination with only one additional comorbidity.

14 This association between obesity and adverse outcomes has been reported in the
15 context of other viral diseases that course with severe pneumonia, such as influenza
16 A H1N1, for which obesity is an independent risk factor for severe disease,
17 hospitalisation, IMV, and mortality [25]. Immune dysregulation and disturbances in
18 hormones (i.e. leptin) in patients with obesity have been proposed as the main
19 mechanisms underlying increased susceptibility to influenza viruses [26].
20 Importantly, obese individuals experience diminished production of type I interferons
21 (IFN) (IFN- α and IFN- β) and delayed pro-inflammatory responses when infected with
22 the influenza A H1N1 virus [27]. This could partly explain increased susceptibility of
23 patients with obesity to SARS-CoV-2 infection since impaired type I IFN responses

1 and altered pro-inflammatory responses are known to occur in patients who
2 experience COVID-19 progression [28].

3 The mechanical component of patients with obesity may be an essential component
4 that complicates the management of COVID-19. In a multicentre study that included
5 1,317 patients with diabetes, obstructive sleep apnoea (OSA) under treatment was
6 an independent risk factor for 7-day mortality (OR=2.8, 95%CI:1.46-2.38);
7 overweight and obesity were highly prevalent in this study [29]. Furthermore, OSA
8 was a significant risk factor for hospitalisation and respiratory failure after
9 multivariable adjustment in another study [30]. Although risk factors associated with
10 severe-to-critical COVID-19 are similar to those found in the population with the
11 highest prevalence of OSA (men, obesity, advanced age), it is estimated that 90%
12 of patients with OSA are undiagnosed [31].

13 Upper airway obstruction due to the collapse of pharyngeal soft tissues with
14 excessive accumulation of adipose tissue is associated with Intermittent periods of
15 hypoxemia that affect the pulmonary circulation; up to 70% of patients with OSA
16 have been reported to have pulmonary arterial hypertension (PAH) [32]. Patients
17 with OSA have impaired right ventricular function characterised by decreased
18 ejection fraction and distensibility, without dependency of PAH [33].

19 Furthermore, it has been shown that, within the pathophysiology of PAH due to OSA,
20 pulmonary microcirculation presents hypoxic vasoconstriction and endothelial
21 dysfunction that promotes a pro-inflammatory and local procoagulant state [34].

22 These factors may be important in the progression of COVID-19 by promoting viral-
23 induced damage of the endothelium of pulmonary capillaries, causing local
24 inflammation, and thrombotic events [35,36]. Therefore, the combination of these

factors could favour severe pulmonary inflammation in patients with obesity, which could explain the greater requirements of IMV, ICU admission, and mortality.

From a critical medicine point of view, obesity represents a challenge in critically ill patients requiring IMV since this condition has been reported to generate functional alterations in the respiratory system with reduced compliance of the chest and abdominal walls, airway obstruction, reduction in tele-expiratory volume and a higher incidence of atelectasis [37]. Additionally, obesity is associated with chronic hypoventilation and OSA. As previously mentioned, these conditions increase the risk of difficult ventilation and intubation scenarios during the rapid intubation sequence, as well as alterations in gas exchange, respiratory mechanics, and hemodynamic disturbances in patients under IMV, thereby complicating ventilatory management [38]. Patients with obesity who progress to critical COVID-19 present a higher frequency of treatment failure with high-flow nasal cannulas, higher IMV requirements, higher frequencies of ventilatory therapy in the prone position, and a higher frequency of retarded removal of IMV and tracheostomies [39].

In conclusion, obesity is a strong independent risk factor for short-term all-cause mortality and critical illness in Mexican patients with COVID-19 when present as the only comorbidity or in combination with other individual comorbidities. The risk conferred by obesity increases when it is present alongside other comorbidities, particularly, DM, hypertension, and immunosuppression.

Ethical disclosures: This article is a retrospective study of an open-source dataset of patients in Mexico. The Ministry of Health of Mexico approved the recollection of information.

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Data Availability Statements

The data that support the findings of this study are openly available in Historical COVID-19 Datasets of the Directorate General of Epidemiology of Mexico at <https://www.gob.mx/salud/documentos/datos-abiertos-bases-historicas-direccion-general-de-epidemiologia>, reference number [13].

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Table 1. Baseline and follow-up characteristics of patients according to RT-PCR for SARS-CoV-2 test result: positive, negative, or pending.

	Positive n=15529	Negative n=46960	Pending- result n=8614	p value
Sex				
Women, n (%)	6552 (42.2)	25005 (53.2)	3950 (45.9)	<0.0001
Men, n (%)	8977 (57.8)	21955 (46.8)	4664 (54.1)	
Age, years	46.6 (15.5)	39.6 (17.9)	43.2 (17.3)	<0.0001
Age, n (%)				
≤20	372 (2.4)	4858 (10.3)	622 (7.2)	<0.0001
21-30	2029 (13.1)	10080 (21.5)	1346 (15.6)	
31-40	3408 (21.9)	11596 (24.7)	2084 (24.2)	
41-50	3717 (23.9)	8816 (18.8)	1794 (20.8)	
51-60	3717 (23.9)	5778 (12.3)	1376 (16)	

>60	3113 (20)	5832 (12.4)	1392 (16.2)	
Smoker, n (%)	1374 (8.8)	4835 (10.3)	811 (9.4)	0.009
Pregnancy, n (%)	91 (0.6)	649 (1.4)	58 (0.7)	0.006
Contact with confirmed case, n (%)	4230 (27.2)	13273 (28.3)	3251 (37.7)	<0.0001
Comorbidities, n (%)				
DM	2831 (18.2)	5163 (11)	1323 (15.4)	<0.0001
COPD	389 (2.5)	1330 (2.8)	214 (2.5)	0.6
Asthma	542 (3.5)	2571 (5.5)	337 (3.9)	<0.0001
Immunosuppression	296 (1.9)	1402 (3)	183 (2.1)	0.004
Hypertension	3370 (21.7)	7553 (15.7)	1611 (18.7)	<0.0001
CVD	453 (2.9)	1610 (3.4)	267 (3.1)	0.1
Obesity	3215 (20.7)	6570 (14)	1532 (17.8)	<0.0001
CKD	359 (2.3)	1130 (2.4)	262 (3)	0.002
Number of comorbidities, n (%)				
No comorbidities	8422 (54.2)	30316 (63.9)	5057 (58.7)	<0.0001

One comorbidity	4073 (26.2)	10220 (21.8)	2086 (24.2)	
Two comorbidities	2029 (13.1)	4250 (9.1)	959 (11.1)	
≥3 comorbidities	1005 (6.5)	2474 (5.3)	512 (5.9)	
Time from symptom onset to medical care, days	4 (2-6)	3 (1-5)	3 (1-5)	<0.0001
Hospitalisation, n (%)	6042 (38.9)	9974 (21.2)	2607 (30.3)	<0.0001
Pneumonia, n (%)	4588 (29.5)	6341 (13.5)	1841 (21.4)	<0.0001
IMV, n (%)	669 (4.3)	598 (1.3)	197 (2.3)	<0.0001
ICU admission, n (%)	676 (4.4)	774 (1.6)	211 (2.4)	<0.0001
Case-fatality rate, n (%)	1434 (9.2)	881 (1.9)	137 (1.6)	<0.0001
<p>Data are presented as mean (SD) or median (1Q-3Q).</p> <p>Comparisons between groups were made by chi-square or t-Tests.</p> <p>CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; ICU, intensive care unit; Immunosupp, immunosuppression; IMV, invasive mechanical ventilation.</p>				

Table 2. Mortality risk of patients according to RT-PCR for SARS-CoV-2 test result: positive, negative, or pending.

	Positive ^a		Negative ^b		Pending-result ^c	
	Crude model	Adjusted model	Crude model	Adjusted model	Crude model	Adjusted model
Obesity model						
Without comorbidities	REFERENCE					
Obesity alone	2.37 (1.96-2.86)	2.51 (2.08-3.04)	1.18 (0.81-1.73)	1.09 (0.74-1.59)	1.79 (0.89-3.61)	1.73 (0.86-3.49)
DM model						
Without comorbidities	REFERENCE					
DM alone	3.66 (2.99-4.49)	1.96 (1.59-2.41)	5.92 (4.46-7.85)	3.15 (2.34-4.24)	3.17 (1.58-6.38)	1.88 (0.92-3.86)
Obesity alone	2.36 (1.95-2.84)	2.44 (2.02-2.95)	1.18 (0.81-1.73)	1.08 (0.74-1.57)	1.79 (0.89-3.61)	1.74 (0.87-3.49)
DM + Obesity	3.88 (2.85-5.29)	2.93 (2.15-3.99)	3.78 (2.07-6.92)	2.47 (1.35-4.55)	1.91 (0.46-7.92)	1.49 (0.36-6.19)
COPD model						
Without comorbidities	REFERENCE					
COPD alone	5.92 (3.64-9.64)	1.76 (1.07-2.09)	11.98 (8.23-17.44)	3.71 (2.43-5.63)	1.95 (0.27-14.24)	0.58 (0.08-4.48)
Obesity alone	2.36 (1.96-2.86)	2.48 (2.05-3.00)	1.18 (0.81-1.73)	1.07 (0.74-1.58)	1.79 (0.89-3.61)	1.74 (0.86-3.49)
COPD + Obesity	4.29 (1.60-11.5)	2.25 (0.83-6.07)	5.84 (1.45-23.5)	2.03 (0.49-8.25)	9.86 (1.35-72.01)	4.43 (0.59-32.71)

Asthma model						
Without comorbidities	REFERENCE					
Asthma alone	0.35 (0.13-0.96)	0.64 (0.24-1.71)	0.49 (0.22-1.11)	0.59 (0.26-1.33)	0.83 (0.14-6.05)	1.28 (0.17-9.41)
Obesity alone	2.37 (1.96-2.86)	2.49 (2.06-3.01)	1.18 (0.81-1.72)	1.08 (0.74-1.58)	1.80 (0.89-3.62)	1.75 (0.87-3.51)
Asthma + Obesity	1.42 (0.59-3.45)	2.57 (2.08-3.18)	1.63 (0.61-4.39)	1.76 (0.66-4.80)	Not estimable	
Immunosuppression model						
Without comorbidities	REFERENCE					
Immunosupp. alone	3.04 (1.75-5.28)	2.43 (1.39-4.22)	5.96 (4.05-8.77)	5.16 (3.50-7.62)	4.13 (1.27-13.41)	3.69 (1.13-12.05)
Obesity alone	2.36 (1.96-2.86)	2.47 (2.05-2.98)	1.18 (0.81-1.73)	1.08 (0.74-1.58)	1.79 (0.89-3.61)	1.73 (0.86-3.47)
Immunosupp. + Obesity	5.62 (2.51-12.6)	4.68 (2.09-10.5)	6.33 (2.03-19.79)	4.66 (1.49-14.59)	37.6 (5.11-276.44)	33.92 (4.58-250.88)
Hypertension model						
Without comorbidities	REFERENCE					
Hypertension alone	2.98 (2.45-3.65)	1.32 (1.07-1.63)	3.31 (2.48-4.41)	1.39 (1.03-1.90)	2.38 (1.19-4.78)	1.15 (0.55-2.39)
Obesity alone	2.37 (1.96-2.86)	2.47 (2.05-2.98)	1.18 (0.81-1.73)	1.08 (0.73-1.58)	1.78 (0.88-3.57)	1.73 (0.86-3.47)
Hypertension + Obesity	3.44 (2.64-4.48)	2.31 (1.77-3.02)	2.43 (1.48-3.97)	1.38 (0.84-2.28)	2.25 (0.81-6.31)	1.48 (0.53-4.19)
CVD model						

Without comorbidities	REFERENCE					
CVD alone	3.55 (2.05-6.18)	1.98 (1.14-3.45)	4.75 (2.47-8.14)	2.90 (1.67-5.04)	2.75 (0.95-11.64)	1.21 (0.25-5.74)
Obesity alone	2.37 (1.96-2.86)	2.48 (2.06-3.01)	1.18 (0.81-1.73)	1.08 (0.74-1.58)	1.79 (0.89-3.59)	1.72 (0.86-3.45)
CVD + Obesity	2.82 (0.70-11.3)	1.49 (0.37-6.02)	7.82 (2.91-21.02)	4.73 (1.75-12.77)	7.53 (1.03-55.03)	9.61 (1.31-70.38)
CKD model						
Without comorbidities	REFERENCE					
CKD alone	1.77 (0.66-4.76)	1.31 (0.49-3.51)	6.81 (3.51-13.26)	3.16 (1.83-7.11)	8.07 (1.95-33.46)	5.02 (1.19-21.13)
Obesity alone	2.37 (1.96-2.86)	2.48 (2.06-3.00)	1.18 (0.81-1.73)	1.07 (0.74-1.58)	1.79 (0.89-3.61)	1.74 (0.87-3.51)
CKD + Obesity	2.69 (0.38-19.2)	4.39 (0.62-31.3)	10.37 (2.57-41.71)	7.40 (1.84-29.79)	15.96 (2.18-116.79)	8.91 (1.21-65.45)
<p>Data are presented as HR (95%CI)</p> <p>a: Model adjusted by sex, age, and time from symptom onset to care. b: Model adjusted by sex, age, and time from symptom onset to care. c: Model adjusted by sex, age, smoking, and time from symptom onset to care.</p> <p>95%CI, 95% confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; Immunosupp, immunosuppression.</p>						

Table 3. Sensitivity analyses of mortality risk in SARS-CoV-2-positive cases

	Excluding hospitalised patients	Excluding patients requiring IMV	Excluding patients admitted to ICU
Obesity model			
Without comorbidities	Reference		
Obesity alone	3.17 (1.73-5.79)	2.42 (1.93-3.02)	2.55 (2.06-3.15)
DM model			
Without comorbidities	Reference		
DM alone	3.26 (1.73-6.13)	2.25 (1.79-2.82)	2.14 (1.70-2.68)
Obesity alone	3.13 (1.71-5.71)	2.36 (1.89-2.95)	2.49 (2.02-3.09)
DM + obesity	2.54 (0.79-8.25)	2.78 (1.92-4.04)	3.05 (2.15-4.31)
COPD model			
Without comorbidities	Reference		
COPD alone	2.71 (0.64-11.59)	1.67 (0.92-3.00)	1.63 (0.91-3.94)
Obesity alone	3.15 (1.72-5.75)	2.41 (1.93-3.02)	2.54 (2.06-3.15)
COPD + obesity	5.25 (0.69-39.73)	2.10 (0.67-6.62)	2.05 (0.65-6.46)
Asthma model			
Without comorbidities	Reference		

Asthma alone	Not estimable	0.43 (0.11-1.71)	0.19 (0.03-1.42)
Obesity alone	3.17 (1.73-5.79)	2.41 (1.93-3.02)	2.55 (2.06-3.15)
Asthma + obesity	Not estimable	1.68 (0.54-5.23)	1.58 (0.50-4.92)
Immunosuppression model			
Without comorbidities	Reference		
Immunosupp. alone	2.45 (0.34-17.92)	2.60 (1.42-4.77)	2.83 (1.58-5.05)
Obesity alone	3.16 (1.73-5.77)	2.39 (1.92-3.00)	2.53 (2.04-3.13)
Immunosuppression + obesity	Not estimable	5.94 (2.65-13.34)	5.07 (2.09-12.3)
Hypertension model			
Without comorbidities	Reference		
Hypertension alone	1.33 (0.69-2.58)	1.34 (1.05-1.70)	1.40 (1.11-1.76)
Obesity alone	3.18 (1.74-5.79)	2.39 (1.92-2.99)	2.53 (2.05-3.13)
Hypertension + obesity	2.55 (1.07-6.05)	2.02 (1.45-2.81)	2.17 (1.59-2.98)
CVD model			
Without comorbidities	Reference		
CVD alone	Not estimable	1.66 (0.82-3.37)	1.58 (0.78-3.19)
Obesity alone	3.17 (1.73-5.79)	2.42 (1.93-3.03)	2.55 (2.06-3.15)
CVD + obesity	Not estimable	Not estimable	0.88 (0.12-6.25)

CKD model			
Without comorbidities	Reference		
CKD alone	Not estimable	0.93 (0.23-3.72)	0.40 (0.06-2.87)
Obesity alone	3.17 (1.73-5.79)	2.41 (1.93-3.02)	2.54 (2.06-3.15)
CKD + obesity	Not estimable	Not estimable	5.34 (0.75-38.15)
<p>Data presented as HR (95%CI)</p> <p>95%CI, 95% confidence Interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HR, Hazard ratio; ICU, intensive care unit; IMV, invasive mechanical ventilation</p> <p>All models were adjusted by sex and age.</p>			

Figure 1. Risk of secondary adverse outcomes in patients with a positive test for SARS-CoV-2 with obesity or obesity plus one other comorbidity.

A: Risk of hospitalisation, model adjusted by sex, age, smoker; B: Risk of IMV, model adjusted by sex, age, smoker and time from symptom onset to care; C: Risk of pneumonia, model adjusted by sex, age, smoker and time from symptom onset to care; D: Risk of admission to ICU, model adjusted by sex, age, and time from symptom onset to care.

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; Immunosupp, Immunosuppression; ICU, intensive care unit; IMV, invasive mechanical ventilation

Figure 2. Risk of secondary adverse outcomes in patients with a negative test for SARS-CoV-2 with obesity or obesity plus one other comorbidity.

A: Risk of hospitalisation, model adjusted by sex, age smoker and time from symptom onset to care; B: Risk of IMV, model adjusted by sex, age, smoker and time from symptom onset to care; C: Risk of pneumonia, model adjusted by sex, age, smoker and time from symptom onset to care; D: Risk of admission to ICU, model adjusted by sex, age, and smoker. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; Immunosupp, Immunosuppression; ICU, intensive care unit; IMV, invasive mechanical ventilation

Figure 3. Risk of secondary adverse outcomes in patients with a pending result for SARS-CoV-2 test with obesity or obesity plus one other comorbidity.

A: Risk of hospitalisation, model adjusted by sex, age and time from symptom onset to care; B: Risk of IMV, model adjusted by sex, age and time from symptom onset to care; C: Risk of pneumonia, model adjusted by sex, age and time from symptom onset to care; D: Risk of admission to ICU, model adjusted by sex, age, and time from symptom onset to care.

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; Immunosupp, Immunosuppression; ICU, intensive care unit; IMV, invasive mechanical ventilation