

Original Paper

*These authors contributed equally to this work.

Cite this article: Vera-Zertuche JM *et al* (2021). Obesity is a strong risk factor for short-term mortality and adverse outcomes in Mexican patients with COVID-19: a national observational study. *Epidemiology and Infection* **149**, e109, 1–11. <https://doi.org/10.1017/S0950268821001023>

Received: 26 December 2020

Revised: 3 April 2021

Accepted: 22 April 2021

Key words:

Comorbidities; coronavirus; COVID-19; mortality; obesity; SARS-CoV-2

Authors for correspondence:

A. Kammar-García,

E-mail: kammar_nutrition@hotmail.com;

J. de J. Vidal-Mayo,

E-mail: interstrok@hotmail.com

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

J. M. Vera-Zertuche^{1,*}, J. Mancilla-Galindo^{2,*} , M. Tlalpa-Prisco³, P. Aguilar-Alonso⁴, M. M. Aguirre-García², O. Segura-Badilla⁵, M. Lazcano-Hernández⁴, H. I. Rocha-González³, A. R. Navarro-Cruz⁴, A. Kammar-García^{3,6}  and J. de J. Vidal-Mayo⁶

¹Endocrinology Department, Obesity Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; ²Unidad de Investigación UNAM-INC, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico; ³Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina, Instituto Politécnico Nacional, Mexico City, Mexico; ⁴Facultad de Ciencias Químicas, Departamento de Bioquímica y Alimentos, Benemérita Universidad Autónoma de Puebla, Puebla, Mexico; ⁵Facultad de Ciencias de la Salud y de los Alimentos, Departamento de Nutrición y Salud Pública, Programa UBB Saludable, Universidad del Bío-Bío, Bío-Bío, Chile and ⁶Emergency Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Abstract

Conflicting results have been obtained through meta-analyses for the role of obesity as a risk factor for adverse outcomes in patients with coronavirus disease-2019 (COVID-19), possibly due to the inclusion of predominantly multimorbid patients with severe COVID-19. Here, we aimed to study obesity alone or in combination with other comorbidities as a risk factor for short-term all-cause mortality and other adverse outcomes in Mexican patients evaluated for suspected COVID-19 in ambulatory units and hospitals in Mexico. We performed a retrospective observational analysis in a national cohort of 71 103 patients from all 32 states of Mexico from the National COVID-19 Epidemiological Surveillance Study. Two statistical models were applied through Cox regression to create survival models and logistic regression models to determine risk of death, hospitalisation, invasive mechanical ventilation, pneumonia and admission to an intensive care unit, conferred by obesity and other comorbidities (diabetes mellitus (DM), chronic obstructive pulmonary disease, asthma, immunosuppression, hypertension, cardiovascular disease and chronic kidney disease). Models were adjusted for other risk factors. From 24 February to 26 April 2020, 71 103 patients were evaluated for suspected COVID-19; 15 529 (21.8%) had a positive test for SARS-CoV-2; 46 960 (66.1%), negative and 8614 (12.1%), pending results. Obesity alone increased adjusted mortality risk in positive patients (hazard ratio (HR) = 2.7, 95% confidence interval (CI) 2.04–2.98), but not in negative and pending-result patients. Obesity combined with other comorbidities further increased risk of death (DM: HR = 2.79, 95% CI 2.04–3.80; immunosuppression: HR = 5.06, 95% CI 2.26–11.41; hypertension: HR = 2.30, 95% CI 1.77–3.01) and other adverse outcomes. In conclusion, obesity is a strong risk factor for short-term mortality and critical illness in Mexican patients with COVID-19; risk increases when obesity is present with other comorbidities.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes an acute respiratory and systemic disease known as coronavirus disease (COVID-19). Increasing number of studies have linked obesity with adverse outcomes in patients who develop COVID-19 [1]. Systemic adiposity at all levels (subcutaneous, visceral and ectopic) may complicate the management of acute lung and systemic diseases such as COVID-19 through mechanical and inflammatory complications that commonly occur in the ‘chronic diseases associated with adiposity’ [2].

Mechanical consequences derive from the accumulation of adipose tissue in soft tissues of the pharynx, which may compromise ventilation, and the visceral compartment at the mesenteric and omental levels, causing renal compression that favours systemic arterial hypertension and other dysregulations [3]. Inflammatory mechanisms are promoted when adipocytes saturate their storage capacity and undergo apoptosis, leading to a local inflammatory response that favours remodelling of adipose tissue with a phenotypic switch of regulatory

© The Author(s), 2021. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution, and reproduction in any medium, provided the original work is properly cited.

M2 macrophages to pro-inflammatory M1 macrophages which release pro-inflammatory cytokines (i.e. interleukin (IL)-1 β , TNF- α , IL-6) at the systemic level [4]. The chronic pro-inflammatory state that characterises obesity could contribute to disease progression in COVID-19 due to a strong, uncontrolled and sustained systemic inflammatory response.

The Mexican population is metabolically different from people of Asian and European descent, having a higher prevalence of early-onset overweight and obesity [5]. Chronic overfeeding in quantity and frequency of highly processed foods has unleashed an epidemic of obesity in recent decades [6]. Currently, 75.2% of the Mexican population over 20 years of age is overweight (39.1%) or obese (36.1%) [7]; thus, the toll of COVID-19 could be higher in Mexico by affecting younger people compared to populations with a lower burden of disease among young adults.

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

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

Study design

We carried out a retrospective observational study in a national cohort of individuals included in Mexico's COVID-19 National Epidemiologic Surveillance Study, in COVID-19-accredited medical units across the national territory of Mexico. 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 24

February and 26 April 2020. Patients were grouped according to SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) result into positive, negative or pending.

Exposures and outcomes

Patients with obesity as their unique comorbidity, and patients with obesity plus one other comorbidity who were suspected of having COVID-19 were considered as the exposures of interest. The main outcome of interest was all-cause mortality, defined as the occurrence of death up to 56 days after inclusion. The secondary outcomes of interest were the occurrence of hospitalisation, invasive mechanical ventilation (IMV), pneumonia or admission to an intensive care unit (ICU).

Source of data

We used an open dataset made available through the Directorate General of Epidemiology of Mexico's Secretariat of Health [14], in their Historical Dataset Repository [15]. Criteria for suspected COVID-19 case were at least two of three signs/symptoms (cough, fever or headache) plus at least one other (dyspnoea, arthralgias, myalgias, sore throat, rhinorrhoea, 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 (BMI) \geq 95th percentile for age and sex in patients younger than 18 years, and as a BMI $P \geq 30$ in patients 18 years or older) [16] and CKD), clinical diagnosis of pneumonia, IMV and admission to an ICU.

Management of variables

Age was categorised into six 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 through anamnesis during the initial medical evaluation in ambulatory units or hospitals, 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.

Socio-demographic characterisation of the population was performed according to poverty and social lag indicators for every municipality in which people who were suspected of having COVID-19 lived at the moment of inclusion in the

study. The socio-demographic variables obtained were social lag index (SLI), ageing index, afro-descendants per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, hospital evaluating rooms per 10 000 inhabitants, hospital beds per 10 000 inhabitants and members per household [17–19].

The SLI is a pondered measure derived from a principal component analysis of 11 variables that are determinants of education, health, basic urbanisation services and household spaces [18]. The ageing index is the estimated population >65 years divided by those 15 years or younger, and multiplied by 100 [19].

Statistical analysis

Categorical variables are presented as frequencies and percentages; quantitative variables, as mean and standard deviation (s.d.) or median with interquartile range (IQR). Comparisons between categorical variables were performed with χ^2 tests. For quantitative variables, with Student's *t* test, Mann–Whitney *U* or one-way analysis of variance (ANOVA) with Welch's test and post-hoc analysis by Tukey's test or Games–Howell's test.

Multivariate regression analyses were carried out 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; this model was used since it was considered suitable to the presentation of data for a time-dependent event (mortality) which is a function of survival. Logistic regression models were performed to determine the risk of other adverse events accordingly. Models for each group were adjusted for sex, age, smoker and time from symptom onset to medical care according to a *o* value <0.1 in the crude model. To control the confounding effect of socio-demographic variables for severe COVID-19 cases [20], all models were adjusted for the previously described socio-demographic variables.

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 three 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.9.0.2.

Results

A total of 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 8614 (12.1%) had pending results. Patients were residents of 1468 municipalities from all 32 states of Mexico. In total, 20.5% (*n* = 14 590) of all patients were residents of Mexico City and 11.2% (*n* = 8316) from the State of Mexico. 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. The 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 that of negative (1.9%) and pending-result (1.6%) patients. Of hospitalised patients, 21% of positive-test cases died, whereas 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, s.d.: 14.2), negative (57.9, s.d.: 22.4) and pending-result (57.2, s.d.: 17.5) groups. Non-survivors were older than survivors (*P* < 0.0001): positive-test (59.3, s.d.: 14.2 vs. 45.3, s.d.: 15.04), negative-test (57.9, s.d.: 22.4 vs. 39.2, s.d.: 17.6) and pending-result (57.2, s.d.: 17.5 vs. 42.9, s.d.: 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.

Patients with a positive test who died lived in municipalities with greater SLI than those who survived (−1.33, IQR: −1.42 to −1.11 vs. −1.26, IQR: −1.38 to −1.02, *P* < 0.0001); patients who survived lived in municipalities with a higher ageing index (29.1, IQR: 21.8–39.6 vs. 26.9, IQR: 20.9–35.7, *P* < 0.0001), and more hospitals per 10 000 inhabitants (3.57, IQR: 2.42–5.53, vs. 3.21, IQR: 2.42–5.40, *P* = 0.03).

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 one of the leading risk factors for death in positive-test patients. In all mortality risk models (Table 2) for individual comorbidities compared with no comorbidities, patients with obesity had higher adjusted mortality risk than those with DM, COPD, asthma, hypertension and CVD. When obesity was present with another comorbidity, the risk was higher.

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

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

Discussion

The role of obesity as a risk factor for COVID-19-related adverse outcomes is controversial since most studies including largely old, multimorbid and severe-to-critical patients often fail to detect differences in risks [12], but not when including younger patients with lower COVID-19 severity and burden of disease [13]. In this retrospective national cohort study, we sought to study the impact of obesity alone and in combination with other comorbidities as a risk factor for death and other adverse outcomes (hospitalisation, pneumonia, IMV and admission to ICU) in patients evaluated for suspected COVID-19 in ambulatory units and hospitals during the early stage of the pandemic in Mexico.

We observed that obesity was a strong risk factor for mortality and other COVID-19-related adverse outcomes when present alone or in combination with other individual comorbidities;

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

	Positive <i>n</i> = 15 529	Negative <i>n</i> = 46 960	Pending-result <i>n</i> = 8614	<i>P</i> value
Sex				
Women, <i>n</i> (%)	6552 (42.2)	25 005 (53.2)	3950 (45.9)	<0.0001
Men, <i>n</i> (%)	8977 (57.8)	21 955 (46.8)	4664 (54.1)	
Age, years	46.6 (15.5)	39.6 (17.9)*	43.2 (17.3)*	<0.0001
Age, <i>n</i> (%)				
≤20	372 (2.4)	4858 (10.3)	622 (7.2)	<0.0001
21–30	2029 (13.1)	10 080 (21.5)	1346 (15.6)	
31–40	3408 (21.9)	11 596 (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, <i>n</i> (%)	1374 (8.8)	4835 (10.3)	811 (9.4)	0.009
Pregnancy, <i>n</i> (%)	91 (0.6)	649 (1.4)	58 (0.7)	0.006
Contact with confirmed case, <i>n</i> (%)	4230 (27.2)	13 273 (28.3)	3251 (37.7)	<0.0001
Comorbidities, <i>n</i> (%)				
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, <i>n</i> (%)				
No comorbidities	8422 (54.2)	30 316 (63.9)	5057 (58.7)	<0.0001
One comorbidity	4073 (26.2)	10 220 (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, <i>n</i> (%)	6042 (38.9)	9974 (21.2)	2607 (30.3)	<0.0001
Pneumonia, <i>n</i> (%)	4588 (29.5)	6341 (13.5)	1841 (21.4)	<0.0001
IMV, <i>n</i> (%)	669 (4.3)	598 (1.3)	197 (2.3)	<0.0001
ICU admission, <i>n</i> (%)	676 (4.4)	774 (1.6)	211 (2.4)	<0.0001
Case-fatality rate, <i>n</i> (%)	1434 (9.2)	881 (1.9)	137 (1.6)	<0.0001
Socio-geographical variables				
SLI	−1.32 (−1.41 to −1.11)	−1.29 (−1.41 to −1.06)*	−1.29 (−1.39 to −1.02)*	<0.0001
Ageing index	28.7 (21.8–39.6)	28.6 (21.8–38.6)*	29.2 (21.5–38.6)*	<0.0001
Afro-descendant per 100 inhabitants	0.61 (0.07–1.80)	0.23 (0.03–1.39)*	0.35 (0.03–1.74)*	<0.0001
Indigenous language-speaking per 100 inhabitants	1.22 (0.63–1.89)	0.96 (0.00–1.74)*	1.1 (0.00–1.79)*	<0.0001
Affiliation to health services per 100 inhabitants	80.2 (77.6–84.3)	82.6 (78.6–86.0)*	81.3 (77.4–85.5)	<0.0001
Members per household	3.59 (3.45–3.71)	3.66 (3.50–3.80)*	3.68 (3.50–3.84)*	<0.0001
Hospitals per 10 000 inhabitants	3.50 (2.42–5.51)	4.07 (2.31–6.30)*	3.43 (2.02–5.40)*	<0.0001

(Continued)

Table 1. (Continued.)

	Positive <i>n</i> = 15 529	Negative <i>n</i> = 46 960	Pending-result <i>n</i> = 8614	<i>P</i> value
Hospital beds per 10 000 inhabitants	11.8 (6.9–18.7)	11.8 (6.9–18.5)	11.2 (5.3–17.9)*	<0.0001

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; SLI, social lag index.
Data are presented as mean (s.d.) or median (1Q–3Q).

Comparisons between groups were made by χ^2 or one-way ANOVA.

*Significantly different from positive patients ($P < 0.05$) by post-hoc analysis by Tukey's test or Games-Howell's test.

when compared with other individual comorbidities different from obesity, having the strongest association with mortality risk. Increased risk for short-term all-cause mortality and adverse outcomes was greater in patients with a positive test for SARS-CoV-2 with obesity alone or in combination with one accompanying disease. Importantly, in patients with a negative test for SARS-CoV-2 and patients without a definitive result, obesity was not a risk factor for all these outcomes or had a lower increase in risk compared to patients with a positive test.

Our study included both ambulatory and hospitalised patients, with a large representation of COVID-19 patients who did not require hospitalisation (61.1%). SARS-CoV-2-positive patients in our study were younger (46.6, s.d.: 15.5 years) than the majority of studies included in one systematic review to determine mortality risk attributable to comorbidities in patients with COVID-19 [13]; 47.8% of cases in our cohort were between 41 and 60 years old, reflecting that the pandemic affected younger patients in Mexico during its early period. Similar to most other studies, men (57.8%) comprised of a greater proportion of confirmed COVID-19 cases [13]. Hypertension (21.7%), obesity (20.7%) and DM (18.2%) were the most prevalent comorbidities in SARS-CoV-2-positive patients, being higher in non-survivors (43%, 30.5% and 38.8%, respectively). The prevalence of hypertension (18.4%) in people 20 years and older reported in the 2018 National Health and Nutrition Survey is similar to that in our study, whereas numbers for obesity (36.1%) and DM (10.3%) were reported to be higher and lower, respectively, in the Mexican population [7]. Despite being younger, patients in our cohort had a higher prevalence of obesity compared to both survivors (14.2%) and non-survivors (17.1%) included in a systematic review [13].

Variables for adjustment in our study included age, sex, time from symptom onset to medical care, smoking and socio-demographic variables since these have been associated with the risk of developing severe disease and mortality in patients with COVID-19 [10, 20–23]. These covariates have been used in other studies, too [24, 25].

After multivariable adjustment, obesity alone was a strong risk factor for short-term all-cause mortality in patients with a positive test for SARS-CoV-2 (hazard ratio (HR) = 2.47, 95% confidence interval (CI) 2.04–2.98), but not in patients with a negative test (HR = 1.05, 95% CI 0.71–1.53) or with unreleased results (HR = 1.73, 95% CI 0.86–3.48). In the sensitivity analyses, obesity persisted as a strong and significant risk factor for death after excluding patients requiring hospitalisation, IMV or ICU. Obesity alone was also associated with increased risk of secondary adverse outcomes (pneumonia, hospitalisation, IMV and ICU admission). This is consistent with a recent meta-analysis which found that obesity was a significant risk factor for having a positive test for SARS-CoV-2, COVID-19 severity, hospitalisation, IMV, ICU admission and mortality [26].

Other individual comorbidities associated with increased mortality after multivariable adjustment were DM, COPD, immunosuppression, hypertension and CVD, which have also been found as risk factors in other studies [13, 27]. However, obesity alone had larger increases in mortality risk than all these diseases alone, except for immunosuppression. After sensitivity analyses, hypertension, DM and immunosuppression remained as significant risk factors; COPD and CVD alone were not risk factors for death in these analyses, which could be due to the loss of statistical power after the exclusion of patients, although this could reflect that rather than favouring disease progression, COPD and CVD could complicate in-hospital management of patients [28, 29]. Furthermore, distinguishing between current and former smoker statuses is important to adequately assess risks of adverse outcomes in patients with COPD [30]. Similar to other studies, asthma was not a significant risk factor for COVID-19-related adverse outcomes [27, 31]; the combination of asthma and obesity increased mortality risk, but this association was lost after sensitivity analyses. We were not able to assess the effect of recent use of systemic corticosteroids in asthmatic patients, which has been shown to be a significant risk factor for adverse outcomes in patients with COVID-19 rather than history of asthma alone [27, 31]. CKD alone did not increase mortality risk, which could be due to the low number of patients with only CKD included in our study since CKD has been found to be a risk factor in others [27, 32]. However, the role of CKD as an individual risk factor for adverse outcomes in COVID-19 should be explored since CKD is often present in combination with DM and hypertension [33], which were individual risk factors in our study.

Obesity combined with DM, immunosuppression and hypertension, had higher increases in mortality risk than in patients with these comorbidities but without obesity. For COPD, asthma, CVD or CKD combined with obesity, mortality risks were not statistically significantly increased, possibly due to the low number of patients presenting these comorbidities combined ($n = 24$, $n = 84$, $n = 20$ and $n = 11$, respectively), which reflects that these comorbidities are often present with more than one concomitant disease in the general population [33–35].

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

The main limitation of our study is that obesity was classified as a dichotomous variable in this dataset. Therefore, we were not able to assess if the magnitude of obesity according to different BMI significantly modifies risks. One study found that higher obesity classes gradually increase short-term mortality risk [27]. However, one meta-analysis found that obesity increases the risk of mortality, COVID-19 severity and other adverse outcomes

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)	2.47 (2.04–2.98)	1.18 (0.81–1.73)	1.05 (0.71–1.53)	1.79 (0.89–3.61)	1.73 (0.86–3.48)
DM model						
Without comorbidities	Reference					
DM alone	3.66 (2.99–4.49)	1.91 (1.55–2.35)	5.92 (4.46–7.85)	2.99 (2.22–4.03)	3.17 (1.58–6.38)	1.74 (0.85–3.59)
Obesity alone	2.36 (1.95–2.84)	2.42 (2.01–2.93)	1.18 (0.81–1.73)	1.05 (0.72–1.54)	1.79 (0.89–3.61)	1.71 (0.85–3.44)
DM + obesity	3.88 (2.85–5.29)	2.79 (2.04–3.80)	3.78 (2.07–6.92)	2.33 (1.27–4.29)	1.91 (0.46–7.92)	1.60 (0.38–6.68)
COPD model						
Without comorbidities	Reference					
COPD alone	5.92 (3.64–9.64)	1.72 (1.05–2.84)	11.98 (8.23–17.44)	3.05 (1.97–4.72)	1.95 (0.27–14.24)	0.58 (0.08–4.44)
Obesity alone	2.36 (1.96–2.86)	2.47 (2.04–2.99)	1.18 (0.81–1.73)	1.05 (0.72–1.54)	1.79 (0.89–3.61)	1.74 (0.86–3.49)
COPD + obesity	4.29 (1.60–11.5)	2.42 (0.89–6.53)	5.84 (1.45–23.5)	1.80 (0.44–7.64)	9.86 (1.35–72.01)	5.13 (0.68–38.59)
Asthma model						
Without comorbidities	Reference					
Asthma alone	0.35 (0.13–0.96)	0.63 (0.24–1.70)	0.49 (0.22–1.11)	0.57 (0.25–1.29)	0.83 (0.14–6.05)	1.40 (0.19–10.37)
Obesity alone	2.37 (1.96–2.86)	2.47 (2.04–2.99)	1.18 (0.81–1.72)	1.04 (0.71–1.53)	1.80 (0.89–3.62)	1.72 (0.85–3.46)
Asthma + obesity	1.42 (0.59–3.45)	2.18 (0.90–5.28)	1.63 (0.61–4.39)	1.81 (0.67–4.87)	Not estimable	
Immunosuppression model						
Without comorbidities	Reference					
Immunosupp. alone	3.04 (1.75–5.28)	2.54 (1.46–4.43)	5.96 (4.05–8.77)	5.22 (3.54–7.70)	4.13 (1.27–13.41)	2.71 (0.79–9.27)
Obesity alone	2.36 (1.96–2.86)	2.45 (2.03–2.97)	1.18 (0.81–1.73)	1.05 (0.72–1.54)	1.79 (0.89–3.61)	1.69 (0.84–3.40)
Immunosupp. + obesity	5.62 (2.51–12.6)	5.06 (2.26–11.41)	6.33 (2.03–19.79)	4.64 (1.49–14.55)	37.6 (5.11–276.44)	34.63 (4.48–267.43)
Hypertension model						
Without comorbidities	Reference					
Hypertension alone	2.98 (2.45–3.65)	1.33 (1.08–1.64)	3.31 (2.48–4.41)	1.39 (1.03–1.89)	2.38 (1.19–4.78)	1.15 (0.55–2.39)
Obesity alone	2.37 (1.96–2.86)	2.46 (2.03–2.97)	1.18 (0.81–1.73)	1.04 (0.71–1.53)	1.78 (0.88–3.57)	1.72 (0.85–3.45)
Hypertension + obesity	3.44 (2.64–4.48)	2.30 (1.77–3.01)	2.43 (1.48–3.97)	1.34 (0.82–2.21)	2.25 (0.81–6.31)	1.49 (0.53–4.22)
CVD model						
Without comorbidities	Reference					
CVD alone	3.55 (2.05–6.18)	2.00 (1.15–3.48)	4.75 (2.47–8.14)	2.89 (1.66–5.02)	2.75 (0.95–11.64)	1.57 (0.34–7.21)
Obesity alone	2.37 (1.96–2.86)	2.47 (2.04–2.98)	1.18 (0.81–1.73)	1.05 (0.72–1.53)	1.79 (0.89–3.59)	1.69 (0.84–3.40)
CVD + obesity	2.82 (0.70–11.3)	1.44 (0.36–5.78)	7.82 (2.91–21.02)	4.33 (1.59–11.72)	7.53 (1.03–55.03)	4.87 (0.55–43.34)
CKD model						
Without comorbidities	Reference					
CKD alone	1.77 (0.66–4.76)	1.24 (0.46–3.34)	6.81 (3.51–13.26)	3.55 (1.80–6.98)	8.07 (1.95–33.46)	5.79 (1.34–24.89)
Obesity alone	2.37 (1.96–2.86)	2.47 (2.04–2.98)	1.18 (0.81–1.73)	1.05 (0.72–1.53)	1.79 (0.89–3.61)	1.74 (0.86–3.50)
CKD + obesity	2.69 (0.38–19.2)	4.63 (0.65–33.1)	10.37 (2.57–41.71)	6.24 (1.55–25.19)	15.96 (2.18–116.79)	10.35 (1.39–76.83)

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.

Data are presented as HR (95% CI).

^aModel adjusted by sex, age and time from symptom onset to care, SLI, ageing index, afro-descendant per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, members per household, hospitals per 10 000 inhabitants, hospital beds per 10 000 inhabitants.

^bModel adjusted by sex, age and time from symptom onset to care, SLI, ageing index, afro-descendant per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, members per household, hospitals per 10 000 inhabitants, hospital beds per 10 000 inhabitants.

^cModel adjusted by sex, age, smoking and time from symptom onset to care, SLI, ageing index, afro-descendant per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, members per household, hospitals per 10 000 inhabitants, hospital beds per 10 000 inhabitants.

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	3.13 (1.71–5.75)	2.37 (1.89–2.97)	2.50 (2.02–3.09)
DM model			
Without comorbidities	Reference		
DM alone	2.90 (1.53–5.50)	2.17 (1.73–2.74)	2.06 (1.64–2.59)
Obesity alone	2.98 (1.63–5.45)	2.32 (1.85–2.90)	2.46 (1.99–3.05)
DM + obesity	2.04 (0.62–6.73)	2.66 (1.83–3.85)	2.90 (2.05–4.11)
COPD model			
Without comorbidities	Reference		
COPD alone	2.39 (0.51–11.17)	1.66 (0.92–2.99)	1.61 (0.89–2.89)
Obesity alone	3.13 (1.71–5.74)	2.37 (1.89–2.97)	2.52 (2.03–3.12)
COPD + obesity	7.05 (0.93–53.21)	2.25 (0.71–7.08)	1.19 (0.69–6.88)
Asthma model			
Without comorbidities	Reference		
Asthma alone	Not estimable	0.42 (0.10–1.68)	0.20 (0.03–1.40)
Obesity alone	3.13 (1.71–5.75)	2.37 (1.89–2.97)	2.50 (2.02–3.10)
Asthma + obesity	Not estimable	1.71 (0.55–2.97)	1.63 (0.52–5.11)
Immunosuppression model			
Without comorbidities	Reference		
Immunosupp. alone	2.68 (0.36–19.71)	2.65 (1.45–4.87)	2.83 (1.58–5.07)
Obesity alone	3.11 (1.69–5.70)	2.35 (1.88–2.95)	2.49 (2.01–3.08)
Immunosuppression + obesity	Not estimable	6.38 (2.84–14.35)	5.63 (2.32–13.66)
Hypertension model			
Without comorbidities	Reference		
Hypertension alone	1.32 (0.67–2.58)	1.31 (0.03–1.67)	1.39 (1.10–1.76)
Obesity alone	3.17 (1.74–5.80)	2.37 (1.89–2.96)	2.50 (2.02–3.09)
Hypertension + obesity	2.51 (1.05–6.01)	1.99 (1.43–2.77)	2.14 (1.59–2.93)
CVD model			
Without comorbidities	Reference		
CVD alone	Not estimable	1.64 (0.81–3.32)	1.57 (0.78–3.17)
Obesity alone	3.13 (1.71–5.75)	2.38 (1.89–2.97)	2.51 (2.03–3.10)
CVD + obesity	Not estimable	Not estimable	0.81 (0.11–5.77)
CKD model			
Without comorbidities	Reference		
CKD alone	Not estimable	0.92 (0.23–3.369)	0.38 (0.05–2.72)
Obesity alone	3.13 (1.71–5.75)	2.37 (1.89–2.97)	2.50 (0.02–3.09)
CKD + obesity	Not estimable	Not estimable	5.65 (0.79–40.52)

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.

Data presented as HR (95% CI).

All models were adjusted by sex, age, SLI, ageing index, afro-descendant per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, members per household, hospitals per 10 000 inhabitants, hospital beds per 10 000 inhabitants.

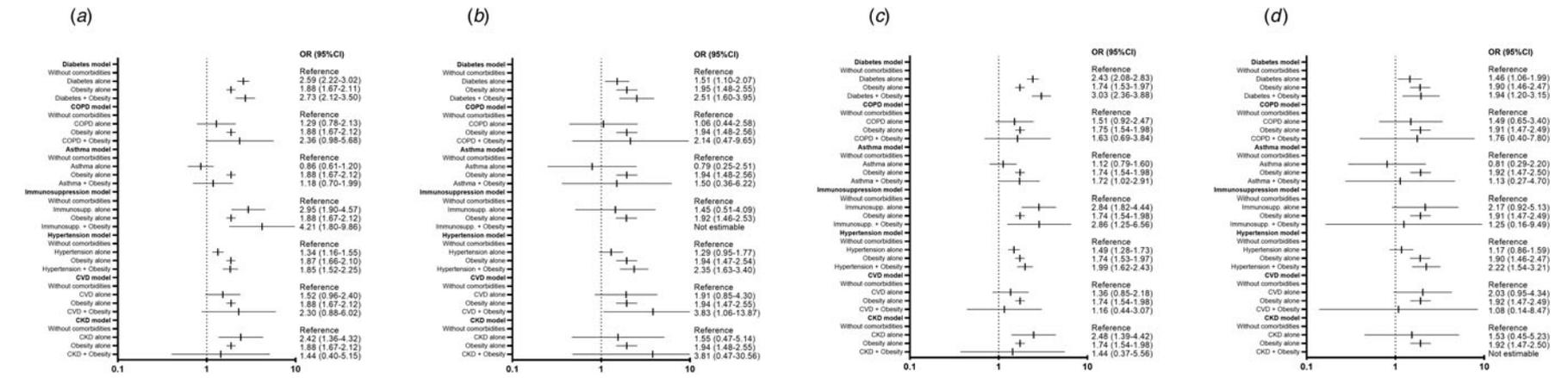


Fig. 1. Risk of secondary adverse outcomes in patients with a positive test for SARS-CoV-2 with obesity or obesity plus one other comorbidity. (a) Risk of hospitalisation, model adjusted by sex, age, smoker, SLI, ageing index, afro-descendant per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, members per household, hospitals per 10 000 inhabitants, hospital beds per 10 000 inhabitants. (b) Risk of IMV, model adjusted by sex, age, smoker and time from symptom onset to care, SLI, ageing index, afro-descendant per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, members per household, hospitals per 10 000 inhabitants, hospital beds per 10 000 inhabitants. (c) Risk of pneumonia, model adjusted by sex, age, smoker and time from symptom onset to care, SLI, ageing index, afro-descendant per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, members per household, hospitals per 10 000 inhabitants, hospital beds per 10 000 inhabitants. (d) Risk of admission to ICU, model adjusted by sex, age and time from symptom onset to care, SLI, ageing index, afro-descendant per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, members per household, hospitals per 10 000 inhabitants, hospital beds per 10 000 inhabitants. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; Immunosupp, immunosuppression; ICU, intensive care unit; IMV, invasive mechanical ventilation.

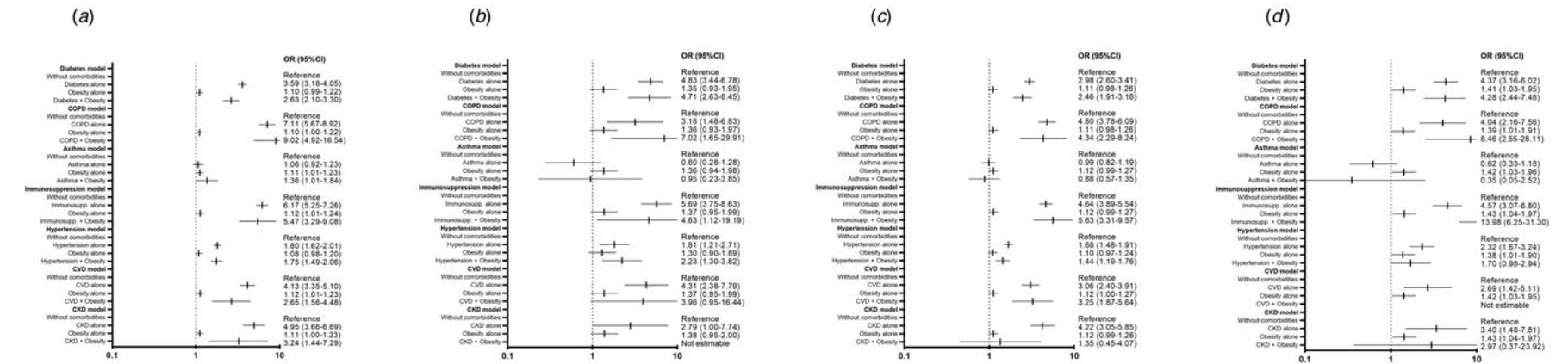


Fig. 2. Risk of secondary adverse outcomes in patients with a negative test for SARS-CoV-2 with obesity or obesity plus one other comorbidity. (a) Risk of hospitalisation, model adjusted by sex, age, smoker and time from symptom onset to care, SLI, ageing index, afro-descendant per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, members per household, hospitals per 10 000 inhabitants, hospital beds per 10 000 inhabitants. (b) Risk of IMV, model adjusted by sex, age, smoker and time from symptom onset to care, SLI, ageing index, afro-descendant per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, members per household, hospitals per 10 000 inhabitants, hospital beds per 10 000 inhabitants. (c) Risk of pneumonia, model adjusted by sex, age, smoker and time from symptom onset to care, SLI, ageing index, afro-descendant per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, members per household, hospitals per 10 000 inhabitants, hospital beds per 10 000 inhabitants. (d) Risk of admission to ICU, model adjusted by sex, age and smoker, SLI, ageing index, afro-descendant per 100 inhabitants, indigenous language-speaking per 100 inhabitants, affiliation to health services per 100 inhabitants, members per household, hospitals per 10 000 inhabitants, hospital beds per 10 000 inhabitants. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; Immunosupp, immunosuppression; ICU, intensive care unit; IMV, invasive mechanical ventilation.

thrombotic events [46, 47]. 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 [48]. 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 haemodynamic disturbances in patients under IMV, thereby complicating ventilatory management [49]. 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 [50].

In conclusion, obesity is a strong 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.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0950268821001023>

Acknowledgements. The authors thank Estherly María Solis-Rodríguez, MA from *Instituto Politécnico Nacional* for English grammar and style corrections. Javier Mancilla-Galindo thanks *Dirección General de Calidad y Educación en Salud* for supporting his participation in *Programa Nacional de Servicio Social en Investigación en Salud*.

Author contributions. Juan Mauricio Vera-Zertuche: investigation, visualisation, writing – original draft, writing – review and editing. Javier Mancilla-Galindo: conceptualisation, formal analysis, project administration, supervision, visualisation, writing – original draft, writing – review and editing. Mariana Tlalpa-Prisco: data curation, investigation, resources. Patricia Aguilar-Alonso: conceptualisation, data curation, funding acquisition, resources, software. María Magdalena Aguirre-García: investigation, methodology, resources. Orietta Lizet Segura-Badilla: data curation, formal analysis, funding acquisition. Martín Lazcano-Hernández: investigation, Methodology, resources, software. Héctor Isaac Rocha-González: data curation, methodology, resources, software. Addi Rhode Navarro-Cruz: conceptualisation, data curation, formal analysis, supervision. Ashuin Kammar-García: conceptualisation, data curation, formal analysis, methodology, software, supervision, visualisation, writing – original draft. José de Jesús Vidal-Mayo: conceptualisation, validation, visualisation, writing – original draft, writing – review and editing.

Financial support. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Conflict of interest. None.

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

Data availability statement. 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> [14].

References

1. Yu W *et al.* (2021) Impact of obesity on COVID-19 patients. *Journal of Diabetes and its Complications* **35**, 107817.
2. Mechanick JL, Hurley DL and Garvey WT (2017) Adiposity-based chronic disease as a new diagnostic term: the American association of clinical endocrinologists and American college of endocrinology position statement. *Endocrine Practice* **23**, 372–378.
3. Heysfield SB and Wadden TA (2017) Mechanisms, pathophysiology, and management of obesity. *New England Journal of Medicine* **376**, 254–266.
4. Lumeng CN, Bodzin JL and Saltiel AR (2007) Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *Journal of Clinical Investigation* **117**, 175–184.
5. Rivera-Dommarco JA *et al.* (2018) Recomendaciones para una política de Estado para la prevención y control de la obesidad en México en el periodo 2018–2024. In Rivera Dommarco JA, Colchero A, Fuentes ML, Gonzáles de Cosío-Martínez T, Aguilar-Salinas CA, Hernández-Licona G and Barquera S (eds), *La obesidad en México. Estado de la política pública y recomendaciones para su prevención y control*, 1st Edn., Morelos: Instituto Nacional de Salud Pública, pp. 15–30.
6. OECD (2017) Obesity Update 2017. *Organisation for Economic Cooperation and Development*. p. 16. Available at <https://www.oecd.org/els/health-systems/Obesity-Update-2017.pdf> (Accessed 8 December 2020).
7. Instituto Nacional de Estadística y Geografía and Instituto Nacional de Salud Pública (2020) *Encuesta Nacional de Salud y Nutrición 2018-19: Resultados Nacionales*. Cuernavaca, México: Instituto Nacional de Salud Pública.
8. Kammar-García A *et al.* (2020) Impact of comorbidities in Mexican SARS-CoV-2-positive patients: a retrospective analysis in a national cohort. *Revista de Investigación Clínica* **72**, 151–158.
9. Prado-Galbarro F-J *et al.* (2020) Determinants of survival after severe acute respiratory syndrome coronavirus 2 infection in Mexican outpatients and hospitalised patients. *Public Health* **189**, 66–72.
10. Mancilla-Galindo J *et al.* (2020) Development and validation of the patient history COVID-19 (PH-Covid-19) scoring system: a multivariable prediction model of death in Mexican patients with COVID-19. *Epidemiology and Infection* **148**, e286.
11. Hernández-Garduño E (2020) Obesity is the comorbidity more strongly associated for Covid-19 in Mexico. A case-control study. *Obesity Research & Clinical Practice* **14**, 375–379.
12. Zhou Y *et al.* (2020) Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: a systematic review and meta-analysis. *International Journal of Infectious Diseases* **99**, 47–56.
13. Mesas AE *et al.* (2020) Predictors of in-hospital COVID-19 mortality: a comprehensive systematic review and meta-analysis exploring differences by age, sex and health conditions. *PLoS ONE* **15**, e0241742.
14. Mexican Secretariat of Health (2020) *Information regarding COVID-19 cases in Mexico (in Spanish)*. Datos Abiertos. Available at <https://datos.gob.mx/busca/dataset/informacion-referente-a-casos-covid-19-en-mexico> (Accessed 14 September 2020).
15. Directorate General of Epidemiology of Mexico (2020) *Historical COVID-19 Datasets (in Spanish)*. Datos Abiertos – Bases Históricas. Available at <https://www.gob.mx/salud/documentos/datos-abiertos-bases-historicas-direccion-general-de-epidemiologia> (Accessed 14 September 2020).
16. Directorate General of Epidemiology of Mexico (2010) *NORMA Oficial Mexicana NOM-008-SSA3-2010, Para el tratamiento integral del sobrepeso y la obesidad*. Mexican Secretariat of Health. Available at <http://www.dof.gob.mx/normasOficiales/4127/Salud/Salud.htm#:~:text=NORMAOficial MexicanaNOM-008,serviciosdeatenciónmédica%3B2o> (Accessed 14 September 2020).
17. Instituto Nacional de Estadística y Geografía (2020) 2020 Population and Housing Census, Mexico. INEGI. Available at <https://www.inegi.org.mx/rmm/index.php/catalog/632/study-description?idPro=> (Accessed 15 February 2021).
18. Consejo Nacional de Evaluación de la Política de Desarrollo Social (2015) *Índice de Rezago Social (in Spanish)*. CONEVAL. Available at https://www.coneval.org.mx/Medicion/IRS/Paginas/Indice_Rezago_Social_2015.aspx (Accessed 1 March 2021).

19. **Geografía IN de E y** (2015) *Encuesta Intercensal 2015 – México*. INEGI. Available at <https://www.inegi.org.mx/programas/intercensal/2015/> (Accessed 12 November 2020).
20. **Antonio-Villa NE et al.** (2021) Comprehensive evaluation of the impact of sociodemographic inequalities on adverse outcomes and excess mortality during the COVID-19 pandemic in Mexico City. *medRxiv*. Published online: 12 March 2021. doi: 10.1101/2021.03.11.21253402.
21. **Wang G et al.** (2021) Differences in the clinical characteristics and outcomes of COVID-19 patients in the epicenter and peripheral areas of the pandemic from China: a retrospective, large-sample, comparative analysis. *BMC Infectious Diseases* **21**, 206.
22. **Salah HM, Sharma T and Mehta J** (2020) Smoking doubles the mortality risk in COVID-19: a meta-analysis of recent reports and potential mechanisms. *Cureus* **12**, e10837.
23. **Mancilla-Galindo J et al.** (2021) COVID-19 patients with increasing age experience differential time to initial medical care and severity of symptoms. *Cambridge Open Engage*. Published online: 6 January 2021. doi: 10.33774/coe-2021-sjbcf.
24. **Bello-Chavolla OY et al.** (2020) Profiling cases with nonrespiratory symptoms and asymptomatic severe acute respiratory syndrome coronavirus 2 infections in Mexico City. *Clinical Infectious Diseases*. Published online: 28 August 2020. doi: 10.1093/cid/ciaa1288.
25. **Márquez-Salinas A et al.** (2021) Adaptive metabolic and inflammatory responses identified using accelerated aging metrics are linked to adverse outcomes in severe SARS-CoV-2 infection. *The Journals of Gerontology: Series A*. Published online: 15 March 2021. doi:10.1093/gerona/glab078.
26. **Yang J, Ma Z and Lei Y** (2020) A meta-analysis of the association between obesity and COVID-19. *Epidemiology and Infection*. **149**, e11.
27. **Williamson EJ et al.** (2020) Factors associated with COVID-19-related death using OpenSAFELY. *Nature* **584**, 430–436.
28. **Padro T et al.** (2019) Admission characteristics predictive of in-hospital death from hospital-acquired sepsis: a comparison to community-acquired sepsis. *Journal of Critical Care* **51**, 145–148.
29. **Dai R-X et al.** (2018) The mortality risk factor of community acquired pneumonia patients with chronic obstructive pulmonary disease: a retrospective cohort study. *BMC Pulmonary Medicine* **18**, 12.
30. **Crisafulli E et al.** (2020) Systemic inflammatory response and outcomes in community-acquired pneumonia patients categorized according to the smoking habit or presence of chronic obstructive pulmonary disease. *Journal of Clinical Medicine* **9**, 2884.
31. **Lee SC et al.** (2020) Impact of comorbid asthma on severity of coronavirus disease (COVID-19). *Scientific Reports* **10**, 21805.
32. **Parra-Bracamonte GM et al.** (2020) Chronic kidney disease is a very significant comorbidity for high risk of death in patients with COVID-19 in Mexico. *Nephrology (Carlton)* **26**, 248–251.
33. **Agudelo-Botero M et al.** (2020) Overview of the burden of chronic kidney disease in Mexico: secondary data analysis based on the Global Burden of Disease Study 2017. *BMJ Open* **10**, 1–9.
34. **Díaz-Zavala RG et al.** (2019) Lifestyle intervention for obesity: a call to transform the clinical care delivery system in Mexico. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* **12**, 1841–1859.
35. **Orea-Tejeda A et al.** (2018) Right heart failure as a risk factor for severe exacerbation in patients with chronic obstructive pulmonary disease: prospective cohort study. *The Clinical Respiratory Journal* **12**, 2635–2641.
36. **Gutiérrez-Spillari L, Palma MG and Aceituno-Melgar J** (2020) Obesity, cardiovascular disease, and influenza: how are they connected? *Current Tropical Medicine Reports* **7**, 92–97.
37. **Rojas-Osornio SA et al.** (2019) Immunity to influenza: impact of obesity. *Obesity Research and Clinical Practice* **13**, 419–429.
38. **Terán-Cabanillas E et al.** (2014) Production of interferon α and β , pro-inflammatory cytokines and the expression of suppressor of cytokine signaling (SOCS) in obese subjects infected with influenza A/H1N1. *Clinical Nutrition* **33**, 922–926.
39. **Hadjadj J et al.** (2020) Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science (New York, N.Y.)* **369**, 718–724.
40. **Cariou B et al.** (2020) Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia* **63**, 1500–1515.
41. **Maas MB et al.** (2020) Obstructive sleep apnea and risk of COVID-19 infection, hospitalization and respiratory failure. *Sleep and Breathing*. Published online: 29 September 2020. doi: 10.1007/s11325-020-02203-0.
42. **Singh M et al.** (2013) Proportion of surgical patients with undiagnosed obstructive sleep apnoea. *British Journal of Anaesthesia* **110**, 629–636.
43. **Minai OA et al.** (2009) Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnea syndrome. *The American Journal of Cardiology* **104**, 1300–1306.
44. **Vitarelli A et al.** (2015) Assessment of right ventricular function in obstructive sleep apnea syndrome and effects of continuous positive airway pressure therapy: a pilot study. *Canadian Journal of Cardiology* **31**, 823–831.
45. **Ismail K et al.** (2015) OSA and pulmonary hypertension: time for a new look. *Chest The American College of Chest Physicians* **147**, 847–861.
46. **Carrillo-Esper R et al.** (2020) Alteraciones de la coagulación en la COVID-19. *Cirugía y Cirujanos* **88**, 787–793.
47. **Alvarado-Moreno JA and Majluf-Cruz A** (2020) COVID-19 and dysfunctional endothelium: the Mexican Scenario. *Archives of Medical Research* **51**, 587–588.
48. **Pépin JL et al.** (2016) Prevention and care of respiratory failure in obese patients. *The Lancet Respiratory Medicine* **4**, 407–418.
49. **De Jong A, Chanques G and Jaber S** (2017) Mechanical ventilation in obese ICU patients: from intubation to extubation. *Critical Care* **21**, 63.
50. **Lemyze M et al.** (2020) Implications of obesity for the management of severe coronavirus disease 2019 pneumonia. *Critical Care Medicine* **48**, E761–E767.