Predicting mortality due to SARS-CoV-2: A mechanistic score relating obesity and diabetes to COVID-19 outcomes in Mexico

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ABSTRACT (250 WORDS)

BACKGROUND: The SARS-CoV-2 outbreak poses challenge to healthcare systems due to high complication rates in patients with cardiometabolic diseases. Here, we identify risk factors and propose a clinical score to predict COVID-19 lethality, including specific factors for diabetes and obesity and its role in improving risk prediction.

METHODS: We obtained data of confirmed and negative COVID-19 cases and their demographic and health characteristics from the General Directorate of Epidemiology of Mexican Ministry of Health. We investigated specific risk factors associated to COVID-19 positivity and mortality and explored the impact of diabetes and obesity on modifying COVID-19 related lethality. Finally, we built a clinical score to predict COVID-19 lethality.

RESULTS: Among 71,103 subjects at April 27th, 2020, we observed 15,529 subjects with SARS-CoV-2 and 1,434 deaths. Risk factors for lethality in COVID-19 includes early-onset diabetes obesity, COPD, advanced age, immunosuppression, and CKD; we observed that obesity mediates 45.5% of the effect of diabetes on COVID-19 lethality. Early-onset diabetes conferred an increased risk of hospitalization and obesity conferred an increased risk for ICU admission and intubation. Our predictive score for COVID-19 lethality included age ≥65 years, diabetes, early-onset diabetes, obesity, age <40 years, CKD, hypertension, pregnancy and immunosuppression and significantly discriminates lethal from non-lethal COVID-19 cases (c-statistic=0.830).

CONCLUSIONS: Here, we propose a mechanistic approach to evaluate risk for complications and lethality attributable to COVID-19 considering the effect of obesity and diabetes in Mexico. Our score offers a clinical tool for quick determination of high-risk susceptibility patients in a first contact scenario.

Keywords: COVID-19; SARS-CoV-2; Diabetes; Obesity, Lethality; Mexico

INTRODUCTION

The first cases of SARS-CoV-2 infection in Mexico were reported at the end of February [1]; since then, the number of COVID-19 cases have been steadily increasing, with most fatal cases being associated with the presence of comorbidity and, particularly, cardiometabolic comorbidities. A high prevalence of cardiometabolic diseases worldwide represents a challenge during the COVID-19 epidemic. An elevated number of patients with SARS-CoV-2 infection have a preexisting disease such as obesity, hypertension, cardiovascular disease, diabetes, chronic respiratory disease or cancer [2,3]. Diabetes mellitus and obesity represent a large share of the cardiometabolic morbidity burden of the region [4]; moreover, most cases of diabetes remain either undiagnosed or lack adequate glycemic control, posing them at risk of increased COVID-19 severity. Despite several reports evaluating the burden of comorbidities including obesity, diabetes and hypertension on the clinical course of COVID-19, the joint role of obesity and diabetes in modifying COVID-19 outcomes has not been fully explored [5].

Several studies have demonstrated a higher susceptibility to acute respiratory infectious diseases in people with diabetes [6]. Moreover, diabetes and obesity have been described as independent risk factors for severe pulmonary infection [7,8]. Obesity influences the clinical outcomes during an acute severe respiratory distress syndrome (ASRDS); it has been proposed as a protective factor for mortality following lung injury (due to reverse causality) or as a cause of mortality and adverse clinical outcomes for severe influenza cases (due to mechanical and immunologic factor). In the cases of the COVID-19 outbreak, obesity has been consistently associated with adverse outcomes [9,10]. Furthermore, a large proportion of obesity cases in Mexico lives in geographical areas of increased social vulnerability, which poses a structural inequality that might also increase mortality for COVID-19 associated to both diabetes and obesity [11]. Chronic inflammation in obesity might worsen the acute inflammatory response triggered by SARS-Cov2 infection, which might be associated to a

cytokine release syndrome [5,12]. Here, we investigate the role of both diabetes and obesity in determining propensity for SARS-CoV-2 infection and its associated clinical outcomes including disease severity and COVID-19 lethality; using these associations, we further construct a clinically useful predictive model for COVID-19 mortality using national epidemiological surveillance data from Mexico.

METHODS

Data sources

We extracted this dataset from the General Directorate of Epidemiology of the Mexican Ministry of Heath, which is an open-source dataset comprising daily updated data of suspected COVID-19 cases which have been confirmed with a positive test for SARS-CoV-2 certified by the National Institute for Diagnosis and Epidemiological Referral [13].

Definitions of suspected and confirmed COVID-19 cases

The Ministry of Health defines a suspected COVID-19 case as an individual of any age whom in the last 7 days has presented cough, fever or headache (at least two), accompanied by either dyspnea, arthralgias, myalgias, sore throat, rhinorrhea, conjunctivitis or chest pain. Amongst these suspected cases, the Ministry of Health establishes two protocols for case confirmation: 1) SARS-CoV-2 testing is done widespread for suspected COVID-19 cases with severe acute respiratory infection with signs of breathing difficulty or deaths in suspected COVID-19 cases, 2) for all other suspected cases, a sentinel surveillance model is being utilized, whereby 475 health facilities comprise a nationally representative sample which samples ~10% of mild outpatient cases and all suspected severe acute respiratory infection [14]. Demographic and health data are collected and uploaded to the epidemiologic surveillance database by personnel from the corresponding individual facility.

Variables definitions

Available information for all confirmed, negative and suspected COVID-19 cases includes age, sex, nationality, state and municipality where the case was detected, immigration status

as well as identification of individuals who speak indigenous languages from Mexico. Health information includes status of diabetes, obesity, chronic obstructive pulmonary disease (COPD), immunosuppression, pregnancy, arterial hypertension, cardiovascular disease, chronic kidney disease (CKD) and asthma. Date of symptom onset, hospital admission and death are available for all cases as well as treatment status (outpatient or hospitalized), information regarding diagnosis of pneumonia, ICU admission and whether the patient required invasive mechanical ventilation.

Statistical analysis

Comorbidities associated to SARS-CoV-2 positivity

We investigated the association of demographic and health data associated with SARS-CoV-2 positivity using logistic regression analyses, excluding individuals who were only suspected but unconfirmed cases of COVID-19. Next, we stratified these analyses for individuals with only diabetes or only obesity to identify specific risk factors within these populations, especially focusing on individuals who were <40 years and likely acquired the disease early.

COVID-19 mortality risk

In order to investigate risk factors predictive of COVID-19 related 30-day lethality, we fitted Cox Proportional risk regression models estimating time from symptom onset up to death or censoring, whichever occurred first in cases with confirmed positivity for SARS-CoV-2. To identify diabetes and obesity-specific risk factors, we carried out stratified analyses. Given the availability of SARS-CoV2 negative cases within the dataset, we fitted Cox models for 30-day mortality which included SARS-CoV-2 positivity as an interaction term with different comorbidities, hypothesizing that some factors increase mortality risk specifically for COVID-19. Finally, we fitted a logistic regression model only for mortality cases to evaluate associations with lethality rates in COVID-19 related and non-related deaths.

Influence of obesity and diabetes in COVID-19 related outcomes

Finally, we estimated factors associated to admission to hospital facilities, intensive care units (ICUs) and requirements for mechanical ventilation in all confirmed COVID-19 cases using logistic regression. To identify specific factors for all COVID-19 and non-COVID-19 patients related to outcomes, we included interaction effects with comorbidities factors; we also performed Kaplan-Meier analyses to identify the role of comorbidities in modifying lethality risk in individuals with diabetes and obesity and compared across categories using Breslow-Cox tests. Finally, we performed causal-mediation analyses with causally-ordered mediators using a previously validated approach to investigate whether obesity mediates the decreases COVID-19 survival attributable to diabetes, particularly in early-onset cases <40 years [15].

Mechanistic mortality risk score for COVID-19

Finally, we constructed a clinically useful model to predict 30-day mortality in COVID-19 cases that might be useful to apply in primary care facilities, including variables and interactions which were identified in mortality analyses. Points were assigned by standardizing all β coefficients with the minimum absolute β coefficient obtained from Cox regression. Points were stratified according to categories of Low risk (≤0), Mild risk (1-3), Moderate risk (4-6), High risk (7-9) and very high risk (≥10). Risk across categories was verifies using Kaplan-Meier analyses. C-statistics and D_{xy} values were corrected for over-optimism using k-fold cross-validation (k=10) using the *rms* R package. A p-value <0·05 was considered as statistical significance threshold. All analyses were performed using R software version 3.6.2.

RESULTS

COVID-19 cases in Mexico

At the time of writing this report (April 27th, 2020), a total of 71,103 subjects had been treated initially as suspected COVID-19 cases. Amongst them, 15,529 had been confirmed with as positive and 46,079 tested negatives for SARS-CoV-2 infection; additionally, 8,477 cases were still being studied as suspected cases pending testing reports. Amongst confirmed

cases, 1,434 deaths were reported (9.2%) whilst 881 deaths were SARS-CoV-2 negative cases (1.9%) and 137 deaths of suspected but unconfirmed cases (1.6%) had been reported. Compared to SARS-CoV-2 negative cases, confirmed cases were older, predominantly male (1.35:1 ratio), had higher rates of hospitalization and showed a higher prevalence of diabetes, hypertension and obesity, but less CKD. SARS-CoV-2 cases were also more likely to be treated as inpatients and had higher rates of ICU admission and requirements for invasive ventilation compared to negative cases (**Table 1**).

Factors associated with COVID-19 positivity

We investigated cases related to COVID-19 positivity within Mexico. We found that risk of SARS-CoV-2 positivity was higher with diabetes, hypertension, COPD, immunosuppression, CKD, obesity, age >65 and male sex (**Supplementary Figure 1**). When assessing age, we observed reduced odds of SARS-CoV-2 positivity in patients younger than age 40 and, in contrast, when exploring its interaction with diabetes, we observed an increased probability of SARS-CoV-2 infection. In stratified models, we observed that for patients with diabetes, SARS-CoV-2 positivity was associated with obesity, male sex and an interaction effect was observed between obesity and having less than 40 years; for patients with obesity, diabetes and male sex were also significant.

Predictors for COVID-19 related 30-day mortality

We identified that COVID-19 cases were associated with a near four-fold increase in mortality due to acute respiratory infection (HR 3.864, 95%CI 3.501-4.264) compared to non-COVID-19 cases. Of interest, the only comorbidity which conferred increased lethality risk exclusively for COVID-19 compared to non-COVID-19 was obesity (HR 1.567, 95%CI 1.273-1.928, **Figure 1A**). Factors associated to increased lethality in COVID-19 cases were age >65 years, diabetes mellitus, obesity, CKD, COPD, immunosuppression and hypertension (**Figure 1B**). We searched for an interaction between diabetes mellitus and age <40 years adjusted

for sex and obesity; a higher mortality risk was found for early onset diabetes cases (HR 2.764, 95%CI 1.718-4.447).

COVID-19 in patients with diabetes mellitus

Confirmed COVID-19 cases with diabetes had a mean age of 56·9 (±12·9) years and were predominantly male. This population had particularly higher mortality rate (10.0% vs. 1.6%), hospitalization and confirmed pneumonia compared with those without diabetes. When stratifying mortality for those with early onset diabetes (<40 years) had higher mortality rates compared to individuals <40 years without diabetes (17.1% vs. 4.6%); similarly, those aged >65 years had lower rates compared to those <65 years with diabetes (23.8% vs. 29.7%). As expected, obesity, hypertension, COPD, CKD, CVD, immunosuppression and asthma were also more prevalent in this population. Interestingly, we observed no significant differences in ICU admission and requirements for mechanical ventilation between subjects with and without diabetes (**Supplementary table 1**). In patients with diabetes mellitus, COVID-19 related mortality was higher in those with concomitant immunosuppression, COPD, CKD and those aged >65 years (**Figure 1C)**. When assessing the role of comorbidities, COVID-19 patients with diabetes, coexistent obesity, those with early onset diabetes (<40 years) or an increase in the number of comorbidities had increased risk of COVID-19 lethality (Breslow test p<0.001, **Figure 2**). When comparing cases with and without COVID-19 amongst patients with diabetes mellitus, only obesity displayed a significant interaction with COVID-19 (HR 1.449 95%CI 1.071-1.960) with diabetes after adjustment for age, sex and comorbidities (**Supplementary Figure 2**).

COVID-19 in patients with obesity

Similar to patients with diabetes, confirmed COVID-19 cases with obesity had particularly higher rates of mortality (13.6% vs. 8.17%), hospitalization and confirmed pneumonia. Furthermore, patients with obesity also had higher rates of ICU admission (13.2% vs. 10.5%) and were more likely to be intubated (13.1% vs. 10.3%). As expected, diabetes,

hypertension, COPD, smoking, CVD and asthma were also more prevalent in patients with obesity (**Supplementary table 2**). As previously mentioned, obesity was identified as a risk factor which displayed differential risk for COVID-19 infection, specific risk factors for lethality in obese patients with COVID-19 infection immunosuppression and age >65 (**Figure 1D**); overall, COVID-19 increased risk of mortality in obesity nearly six-fold (HR 5.954, 95%CI 4.939-7.178). The addition of obesity to any number of comorbidities significantly increased the risk for COVID-19 lethality (Breslow test p<0.001, **Figure 2-C**). Using causally ordered mediation analysis we investigated whether the effect of diabetes (E) on COVID-19 related lethality was partially mediated by obesity (M); the direct effect of diabetes on COVID-19 lethality was significant ($\Delta_{E1\rightarrow Y}$=1.72, 95%CI 1.54-1.93) as was the indirect effect of obesity ($\Delta_{M1\rightarrow Y}$ =1.44, 95%CI: 1.32-1.58), representing 45.5% of the total effect of diabetes.

COVID-19 outcomes and comorbidities

Given the increased risk of diabetes and obesity in modifying COVID-19 related lethality, a secondary objective of our study was to investigate its associations with inpatient outcomes, including hospitalization rate, ICU admission and requirement for mechanical ventilation. In general, early-onset diabetes patients and those with obesity had higher risk of hospitalization, whilst patients with obesity also had increased risk for ICU admission and required intubation. Patients with diabetes mellitus overall had higher risk of hospitalization with no significant additional risk of ICU admission and intubation (**Figure 3**).

Mechanistic score for mortality in COVID-19

Using the identified predictors for mortality and the observed interaction for early-onset diabetes, we designed a predictive score for COVID-19 mortality using Cox regression using a random split of 80% of the dataset stratified my mortality (n=12,424, deaths=1,137). We identified as significant predictors age>65 years, diabetes mellitus, obesity, CKD, COVID-19 related pneumonia, COPD, pregnancy and immunosuppression (**Table 2**); age<40 was a protective factor which was modified by its interaction with T2D (R^2=0.160, C-statistic 0.828,

D_{xy}=0.656); assigning the point system did not significantly reduce the model's performance (R^2=0.159, C-statistic=0.829, D_{xy}=0.657). Finally, category stratification reduced only moderately performance statistics (R^2=0.157, C-statistic=0.816, D_{xy}=0.631), and were not significantly modified after cross-validation correction (R^2=0.182, D_{xy}=0.657). The score was then validated using the remaining 20% of the population (n=3,105, deaths=297); we observed that the score retained its predictive and discriminative ability (R^2=0.141, C-statistic=0.801, D_{xy}=0.602) as did the categories (R^2=0.144, C-statistic=0.792, D_{xy}=0.585). Distribution of the score significantly discriminates between lethal and non-lethal COVID-19 cases (**Figure 4**).

DISCUSSION

Our results demonstrate that diabetes, particularly early onset diabetes mellitus, obesity and comorbidity burden modify risk profiles in patients with COVID-19 infection in Mexico and significantly improve mortality prediction related to COVID-19 lethality. These findings position the notion that early-onset type 2 diabetes might carry a higher risk of mortality in younger patients, which is similar to older patients with comorbidities and only higher in older patients with diabetes. Furthermore, our results suggest that obesity is a COVID-19 specific risk factor for mortality, risk of ICU admission, tracheal intubation and hospitalization and even increases risk in patients with diabetes and COVID-19 infection. Overall, this positions the co-existence of obesity and diabetes, particularly early-onset diabetes, as a considerable risk factor for COVID-19 mortality in Mexicans, whom have reported an alarmingly high burden of both conditions in recent health surveys.

The relationship between increased risk of mortality attributable to acute severe respiratory infections in patients with diabetes mellitus has been extensively reported, particularly for the acute respiratory syndrome caused by SARS-CoV-1 [16–18]. Evidence relating SARS-CoV-2 infections in China demonstrated increased rates of diabetes mellitus in hospitalized patients and in those with increased disease severity as assessed by ICU admission and requirement

for invasive ventilation. Additionally, hospitalized patients have shown increased rates of both obesity and diabetes for COVID-19 compared to non-hospitalized cases in the US, China and Italy [5,19,20]. Increased susceptibility for COVID-19 in patients with diabetes may be explained for several potential mechanisms including an increased lung ACE2 expression and elevated circulating levels of furin, a protease involved in viral entry to cells, and a decreased clearance of SARS-CoV-2 viral particles in subjects with diabetes and/or hypertension associated with ACE2 expression [21–24]. Impairments in immunity observed in patients with diabetes are characterized by initial delay in activation of Th1 cell-mediated immunity and late hyper-inflammatory response and are consistent with the increased risk associated with additional immunosuppression observed with our data [25]. Additional factors which have been proposed to modify COVID-19 mortality risk and worsen glycemic control in diabetes include corticosteroid therapy, inadequate glucose monitoring, the effect of social distancing on diabetes care and the use of antihypertensive medication; however these factors remain to be confirmed by clinical evidence [26]. Given the large proportion of undiagnosed diabetes cases in Mexican and poor glycemic control reported by recent estimates, the burden of COVID-19 might be higher than expected in Mexico and poses a challenge for the Mexican healthcare system to give particular attention to this sector as the epidemic moves forward [27–29].

Diabetes mellitus is one of the main causes of morbidity and it accounts for a large proportion of mortality risk in Mexican population [4]. Of relevance, Mexicans have increased risk of diabetes and diabetes-related obesity attributable to genetic variants associated to its Amerindian ancestry, and an earlier age of onset independent of body-mass index [30,31]. Data on the incidence of early-onset type 2 diabetes in Mexican population position obesity and insulin resistance as significant risk factors, which are also highly prevalent in younger patients and increase metabolic risk [32,33]. These associations partly explain the increased risk of COVID-19 lethality in younger patients within our cohort despite the younger average

age of Mexican population and poses early-onset diabetes mellitus as a significant risk factor for COVID-19 mortality and increased severity of infection in younger patients [5,34].

In our work, we demonstrate that compared to non-COVID-19 infections, obesity significantly modifies the risk of mortality attributable to COVID-19 infection. Obesity and, in particular, abdominal obesity, is one of Mexico's main public health problems; in recent years the socio-economic burden of obesity as well as its impact on mortality have increased drastically, with the Ministry of Health declaring a state of epidemiological emergency [35]. Evidence from different regions has supported the notion that obesity increases mortality risk and severity of COVID-19 infections, which holds particularly true for younger patients [2,36]. Obesity is characterized by a low-grade state of inflammation and may impair immune response which in turn also may affect the lung parenchyma, increasing the risk for inflammatory lung diseases [37,38]. In particular, abdominal obesity reduces the compliance of lung, chest wall and entire respiratory system, resulting in impaired ventilation of the base of the lungs and reduced oxygen saturation of blood [39]. Recently, Simonnet et al. explored the high prevalence of obesity in patients with COVID-19 reporting that obesity is a risk factor for SARS-CoV-2 infection severity independent of age, diabetes and hypertension. Notably, ACE2 expression in adipose tissue is higher than in the lung and its expression profile is not different in obese and non-obese subjects; however, obese subjects have more adipocytes; thus, they have a greater number of ACE2-expressing cells and thus higher likelihood of SARS-CoV-2 entry [2,40]. Our data shows that obesity is a specific risk factor for COVID-19 related outcomes and that it partly mediates the risk associated with diabetes mellitus. Public health efforts by the Mexican government in epidemiological surveillance have largely focused in identifying patient's at highest risk of complications; these findings could inform public health decisions and increase awareness on the role of obesity in modifying risk of COVID-18 outcomes.

Our study had some strengths and limitations. First, we analyzed a large dataset which included information on both confirmed positive and negative SARS-CoV-2 cases, which provides a unique opportunity to investigate COVID-19 specific risk factors and develop a predictive model for COVID-19 mortality. Additionally, with the database being nationally-representative it allows for reasonable estimates on the impact of both diabetes and obesity despite the possibility of important regional differences in cardiometabolic risk which might influence risk estimates. A potential limitation of this study is the use of data collected from a sentinel surveillance system model, which is skewed towards investigating high risk cases or only those with specific risk factors which on one hand increases power to detect the effect of comorbidities and on the other hand might not be representative of milder cases of the disease; this is demonstrated in the risk of COVID-19 positivity, which is higher for high risk cases. The updating daily estimates of COVID-19 cases are unlikely to change the direction of the identified associations though it might modify numeric estimates. Implementation of our proposed model might be useful to allocate prompt responses to high risk cases and improve stratification of disease severity.

In conclusion, we show that both diabetes and obesity increase the risk of SARS-CoV-2 infection in Mexico. In particular, diabetes increases the risk of COVID-19 related mortality and, specifically, increases mortality risk in early-onset cases. Obesity is a COVID-19 specific risk factor for mortality and for increased disease severity; obesity also is a partial mediator on the effect of diabetes in decreasing survival associated with COVID-19 infection. This mechanistic interpretation on the risk of comorbidities allowed the development of a model with good performance to predict mortality in COVID-19 cases. Given the burden of obesity and diabetes in Mexico, COVID-19 lethality might be higher in younger cases. Special attention should be given to susceptible individuals and screening should be conducted for all symptomatic cases with either obesity and/or diabetes to decrease the burden associated with COVID-19 in Mexico.

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DATA AVAILABILITY

All data sources and R code are available for reproducibility of results at https://github.com/oyaxbell/covid_diabetesmx.

AUTHOR CONTRIBUTIONS

Research idea and study design OYBC, JPBL, CAAS; data acquisition: OYBC, AGD; data analysis/interpretation: OYBC, JPBL, NEAV, AVV, AGD, JJN, CAAS; statistical analysis: OYBC, NEAV; manuscript drafting: OYBC, NEAV, AVV, JPBL, AMS, CAFM, JJN; supervision or mentorship: OYBC, CAAS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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480 **Table 1.** Descriptive statistics comparing negative, positive and suspected cases for SARS-CoV-2 in Mexico at 04/27/2020.

481 *Abbreviations*: ICU= intense care unit; COPD= chronic obstuctive pulmonary disease; CKD= chronic kidney disease; CVD=

482 cardiovascular disease**.**

Parameter	Positive for SARS-CoV-2 n=15529	Negative for SARS-CoV-2 n=46960	Suspected for SARS-CoV-2 n=8614
Age (mean ± sd)	46.55±15.51	39.56±17.9	43.22±17.27
Male sex (%)	8977(57.8)	21955(46.8)	4664(54.1)
Mortality (%)	1434(9.2)	881(1.9)	137(1.6)
Hospitalization (%)	6042(38.9)	9974(21.2)	2607(30.3)
Pneumonia (%)	4588(29.5)	6341(13.5)	1841(21.4)
ICU admission (%)	676(4.4)	774(1.6)	211(2.4)
Invasive ventilation (%)	669(4.3)	598(1.3)	197(2.3)
Diabetes (%)	2831(18.2)	5163(11)	1323(15.4)
COPD (%)	389(2.5)	1330(2.8)	214(2.5)
Asthma (%)	542(3.5)	2571(5.5)	337(3.9)
Immunosuppression (%)	296(1.9)	1402(3)	183(2.1)
Hypertension (%)	3370(21.7)	7353(15.7)	1611(18.7)

Parameter	Positive for SARS-CoV-2 n=15529	Negative for SARS-CoV-2 n=46960	Suspected for SARS-CoV-2 n=8614
Obesity (%)	3215(20.7)	6570(14)	1532(17.8)
CKD (%)	359(2.3)	1130(2.4)	262(3)
CVD (%)	453(2.9)	1610(3.4)	267(3.1)
Smoking (%)	1374(8.8)	4835(10.3)	811(9.4)

483

484

485 **Table 2.** Cox proportional risk models for lethality using the mechanistic COVID-19 lethality score in confirmed cases of COVID-19
486 using individual components, single score point and risk stratification categories. Abbreviations: COPD= chronic obstructive
487 pulmonary disease; CKD= chronic kidney disease; CVD= cardiovascular disease**.**

Model	Parameter	B	Score	SE	Wald	HR	95% CI	P Value
Individual variables *C-statistic= 0.828*	Age ≥65 years	0.753	3	0.065	11.568	2.12	1.87-2.41	<0.001
	Pregnancy	0.963	4	0.451	2.133	2.62	1.08-6.35	0.033
	Diabetes	0.251	1	0.066	3.802	1.29	1.13-1.46	<0.001
	Diabetes*Age <40 years	1.092	4	0.265	4.119	2.98	1.77-5.01	<0.001
	Age <40 years	-1.397	-6	0.136	-10.283	0.25	0.19-0.32	<0.001
	Obesity	0.374	1	0.066	5.680	1.45	1.28-1.65	<0.001
	Pneumonia	1.697	7	0.072	23.444	5.46	4.74-6.29	<0.001

	CKD	0.568	2	0.120	4.179	1.76	1.39-2.23	<0.001
	COPD	0.277	1	0.117	2.361	1.32	1.05-1.66	0.018
	Immunosuppression	0.500	2	0.137	3.365	1.65	1.26-2.16	<0.001
Score point training *C-statistic= 0.829*	1-Point increment	0.246		0.007	36.15	1.28	1.26-1.30	<0.001
Risk Categories training *C-statistic= 0.816*	Low-Risk (0 pts)				Reference			
	Mild-Risk (1-3 pts)	1.873		0.136	13.73	6.51	4.98-8.50	<0.001
	Moderate-Risk (4-6 pts)	2.727		0.131	20.84	15.28	11.83-19.75	<0.001
	High-Risk (7-9 pts)	3.287		0.125	26.38	26.76	20.96-34.16	<0.001
	Very High-Risk (≥10 pts)	3.824		0.131	29.07	45.78	35.38-59.25	<0.001

FIGURE LEGENDS

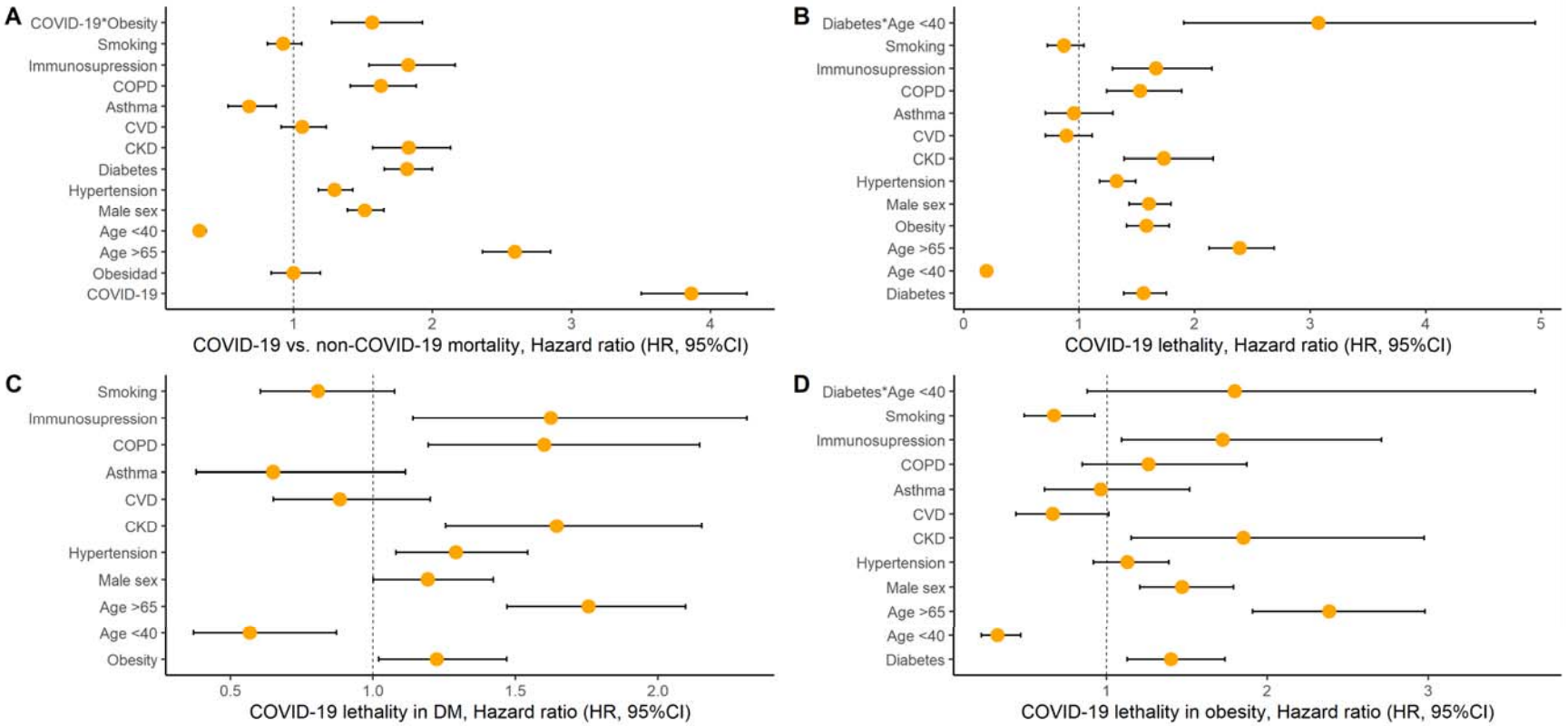

Figure 1. Cox proportional risk regression analysis to evaluate lethality of SARS-CoV-2 in Mexico, compared to SARS-CoV2 negative cases for all suspected cases with SARS-CoV2 status available (A) and stratified by diabetes mellitus (B) and obesity (C). *Abbreviations*: ICU= intense care unit; COPD= chronic obstructive pulmonary disease; CKD= chronic kidney disease; CVD= cardiovascular disease, HR= Hazard ratio.

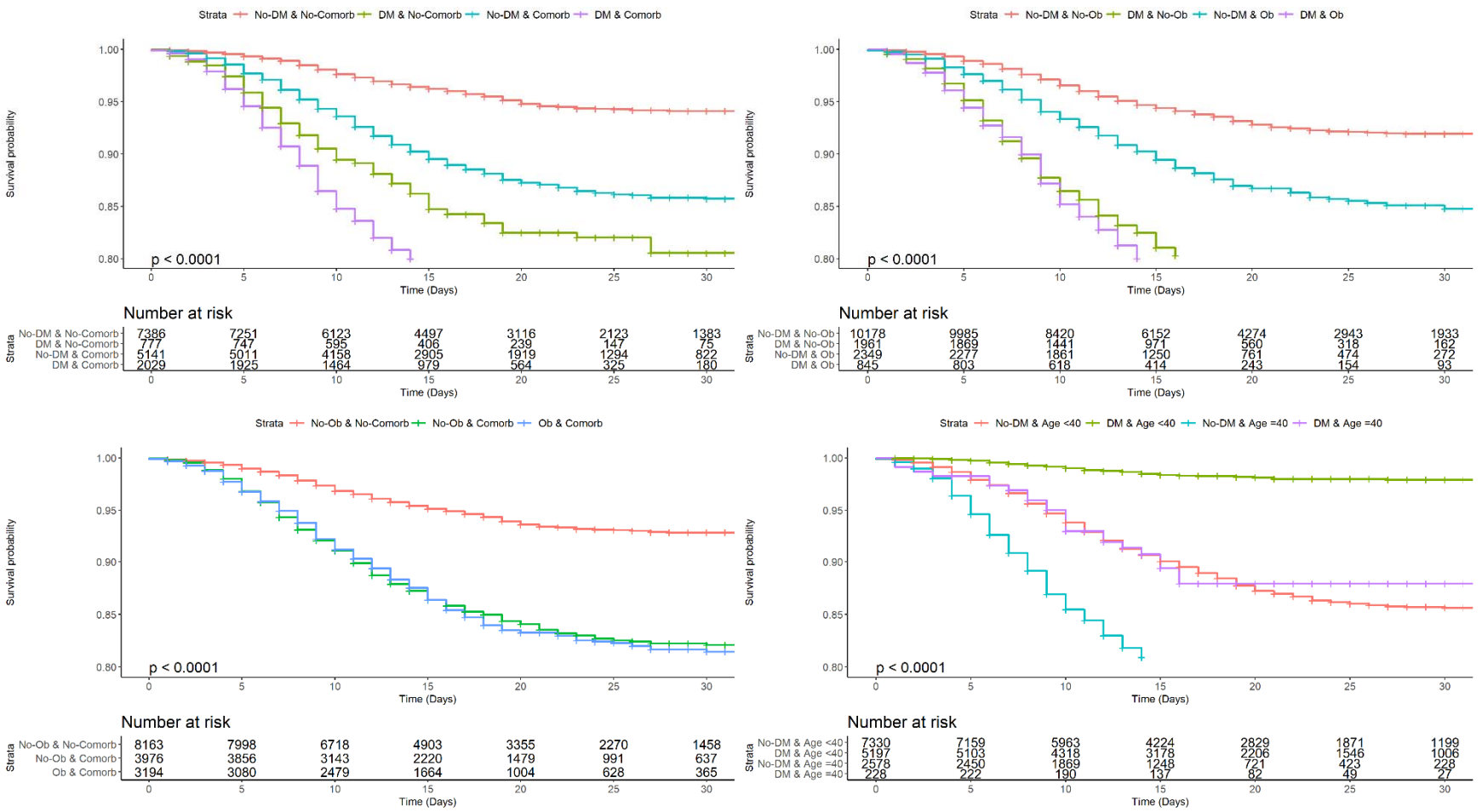

Figure 2. Kaplan-Meier survival curves to evaluate lethality of SARS-CoV-2 positivity in patients with diabetes and comorbidities (A), diabetes and obesity (B), obesity and comorbidities (C) and diabetes with age 40 years (D). Abbreviations: DM= Diabetes mellitus; OB= Obesity; Comorb= Comorbidities.

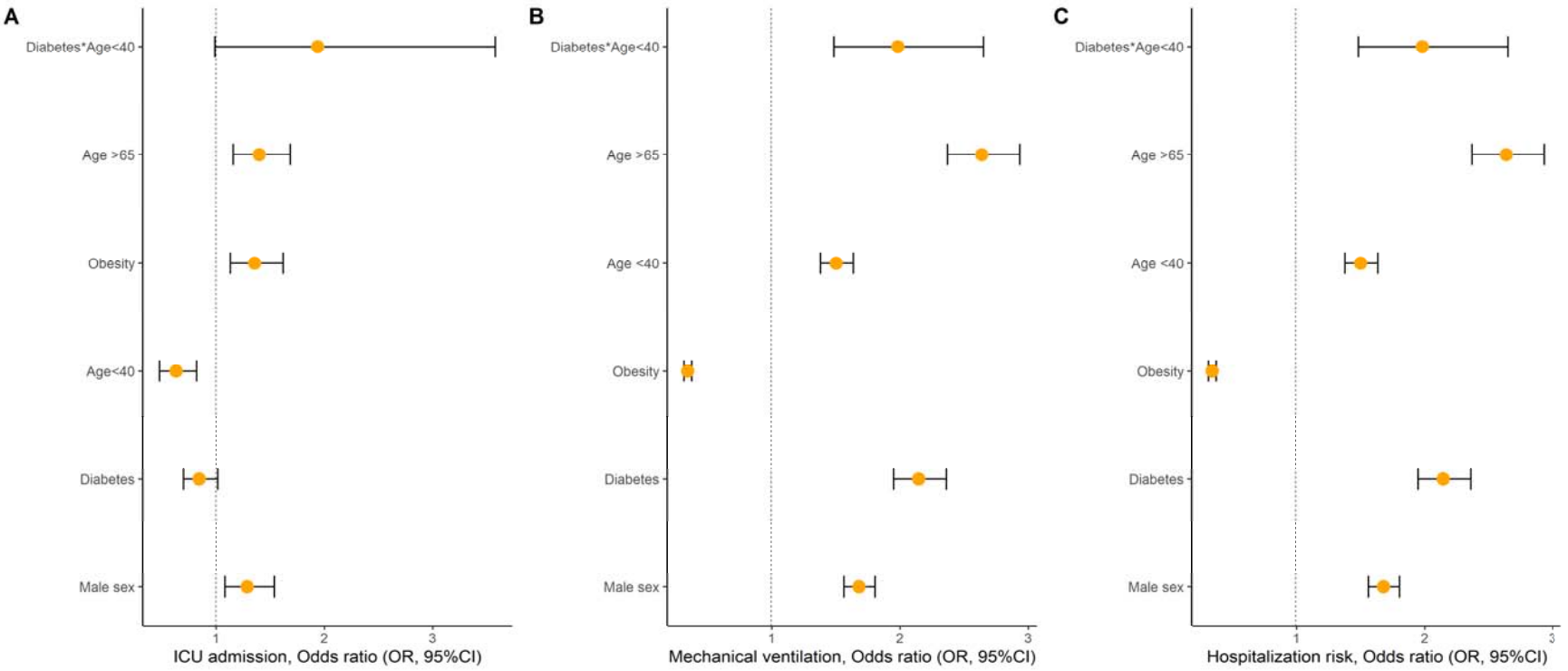

Figure 3. Logistic regression analyses to evaluate COVID-19 related outcomes in all patients with SARS-CoV2 positivity for admission to ICU (A), mechanical ventilation (B) and hospital admission risk (C).

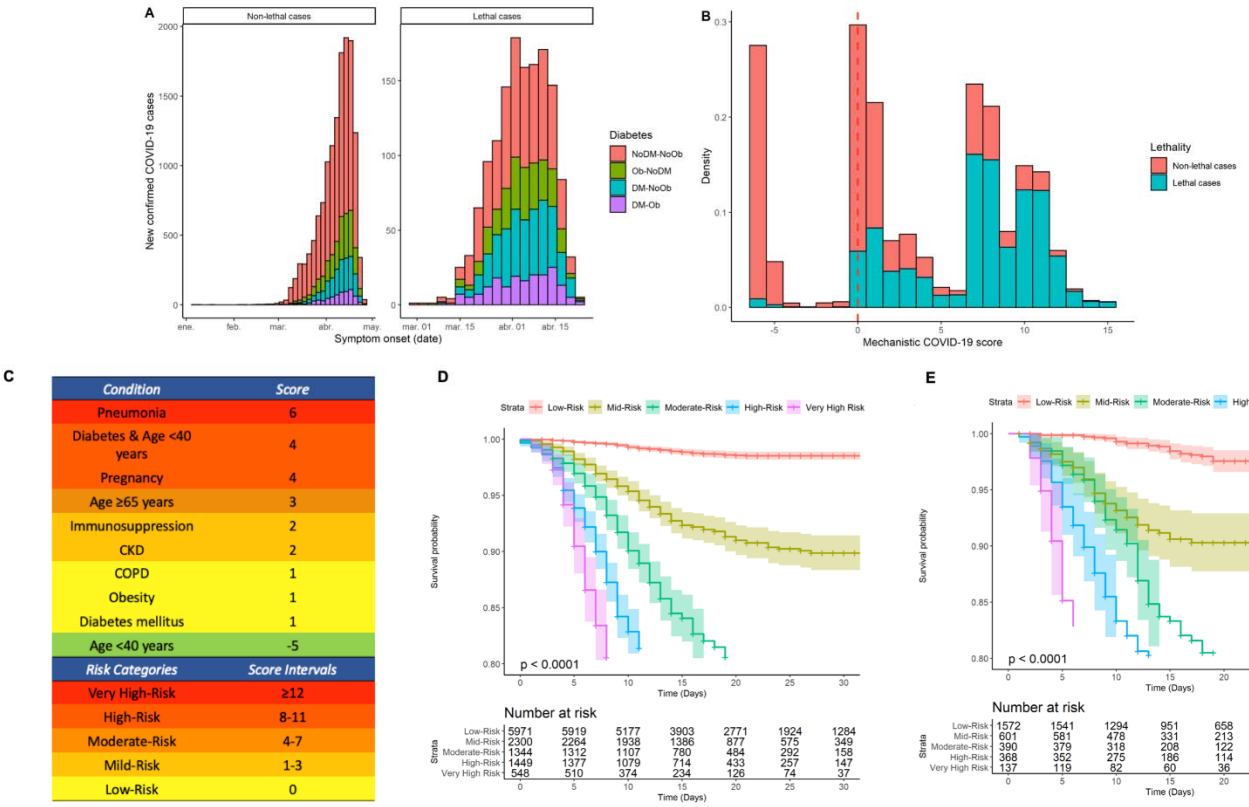

Figure 4. Symptom onset among lethal and non-lethal cases in new-confirmed COVID 19 cases, stratified by diabetes and obesity status (A), density histogram of scores of the mechanistic COVID-19 score (B). Points and score intervals considered for clinical score scale (C) and Kaplan-Meir Survival analysis curves to evaluate lethality using risk categories in the training (D) and validation cohorts (E). Abbreviations: OB= Obesity; DM= Diabetes mellitus; CKD= chronic kidney disease; COPD= Chronic obstructive pulmonary disease.