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Authors

Salvy, Sarah-Jeanne

Datta, Geetanjali D

Yu, Qihan

et al.

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How useful are body mass index and history of diabetes in COVID-19 risk stratification?

Sarah-Jeanne Salvy[1]☯*, Geetanjali D. Datta[1]☯, Qihan Yu[1], Marie Lauzon[2], Shehnaz K. Hussain[3], Susan Cheng[4], Joseph E. Ebinger[5], Mark O. Goodarzi[6], Jane C. Figueiredo[1]

1 Cancer Research Center for Health Equity, Cedars-Sinai Medical Center, West Hollywood, CA, United States of America, 2 Samuel Oschin Comprehensive Cancer Institute, Los Angeles, CA, United States of America, 3 Department of Public Health Sciences, UC Davis School of Medicine and Comprehensive Cancer Center, Davis, CA, United States of America, 4 Department of Cardiology, Smidt Heart Institute and Barbra Streisand Women's Heart Center Cedars-Sinai Medical Center, Los Angeles, CA, United States of America, 5 Department of Cardiology and Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, United States of America, 6 Division of Endocrinology, Diabetes and Metabolism, Cedars-Sinai Medical Center, Los Angeles, CA, United States of America

☯ These authors contributed equally to this work.
* sarah.salvy@cshs.org

Abstract

Objective

This study examines the value of risk stratification by documented diagnosis of diabetes and objectively measured height and weight (BMI) in COVID-19 severity and mortality in a large sample of patients in an urban hospital located in Southern California.

Methods

Data from a retrospective cohort study of COVID-19 patients treated at Cedars-Sinai Medical Center between March 8, 2020, and January 25, 2021, was analyzed. Sociodemographic characteristics and pre-existing conditions were extracted from electronic medical records. Univariable and multivariable logistic regression models identified associated risk factors, and a regression causal mediation analysis examined the role of diabetes in the association between obesity and illness severity. All analyses were stratified by age (<65 and ≥65).

Results

Among individuals <65yo, diabetes accounted for 19–30% of the associations between obesity and COVID-19 illness severity. Among patients $\geq$65yo, having a BMI <18.5 was a risk factor for mortality regardless of diabetes history.

Conclusion

Our findings have clinical implications in documenting which patients may be at elevated risk for adverse outcomes. More in-depth prospective studies are needed to capture how glycemic regulation may influence prognosis.

Introduction

Since the onset of the global COVID-19 pandemic, elucidating risk factors of disease severity and mortality have become of primary importance to the medical and public health communities. Several reports have suggested that obesity is associated with COVID-19 progression [1–12], yet it is not entirely clear whether the association between obesity and adverse outcomes is due to excess weight *per se* [11, 13–17], or whether other metabolic conditions oft-associated with obesity are driving these relationships [18–20]. Outside the context of COVID-19, obesity in absence of metabolic abnormalities is not associated with higher risk for all-cause mortality; whereas elevation of even a single metabolic risk factor is associated with increased mortality risk [21]. While emerging studies do support the implication of metabolic and biomarker profiles in COVID-19 severity and such work contributes to our understanding of the mechanisms of disease progression, scientific pursuits and in-depth considerations of cardiometabolic parameters may not be feasible for front-line workers in the context of high-volume critical care for COVID-19 patients. With the constant emergence of new variants and increase in case rates in many locations, already fatigued clinical staff may benefit from heuristics guided by assessment of patient body mass index (BMI) or prior diagnoses of diabetes to guide risk stratification. Utilizing such readily accessible parameters may ease burdens and enable clinical staff to make critical decisions in the face of uncertainty.

Therefore, this study examines the value of risk stratification by BMI and documented diagnosis of diabetes in COVID-19 severity and mortality in a large sample of patients in an urban hospital located in Southern California. Based on previous reports indicating stronger associations between weight, cardiometabolic profiles and COVID-19 severity in younger patients [5–7], and given that age is a significant predictor of mortality [22], all analyses were stratified by age following definitions used in similar studies and health services research [23].

Materials and methods

Study sample

The Cedars-Sinai Health System (CSHS) is located in Los Angeles, California with a catchment area of 1·8 million individuals and includes Cedars-Sinai Medical Center (CSMC), Marina Del Rey Hospital (MDRH), and affiliated clinics. In the present study, we included all CSHS patients (1) who received a confirmed diagnosis of COVID-19 infection while being evaluated or treated for suspected COVID-19 between March 8, 2020 and January 25, 2021 and (2) who had objective height and weight measurements and a documented diagnosis of diabetes in their medical record. COVID-19 infection was evaluated using reverse transcriptase polymerase chain reaction of extracted RNA from nasopharyngeal swabs. Until March 21, 2020, patient testing was performed by the Los Angeles Department of Public Health, after which the CSMC Department of Pathology and Laboratory Medicine used the A*STAR FORTITUDE KIT 2·0 COVID-19 Real-Time RT- PCR Test (Accelerate Technologies Pte Ltd, Singapore). For the 3·6% of patients who had COVID-19 testing performed at an outside facility, documentation of a positive test was carefully reviewed by medical staff. Quality control and assurance analyses on data extracted directly from the electronic health record (EHR) were conducted and manual chart review was used to verify collected data where appropriate. Patients provided electronic informed consent via the secure, HIPAA- compliant data capturing tool, REDCap [24, 25]. The CSMC institutional review board approved all protocols for the current study (Proposal # Pro00056865).

Measurements: Exposures, outcomes and covariates

Demographics. Race was self-reported in the EHR as White, African American/Black, Asian, other, and unknown. Ethnicity was self-reported in the EHR and was categorized as Hispanic, non-Hispanic, and unknown. We created a variable combining race and ethnicity into five categories (e.g., Non-Hispanic Black) for use in the statistical models. The participants' zip-codes were linked to census data to provide a measure of area-level income. The low-income category was defined based on zip-code with a median household income below 200% of the federal poverty line. In the absence of other available measures, zip-code level median income was used with the knowledge that caution should be used in its interpretation.

Smoking status. Smoking history was ascertained via self-report in the EHR and was categorized as never, current, former, or unknown/not asked.

Body mass index (BMI). BMI was calculated from patients' last known objectively assessed height and weight recorded in their EHR, which could have been either prior to- or after COVID-19 diagnoses. To categorize patients based on their calculated BMI, we used the criteria outlined by the World Health Organization, such that: underweight ($<18\cdot5$ kg/m^2), normal weight ($18\cdot5$ to $24\cdot9$ kg/m^2), overweight ($25\cdot0$ to $29\cdot9$ kg/m^2), and obesity ($\geq30\cdot0$ kg/m^2). Consistent with other studies assessing the relationships between weight status and COVID-19, we used normal weight as the reference group.

Diabetes. Patients' history of diabetes was coded using the Charlson comorbidity score based on ICD codes documented in the medical record [26].

Illness severity. Illness severity was defined in four categories: 1) no hospital admission, 2) requiring any kind of hospital admission, 3) requiring intensive care during hospitalization, and 4) requiring intubation and mechanical ventilation or death. Admission to an intensive care unit (ICU) was identified via time stamps recorded for admission, unit transfers, and discharge. Interventions such as intubation were identified through time stamped orders in the EHR and verified by manual chart review.

Mortality. Death was ascertained from time stamps recorded for admission, unit transfers, and discharge.

Analytic plan

Descriptive analyses were used to assess the distribution of patient demographics and clinical characteristics by mortality status. Median (interquartile range [IQR]) was used to summarize continuous measures, while categorical variables were summarized as counts and percentages. We used Pearson's chi-square test to evaluate statistical differences between patients who were deceased or alive for categorical variables. Bivariate comparisons for continuous variables were evaluated using the Student t-test or Wilcoxon rank sum test. Potential risk factors associated with mortality were identified using univariable and multivariable logistic regression models. Potential risk factors associated with COVID-19 severity were determined using univariable and multivariable ordered logistic regression. Cumulative risk was derived from statistical models including both BMI and diabetes variables with results presented in forest plots.

Because we hypothesized diabetes as a potential mediator on the pathway between obesity and disease outcomes, diabetes was included in the univariate analyses, but not in the multi-variable models. The independent contributions of diabetes are however included in the forest plots. We performed regression-based causal mediation analyses to examine the degree to which diabetes mediates the relationship between obesity and our outcomes of interest where one was observed. Causal mediation analysis was conducted using the mediation package in R [27]. The mediate function and 1,000 bootstrap simulations were used to estimate the proportion mediated, and their respective 95% CIs, adjusting for age and sex to account for potential

confounders. A proportion mediated equal or greater than 10% was considered clinically relevant for mortality and severity.

Furthermore, given that age is a significant predictor of mortality, all analyses were stratified by age (<65 and ≥65). The cut-point of 65 years was selected based on definitions used in similar studies and health services research [23]. Analyses were performed using SAS software, version 9·4 (SAS Institute) and R software, version 4·0·3 (R Foundation, Vienna, Austria) with two-sided tests and a significance level of 0·05. The Bonferroni-Holm correction was used to adjust p-values for multiple comparisons.

Results

Patient characteristics

In our cohort, 2458 participants were younger than 65 years and 1766 participants were over the age of 65 (Table 1). Mortality in the younger age group was 17·4% (308/1766) and in the older age group was 2·2% (55/2458). Over 40% of individuals over the age of 65 had a history of diabetes and 25% had a BMI >30, while among those younger than 65 years of age approximately 21% had a history of diabetes and 43% had a BMI>30.

Models

Among those younger than 65 years of age, obesity was associated with increased disease severity relative to normal weight (OR = 1·5, 95%CI: 1·2–1·9; Table 2). Assuming proportional odds, the odds of a severity score = 3 (vs combined scores of 0, 1, 2) was 1·5 time higher among participants with obesity compared to individuals with normal weight. Among participants 65 years of age and older, male (OR = 1·4, 95%CI: 1·1–1·8) and Hispanic (vs non-Hispanic White) individuals were associated with increased odds of disease severity (OR = 1·7, 95%CI: 1·2–2·3; Table 2). Underweight (vs normal weight) was associated with increased odds (OR = 1·9, 95%CI: 1·1–3·1) of mortality.

Patterns for the joint exposure of BMI and diabetes on disease severity varied according to age group. Among those under the age of 65, and relative to patients with normal weight and no history of diabetes, the lowest odds of disease severity were observed among those with a BMI <18.5 and no prior diagnosis of diabetes (OR = 0·4, 95%CI: 0·2–0·7). By contrast, the highest odds of disease severity were observed among individuals with BMI ≥30 and a documented history of diabetes (OR = 3·5, 95%CI: 2·6–4·8; Fig 1A). Among patients 65 years of age or older, an elevate odds of increased disease severity was observed among those with a history of diabetes and a BMI > 30 (OR = 1.5, 95%CI: 1.0–2.1; Fig 1B).

Age-related differences were also observed for the joint association of BMI and diabetes on mortality. Among patients younger than 65, those with diabetes and normal range BMI (OR = 2·6, 95%CI: 1·4–5·0) and those with diabetes and BMI ≥30 (OR = 2·9, 95%CI: 1.1–7·5) were at elevated odds for mortality (Fig 2A). Among patients over the age of 65, elevated mortality was observed among those with BMI <18·5, both among those without (OR = 2·0, 95%CI: 1·2–3·3) and with (OR = 3·1, 95%CI: 1·7–5·7) history of diabetes (Fig 2B). Increased odds of mortality were also observed for those with diabetes and normal BMI range (OR = 1·6, 95%CI: 1·2–2·1), whereas the odds of mortality were slightly lower for patients with overweight without diabetes (OR = 0·69, 95%CI: 0·48–1·00); albeit these latter findings were of borderline statistical significance.

Causal mediation

In causal mediation models among those younger than 65 years of age, 30% (95%CI:19%-50%) of the association between obesity and disease severity at a level requiring mechanical

Table 1. Characteristics of patients with objective BMI data, stratified by age.

	<65				≥65			
	Alive (N = 2403)	Dead (N = 55)	Total (N = 2458)	p-value	Alive (N = 1458)	Dead (N = 308)	Total (N = 1766)	p-value
Sex	..	..	..	**0.0004**	..	..	..	0.11
Female	1173 (98.9%)	13 (1.1%)	1186 (48.3%)	..	726 (84.0%)	138 (16.0%)	864 (48.9%)	..
Male	1230 (96.7%)	42 (3.3%)	1272 (51.7%)	..	732 (81.2%)	170 (18.8%)	902 (51.1%)	..
Ethnicity	..	..	..	0.19	..	..	..	**0.044**
Non-Hispanic	1333 (98.2%)	24 (1.8%)	1357 (55.2%)	..	1131 (83.1%)	230 (16.9%)	1361 (77.1%)	..
Hispanic	959 (97.3%)	27 (2.7%)	986 (40.1%)	..	299 (82.4%)	64 (17.6%)	363 (20.6%)	..
Unknown	111 (96.5%)	4 (3.5%)	115 (4.7%)	..	28 (66.7%)	14 (33.3%)	42 (2.4%)	..
Race	..	..	..	0.29	..	..	..	**0.0046**
White	1367 (97.4%)	36 (2.6%)	1403 (57.1%)	..	955 (83.4%)	190 (16.6%)	1145 (64.8%)	..
African American/Black	399 (97.3%)	11 (2.7%)	410 (16.7%)	..	272 (84.7%)	49 (15.3%)	321 (18.2%)	..
Asian	182 (98.9%)	2 (1.1%)	184 (7.5%)	..	83 (72.8%)	31 (27.2%)	114 (6.5%)	..
Other	332 (99.1%)	3 (0.9%)	335 (13.6%)	..	123 (83.1%)	25 (16.9%)	148 (8.4%)	..
Unknown	123 (97.6%)	3 (2.4%)	126 (5.1%)	..	25 (65.8%)	13 (34.2%)	38 (2.2%)	..
Diabetes	..	..	..	**<0.0001**	..	..	..	**0.010**
No	1914 (98.4%)	31 (1.6%)	1945 (79.1%)	..	873 (84.5%)	160 (15.5%)	1033 (58.5%)	..
Yes	489 (95.3%)	24 (4.7%)	513 (20.9%)	..	585 (79.8%)	148 (20.2%)	733 (41.5%)	..
BMI (calculated)	..	..	..	**0.027**	..	..	..	**<0.0001**
N	2403	55	2458	..	1458	308	1766	..
Mean (SD)	29.6 (7.5)	32.1 (8.6)	29.7 (7.5)	..	28.6 (66.2)	25.0 (6.3)	28.0 (60.3)	..
Median	28.8	32.1	28.8	..	26.2	24.2	26.0	..
Q1, Q3	24.7, 33.6	26.3, 37.1	24.7, 33.7	..	22.8, 30.3	20.4, 29.0	22.2, 30.1	..
Range	(11.9–74.1)	(18.9–59.5)	(11.9–74.1)	..	(14.0–2541.7)	(11.4–56.6)	(11.4–2541.7)	..
BMI category	..	..	..	0.13	..	..	..	**<0.0001**
Underweight	80 (100.0%)	0 (0.0%)	80 (3.3%)	..	91 (68.9%)	41 (31.1%)	132 (7.5%)	..
Normal weight	554 (97.9%)	12 (2.1%)	566 (23.0%)	..	519 (80.5%)	126 (19.5%)	645 (36.5%)	..
Overweight	741 (98.4%)	12 (1.6%)	753 (30.6%)	..	466 (86.0%)	76 (14.0%)	542 (30.7%)	..
Obesity	1028 (97.1%)	31 (2.9%)	1059 (43.1%)	..	382 (85.5%)	65 (14.5%)	447 (25.3%)	..
Myocardial infarction (Charlson)	..	..	..	**<0.0001**	..	..	..	**<0.0001**
No	2289 (98.4%)	38 (1.6%)	2327 (94.7%)	..	1212 (85.2%)	211 (14.8%)	1423 (80.6%)	..
Yes	114 (87.0%)	17 (13.0%)	131 (5.3%)	..	246 (71.7%)	97 (28.3%)	343 (19.4%)	..
Congestive heart failure	..	..	..	**<0.0001**	..	..	..	**<0.0001**
No	2201 (98.5%)	33 (1.5%)	2234 (90.9%)	..	1039 (85.2%)	180 (14.8%)	1219 (69.0%)	..
Yes	202 (90.2%)	22 (9.8%)	224 (9.1%)	..	419 (76.6%)	128 (23.4%)	547 (31.0%)	..
Chronic pulmonary disease	..	..	..	1.00	..	..	..	1.00
No	2034 (97.8%)	46 (2.2%)	2080 (84.6%)	..	1089 (82.9%)	225 (17.1%)	1314 (74.4%)	..
Yes	369 (97.6%)	9 (2.4%)	378 (15.4%)	..	369 (81.6%)	83 (18.4%)	452 (25.6%)	..
Chronic pulmonary disease (Charlson)				1.00				1.00
No	2036 (97.8%)	46 (2.2%)	2082 (84.7%)	..	1090 (82.9%)	225 (17.1%)	1315 (74.5%)	..
Yes	367 (97.6%)	9 (2.4%)	376 (15.3%)	..	368 (81.6%)	83 (18.4%)	451 (25.5%)	..
Admit	..	..	..	**<0.0001**	..	..	..	**<0.0001**
Not Admitted	1054 (99.9%)	1 (0.1%)	1055 (42.9%)	..	216 (98.2%)	4 (1.8%)	220 (12.5%)	..
Admitted	1349 (96.2%)	54 (3.8%)	1403 (57.1%)	..	1242 (80.3%)	304 (19.7%)	1546 (87.5%)	..
ICU	..	..	..	**<0.0001**	..	..	..	**<0.0001**
No ICU	2172 (99.5%)	11 (0.5%)	2183 (88.8%)	..	1259 (89.3%)	151 (10.7%)	1410 (79.8%)	..
ICU	231 (84.0%)	44 (16.0%)	275 (11.2%)	..	199 (55.9%)	157 (44.1%)	356 (20.2%)	..

(Continued)

Table 1. (Continued)

	<65				≥65			
	Alive (N = 2403)	Dead (N = 55)	Total (N = 2458)	p-value	Alive (N = 1458)	Dead (N = 308)	Total (N = 1766)	p-value
Intubated	··	··	··	<0.0001	··	··	··	<0.0001
No	2354 (98.4%)	38 (1.6%)	2392 (97.3%)	··	1410 (83.9%)	270 (16.1%)	1680 (95.1%)	··
Yes	49 (74.2%)	17 (25.8%)	66 (2.7%)	··	48 (55.8%)	38 (44.2%)	86 (4.9%)	··
Smoking status	··	··	··	0.012	··	··	··	0.0002
Current Smoker	117 (97.5%)	3 (2.5%)	120 (4.9%)	··	765 (86.5%)	119 (13.5%)	884 (50.1%)	··
Former Smoker	315 (97.2%)	9 (2.8%)	324 (13.2%)	··	339 (80.3%)	83 (19.7%)	422 (23.9%)	··
Never Smoker	1523 (98.4%)	24 (1.6%)	1547 (62.9%)	··	321 (77.2%)	95 (22.8%)	416 (23.6%)	··
Unknown/not asked	448 (95.9%)	19 (4.1%)	467 (19.0%)	··	33 (75.0%)	11 (25.0%)	44 (2.5%)	··
Area-level income	··	··	··	0.24	··	··	··	0.62
Missing	23	1	24	··	17	2	19	··
Median income < 200% FPL	982 (97.2%)	28 (2.8%)	1010 (41.5%)	··	478 (81.8%)	106 (18.2%)	584 (33.4%)	··
Median income > = 200% FPL	1398 (98.2%)	26 (1.8%)	1424 (58.5%)	··	963 (82.8%)	200 (17.2%)	1163 (66.6%)	··

ventilation or death was mediated by diabetes (Table 3). The proportion mediated (PM) was slightly smaller for the other severity outcomes (PMICU = 29%, 95%CI 18%-49% and PMHospitalization = 19%, 95%CI 12%-36%).

Discussion

In this sample, diabetes accounted for 19–30% of the association between obesity and COVID-19 severity among individuals younger than 65yo. In both age groups, those with both obesity and diabetes had the highest odds of increased disease severity. Among patients older than 65yo, being underweight increased the risk of mortality regardless of diabetes history, whereas overweight seemed to potentially confer a slight survival benefit among patients without a history of diabetes. Our findings raise key clinical questions about age-specific relationships between weight status and COVID-19 outcomes, while documenting which patients may be at elevated risk for hospitalization and adverse outcomes [22].

By design, this study operationalized the mediator of the relationship between weight and COVID-19 outcomes as prior diagnosis of diabetes to distinguish the contribution of pre-existing diabetes from hyperglycemia occurring during hospitalization among COVID-19 patients without prior history of diabetes. In-depth considerations of glucometabolic parameters are often impractical in the context of critical care, and the concordance between historical glucose regulation documented in the medical chart and glycemic control at the time of admission is equivocal. Conceivably, a greater proportion mediated would be observed if the sample was limited to individuals with poorly controlled blood glucose, and prospective metabolic studies are needed to capture variations in glycemic regulation over the course of COVID-19 progression. Nevertheless, our findings are not trivial in indicating that a prior diagnosis of diabetes, even in absence of additional information, accounted for a meaningful proportion of the association between obesity and COVID-19 severity.

Similar to findings in the younger age group, the combination of obesity and diabetes increased the odds of greater illness severity among patients 65 and older. However, the magnitude of the effect was attenuated. Importantly, individuals with a BMI <18.5 were at increased risk of mortality regardless of diabetes history. This finding contrasts with widely publicized relationships between obesity and COVID-19 severity, while consistent with studies documenting age-specific relationships between obesity and COVID-19 outcomes [5, 6, 28].
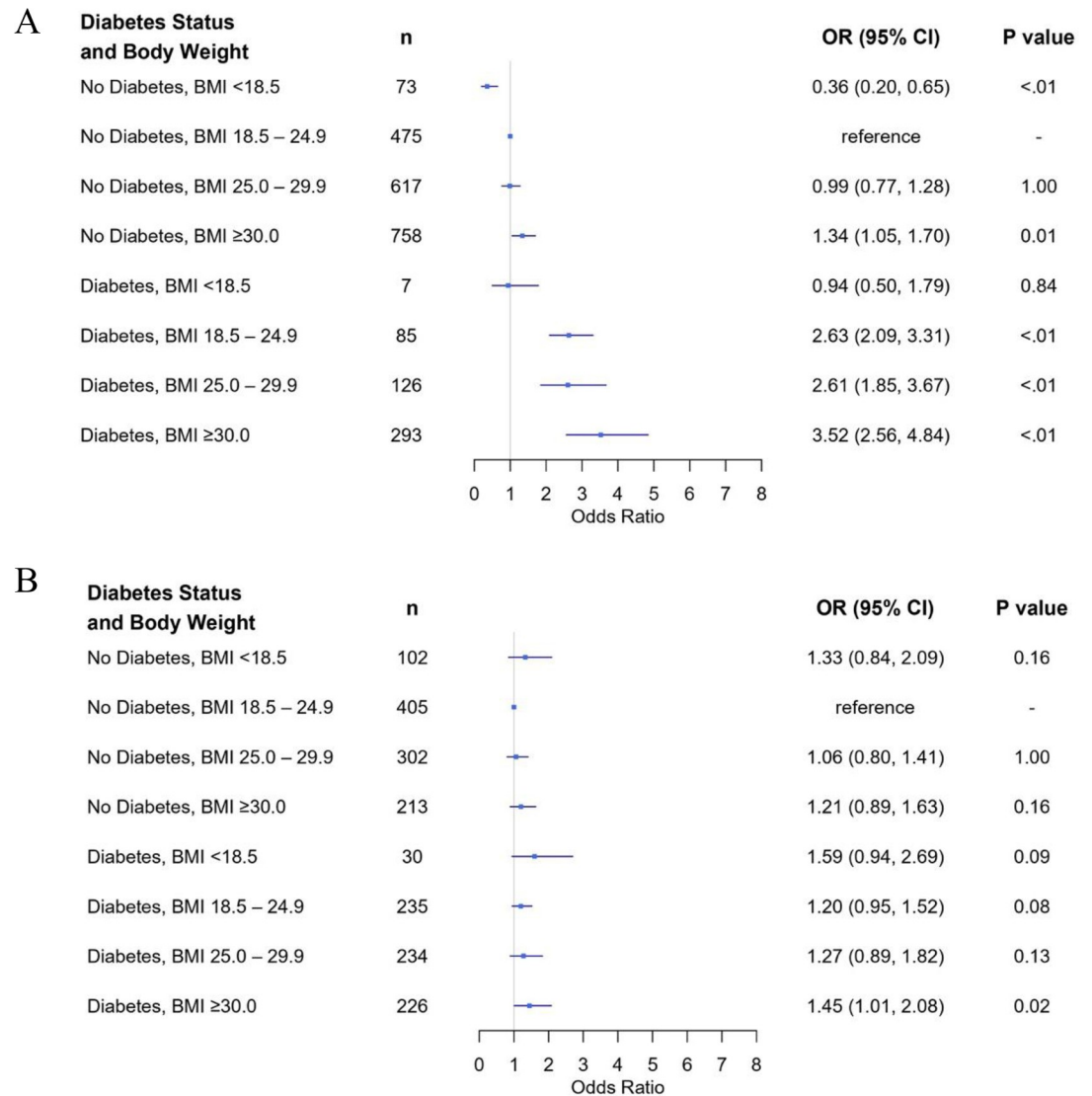
Table 2. Logistic models stratified by outcome and age.

	Ordinal logistic models for illness severity							
	<65				≥65			
	Univariable		Multivariable		Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex (Male vs. Female)	2.2 (1.9, 2.7)	<0.0001	2.0 (1.7, 2.5)	<0.0001	1.4 (1.1, 1.7)	0.0010	1.4 (1.1, 1.8)	0.0006
Race and Ethnicity	..	<0.0001	..	<0.0001	..	0.0004	..	0.022
Hispanic vs Non-Hispanic White	1.0 (0.8, 1.2)	0.95	0.8 (0.6, 1.0)	0.030	1.8 (1.3, 2.4)	<0.0001	1.7 (1.2, 2.3)	0.0008
Non-Hispanic Asian vs Non-Hispanic White	0.4 (0.3, 0.6)	<0.0001	0.5 (0.3, 0.7)	<0.0001	1.0 (0.6, 1.6)	0.98	1.0 (0.6, 1.6)	0.96
Non-Hispanic Black vs Non-Hispanic White	1.0 (0.7, 1.3)	0.79	0.9 (0.7, 1.2)	0.44	1.2 (0.9, 1.6)	0.42	1.3 (0.9, 1.8)	0.25
Non-Hispanic Other vs Non-Hispanic White	0.8 (0.5, 1.3)	0.48	0.7 (0.4, 1.1)	0.12	1.3 (0.8, 2.3)	0.48	1.2 (0.7, 2.1)	0.40
Unknown vs Non-Hispanic White	0.2 (0.2, 0.4)	<0.0001	0.2 (0.1, 0.4)	<0.0001	1.9 (1.0, 3.8)	0.036	1.3 (0.6, 2.6)	0.43
Diabetes	2.8 (2.2, 3.4)	<0.0001	..	..	1.1 (0.9, 1.4)	0.31	..	..
BMI category (normal = reference group)	..	<0.0001	..	<0.0001	..	0.48	..	0.33
Underweight vs normal weight	0.5 (0.3, 0.9)	0.016	0.3 (0.2, 0.6)	<0.0001	1.3 (0.8, 2.0)	0.24	1.3 (0.8, 2.0)	0.20
Overweight vs normal weight	1.2 (1.0, 1.5)	0.17	1.0 (0.8, 1.3)	1.00	1.1 (0.8, 1.4)	0.71	1.1 (0.8, 1.4)	1.00
Obesity vs normal weight	1.6 (1.2, 1.9)	<0.0001	1.5 (1.2, 1.9)	0.0008	1.2 (0.9, 1.6)	0.21	1.2 (0.9, 1.7)	0.11
Smoking status (never = reference group)	..	<0.0001	..	<0.0001	..	<0.0001	..	<0.0001
Current smoker vs. never	1.6 (1.1, 2.4)	0.024	1.3 (0.8, 1.9)	0.47	1.4 (0.7, 2.9)	0.32	1.2 (0.6, 2.5)	0.58
Former smoker vs. never	1.2 (0.9, 1.6)	0.21	1.1 (0.8, 1.4)	1.00	1.1 (0.8, 1.5)	0.43	1.1 (0.8, 1.4)	1.00
Unknown/not asked vs. never	5.5 (4.3, 7.0)	<0.0001	5.1 (3.9, 6.5)	<0.0001	2.8 (2.1, 3.7)	<0.0001	2.7 (2.0, 3.5)	<0.0001
Median <200% vs ≥200% income	1.5 (1.3, 1.8)	<0.0001	1.3 (1.1, 1.6)	0.0016	1.1 (0.9, 1.4)	0.38	0.8 (0.6, 1.1)	0.078
	Binary logistic models for death							
	<65				≥65			
	Univariable		Multivariable		Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex (Male vs. Female)	3.1 (1.5, 6.3)	0.0008	2.8 (1.3, 5.9)	0.0034	1.2 (0.9, 1.6)	0.11	1.2 (0.87, 1.6)	0.23
Race and ethnicity	..	0.63	..	0.72	..	0.0092	..	0.051
Hispanic vs Non-Hispanic White	1.6 (0.7, 3.6)	0.36	1.5 (0.6, 3.5)	0.65	1.1 (0.8, 1.6)	0.60	1.1 (0.7, 1.7)	0.65
Non-Hispanic Asian vs Non-Hispanic White	0.7 (0.1, 3.7)	0.58	0.4 (0.0, 4.1)	0.36	1.9 (1.2, 3.2)	0.0088	1.7 (1.0, 3.0)	0.042
Non-Hispanic Black vs Non-Hispanic White	1.6 (0.6, 4.3)	0.53	1.6 (0.6, 4.2)	0.65	0.9 (0.6, 1.4)	0.61	0.9 (0.6, 1.4)	0.65
Non-Hispanic Other vs Non-Hispanic White	<0.001(-inf, inf)	1.00	<0.001(-inf, inf)	1.00	0.8 (0.4, 1.7)	1.00	0.9 (0.4, 1.8)	1.00
Unknown vs Non-Hispanic White	1.8 (0.5, 6.9)	0.30	1.6 (0.4, 6.1)	0.44	2.5 (1.2, 5.2)	0.012	2.2 (1.0, 4.8)	0.037
Diabetes	3.0 (1.6, 5.6)	0.0001	..	..	1.4 (1.0, 1.9)	0.011	..	..
BMI category (normal as reference group)	..	0.32	..	0.22	..	<0.0001	..	0.0004
Underweight vs normal weight	<0.001 (-inf, inf)	0.98	<0.001 (-inf, inf)	0.98	1.9 (1.2, 3.0)	0.0072	1.9 (1.1, 3.1)	0.0086
Overweight vs normal weight	0.8 (0.3, 1.9)	0.48	0.6 (0.2, 1.5)	0.20	0.7 (0.5, 1.0)	0.024	0.7 (0.5, 1.0)	0.067
Obesity vs normal weight	1.4 (0.6, 3.0)	0.34	1.2 (0.6, 2.7)	0.55	0.7 (0.5, 1.0)	0.066	0.8 (0.5, 1.1)	0.22
Smoking status (never as reference group)	..	0.016	..	0.054	..	0.0002	..	0.0030
Current smoker vs. never	1.6 (0.4, 6.5)	0.43	1.4 (0.3, 5.6)	0.63	2.1 (1.0, 4.8)	0.070	2.0 (0.9, 4.6)	0.14
Former smoker vs. never	1.8 (0.8, 4.4)	0.13	1.7 (0.7, 4.3)	0.18	1.6 (1.1, 2.2)	0.0078	1.6 (1.1, 2.4)	0.0046
Unknown/not asked vs. never	2.7 (1.3, 5.4)	0.0015	2.4 (1.2, 5.0)	0.0065	1.9 (1.4, 2.7)	<0.0001	1.7 (1.2, 2.4)	0.0024
Median <200% vs ≥200% income	1.5 (0.8, 2.8)	0.24	1.2 (0.6, 2.3)	1.00	1.1 (0.8, 1.4)	0.62	1.0 (0.7, 1.5)	1.00

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For instance, a study conducted in Southern California found associations between BMI and mortality in COVID-19 patients, particularly among individuals under the age of 60 [8]. In another study conducted in New York City, obesity was associated with respiratory failure but not in-hospital mortality [28]. To our knowledge, our findings linking underweight status and increased mortality risks have not been widely reported in the literature. Underlying frailty or associated diseases are possible explanators of underweight-associated mortality.

A

Diabetes Status and Body Weight	n		OR (95% CI)	P value
No Diabetes, BMI <18.5	73		0.36 (0.20, 0.65)	<.01
No Diabetes, BMI 18.5 – 24.9	475		reference	-
No Diabetes, BMI 25.0 – 29.9	617		0.99 (0.77, 1.28)	1.00
No Diabetes, BMI ≥30.0	758		1.34 (1.05, 1.70)	0.01
Diabetes, BMI <18.5	7		0.94 (0.50, 1.79)	0.84
Diabetes, BMI 18.5 – 24.9	85		2.63 (2.09, 3.31)	<.01
Diabetes, BMI 25.0 – 29.9	126		2.61 (1.85, 3.67)	<.01
Diabetes, BMI ≥30.0	293		3.52 (2.56, 4.84)	<.01

Odds Ratio: 0 1 2 3 4 5 6 7 8

B

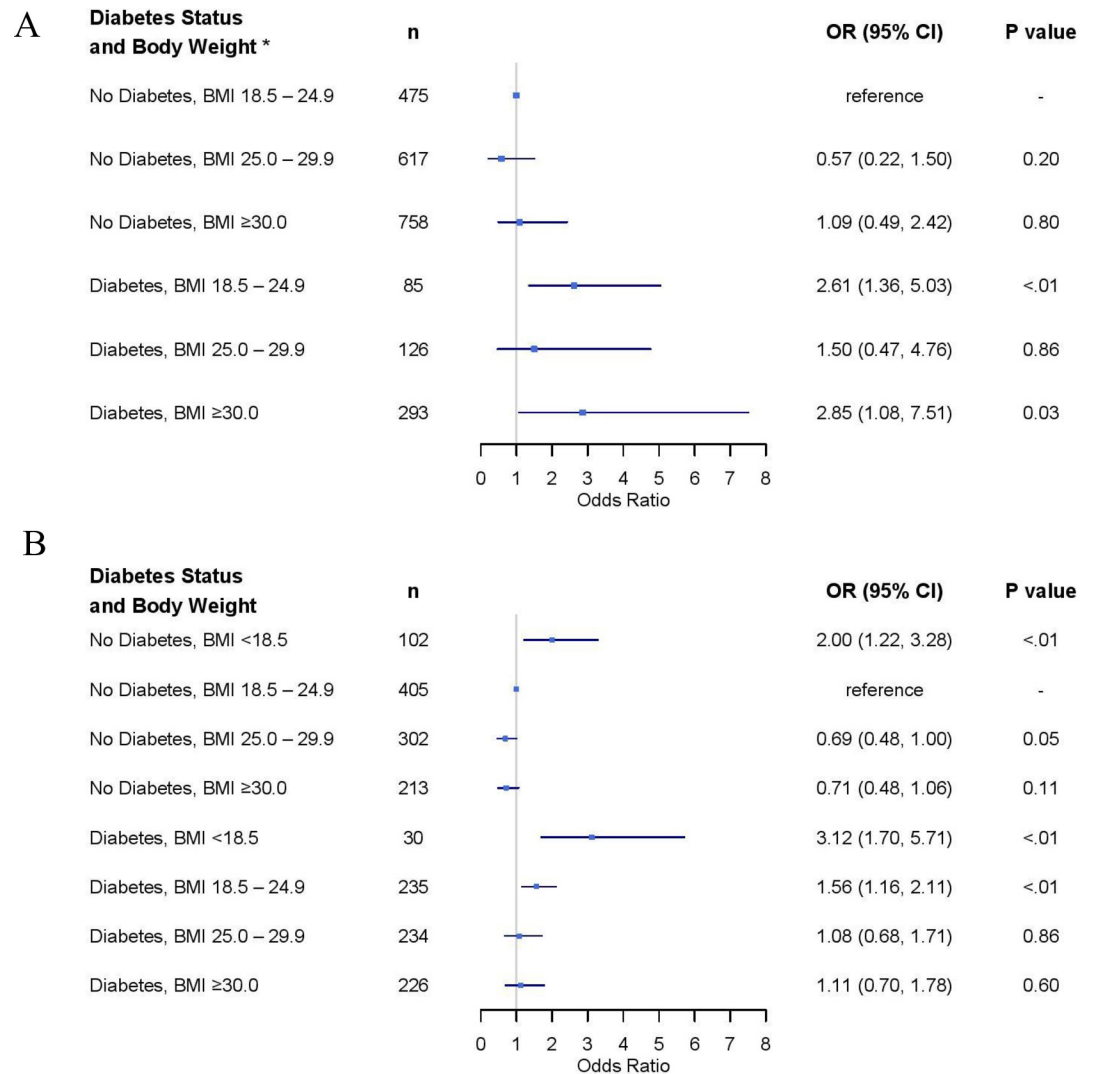| Diabetes Status and Body Weight	n		OR (95% CI)	P value
No Diabetes, BMI <18.5	102		1.33 (0.84, 2.09)	0.16
No Diabetes, BMI 18.5 – 24.9	405		reference	-
No Diabetes, BMI 25.0 – 29.9	302		1.06 (0.80, 1.41)	1.00
No Diabetes, BMI ≥30.0	213		1.21 (0.89, 1.63)	0.16
Diabetes, BMI <18.5	30		1.59 (0.94, 2.69)	0.09
Diabetes, BMI 18.5 – 24.9	235		1.20 (0.95, 1.52)	0.08
Diabetes, BMI 25.0 – 29.9	234		1.27 (0.89, 1.82)	0.13
Diabetes, BMI ≥30.0	226		1.45 (1.01, 2.08)	0.02

Odds Ratio: 0 1 2 3 4 5 6 7 8

Note: Multivariable regression models are adjusted for sex, race, ethnicity, smoking status and socioeconomic status relative to the federal poverty line.

Fig 1. Forest plot of adjusted risk factors for COVID-19 disease severity among patients (A) <65yo and (B) ≥65yo.

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The current results are not entirely consistent with previous studies have reported greater odds of poor outcomes among African Americans and Hispanics and those with lower SES [29]. Racial and ethnic minorities, and those with lower SES who seek regular care within the CSHS may not be representative of the larger population in Los Angeles. This explanation is in-line with the null association reported between race and ethnicity and COVID-19 related mortality from an analysis of data from Kaiser Permanente Southern California, an integrated health care organization [8]. Missing data on race and ethnicity might also mask inequalities [30]. Additionally, the limitations of zip-code based measures as proxy for individual-level income are well documented.

A

Diabetes Status and Body Weight *	n		OR (95% CI)	P value
No Diabetes, BMI 18.5 – 24.9	475		reference	-
No Diabetes, BMI 25.0 – 29.9	617		0.57 (0.22, 1.50)	0.20
No Diabetes, BMI ≥30.0	758		1.09 (0.49, 2.42)	0.80
Diabetes, BMI 18.5 – 24.9	85		2.61 (1.36, 5.03)	<.01
Diabetes, BMI 25.0 – 29.9	126		1.50 (0.47, 4.76)	0.86
Diabetes, BMI ≥30.0	293		2.85 (1.08, 7.51)	0.03

B

Diabetes Status and Body Weight	n		OR (95% CI)	P value
No Diabetes, BMI <18.5	102		2.00 (1.22, 3.28)	<.01
No Diabetes, BMI 18.5 – 24.9	405		reference	-
No Diabetes, BMI 25.0 – 29.9	302		0.69 (0.48, 1.00)	0.05
No Diabetes, BMI ≥30.0	213		0.71 (0.48, 1.06)	0.11
Diabetes, BMI <18.5	30		3.12 (1.70, 5.71)	<.01
Diabetes, BMI 18.5 – 24.9	235		1.56 (1.16, 2.11)	<.01
Diabetes, BMI 25.0 – 29.9	234		1.08 (0.68, 1.71)	0.86
Diabetes, BMI ≥30.0	226		1.11 (0.70, 1.78)	0.60

Note: Multivariable regression models are adjusted for sex, race, ethnicity, smoking status and socioeconomic status relative to the federal poverty line.
* No death reported in the population of patients who were <65yo and underweight.

Fig 2. Forest plot of adjusted risk factors for COVID-19 mortality among patients (A) <65yo and (B) ≥65yo.

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Table 3. Proportion of the association between obesity and disease severity mediated by diabetes in participants age <65 years.

Severity score response	Average proportion mediated (95% CI)
Not admitted into the hospital	0.24 (0.15, 0.42)
Admitted into the hospital	0.19 (0.12, 0.36)
Admitted into ICU	0.29 (0.18, 0.49)
Mechanical ventilation or death	0.30 (0.19, 0.50)

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Limitations

First, it is important to acknowledge that our sample was limited to patients who regularly receive care at a large, urban hospital system. While the availability of objective anthropometric measurements, documented diabetes history and other EHR data increases the rigor of our results, our findings may not be representative of the larger population of individuals with COVID-19 who sought care at a tertiary medical center. Second, history of diabetes and height and weight data were extracted from EHR, however the recency of the data was not considered, thus potentially introducing discrepancy between current and historical data and overall lack of granular specificity of the Charlson comorbidity score used. Finally, the cut-point of 65 years used in the stratification was selected based on definitions used in similar studies [23] and health services research. Conceivably, different cut-offs may reveal different findings.

Conclusions

This study raises interesting clinical questions about age-specific relationships between weight status, metabolic risk factors and COVID-19 outcomes, while documenting which patients may be at elevated risk for hospitalization and adverse outcomes. Identifying heuristics that clinical staff can utilize to make decisions considering the persistent strain of the COVID-19 pandemic may improve patient outcomes and relieve staff burnout. In the absence of risk markers in the general population, these findings and others highlight the importance of self-management skills and regular medical care among patients with diabetes. COVID-19 has had a disproportionate impact on people with diabetes in challenging adherence and access to diabetes care, thereby potentially resulting in poorer diabetes control and related complications. More in-depth prospective studies are needed to document how glycemic regulation before and after infection influence prognosis.

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Author Contributions

Conceptualization: Sarah-Jeanne Salvy, Geetanjali D. Datta, Shehnaz K. Hussain.

Data curation: Susan Cheng, Joseph E. Ebinger, Jane C. Figueiredo.

Formal analysis: Marie Lauzon.

Investigation: Susan Cheng.

Methodology: Sarah-Jeanne Salvy, Geetanjali D. Datta.

Visualization: Qihan Yu.

Writing – original draft: Sarah-Jeanne Salvy, Geetanjali D. Datta, Qihan Yu.

Writing – review & editing: Sarah-Jeanne Salvy, Geetanjali D. Datta, Shehnaz K. Hussain, Susan Cheng, Joseph E. Ebinger, Mark O. Goodarzi, Jane C. Figueiredo.

References

1. Bello-Chavolla OY, Bahena-Lopez JP, Antonio-Villa NE, Vargas-Vazquez A, Gonzalez-Diaz A, Marquez-Salinas A, et al. Predicting Mortality Due to SARS-CoV-2: A Mechanistic Score Relating Obesity and Diabetes to COVID-19 Outcomes in Mexico. J Clin Endocrinol Metab. 2020; 105(8). Epub 2020/06/01. https://doi.org/10.1210/clinem/dgaa346 PMID: 32474598; PubMed Central PMCID: PMC7313944.

2. Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, et al. Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships. Obes Rev. 2020; 21 (11):e13128. Epub 2020/08/28. https://doi.org/10.1111/obr.13128 PMID: 32845580; PubMed Central PMCID: PMC7461480.

3. Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in Patients Younger Than 60 Years Is a Risk Factor for COVID-19 Hospital Admission. Clin Infect Dis. 2020; 71(15):896–7. Epub 2020/04/10. https://doi.org/10.1093/cid/ciaa415 PMID: 32271368; PubMed Central PMCID: PMC7184372.

4. Cai Q, Chen F, Wang T, Luo F, Liu X, Wu Q, et al. Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China. Diabetes Care. 2020; 43(7):1392–8. Epub 2020/05/16. https://doi.org/10.2337/dc20-0576 PMID: 32409502.

5. Smith SM, Boppana A, Traupman JA, Unson E, Maddock DA, Chao K, et al. Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. J Med Virol. 2020. Epub 2020/06/27. https://doi.org/10.1002/jmv.26227 PMID: 32589756; PubMed Central PMCID: PMC7361926.

6. Bhasin A, Nam H, Yeh C, Lee J, Liebovitz D, Achenbach C. Is BMI Higher in Younger Patients with COVID-19? Association Between BMI and COVID-19 Hospitalization by Age. Obesity (Silver Spring). 2020; 28(10):1811–4. Epub 2020/07/02. https://doi.org/10.1002/oby.22947 PMID: 32610371; PubMed Central PMCID: PMC7361943.

7. Pettit NN, MacKenzie EL, Ridgway JP, Pursell K, Ash D, Patel B, et al. Obesity is Associated with Increased Risk for Mortality Among Hospitalized Patients with COVID-19. Obesity (Silver Spring). 2020; 28(10):1806–10. Epub 2020/06/27. https://doi.org/10.1002/oby.22941 PMID: 32589784; PubMed Central PMCID: PMC7362135.

8. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, et al. Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization. Ann Intern Med. 2020. Epub 2020/08/14. https://doi.org/10.7326/M20-3742 PubMed Central PMCID: PMC7429998. PMID: 32783686

9. Nakeshbandi M, Maini R, Daniel P, Rosengarten S, Parmar P, Wilson C, et al. The impact of obesity on COVID-19 complications: a retrospective cohort study. Int J Obes (Lond). 2020; 44(9):1832–7. Epub 2020/07/28. https://doi.org/10.1038/s41366-020-0648-x PMID: 32712623; PubMed Central PMCID: PMC7382318.

10. Stefan N, Birkenfeld AL, Schulze MB. Global pandemics interconnected—obesity, impaired metabolic health and COVID-19. Nat Rev Endocrinol. 2021. Epub 2021/01/23. https://doi.org/10.1038/s41574-020-00462-1 PMID: 33479538.

11. Longmore DK, Miller JE, Bekkering S, Saner C, Mifsud E, Zhu Y, et al. Diabetes and Overweight/Obesity Are Independent, Nonadditive Risk Factors for In-Hospital Severity of COVID-19: An International, Multicenter Retrospective Meta-analysis. Diabetes Care. 2021; 44(6):1281–90. Epub 2021/04/17. https://doi.org/10.2337/dc20-2676 PMID: 33858854; PubMed Central PMCID: PMC8247499.

12. Caussy C, Pattou F, Wallet F, Simon C, Chalopin S, Telliam C, et al. Prevalence of obesity among adult inpatients with COVID-19 in France. The Lancet Diabetes & Endocrinology. 2020; 8(7):562–4. https://doi.org/10.1016/S2213-8587(20)30160-1 PMID: 32437642

13. Klein O, Krishnan J, Glick S, Smith L. Systematic review of the association between lung function and Type 2 diabetes mellitus. Diabetic medicine. 2010; 27(9):977–87. https://doi.org/10.1111/j.1464-5491.2010.03073.x PMID: 20722670

14. Liu S, Zhang B, You J, Chen L, Yuan H, Zhang S. Elevated fasting blood glucose at admission is associated with poor outcomes in patients with COVID-19. Diabetes Metab. 2021; 47(2):101189. Epub 2020/09/09. https://doi.org/10.1016/j.diabet.2020.08.004 PMID: 32896652; PubMed Central PMCID: PMC7472974.

15. Wu J, Huang J, Zhu G, Wang Q, Lv Q, Huang Y, et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ Open Diabetes Res Care. 2020; 8(1). Epub 2020/06/07. https://doi.org/10.1136/bmjdrc-2020-001476 PMID: 32503812; PubMed Central PMCID: PMC7298690.

16. Zhang B, Liu S, Zhang L, Dong Y, Zhang S. Admission fasting blood glucose predicts 30-day poor outcome in patients hospitalized for COVID-19 pneumonia. Diabetes Obes Metab. 2020; 22(10):1955–7. Epub 2020/07/07. https://doi.org/10.1111/dom.14132 PMID: 32627338; PubMed Central PMCID: PMC7361510.

17. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab. 2020; 31(6):1068–77 e3. Epub 2020/05/06. https://doi.org/10.1016/j.cmet.2020.04.021 PMID: 32369736; PubMed Central PMCID: PMC7252168.

18. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, da Silva LFF, de Oliveira EP, Saldiva PHN, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemost. 2020; 18(6):1517–9. Epub 2020/04/16. https://doi.org/10.1111/jth.14844 PMID: 32294295; PubMed Central PMCID: PMC7262093.

19. Pontiroli AE, La Sala L, Chiumello D, Folli F. Is blood glucose or obesity responsible for the bad prognosis of COVID-19 in obesity—diabetes? Diabetes Res Clin Pract. 2020; 167:108342. Epub 2020/07/31. https://doi.org/10.1016/j.diabres.2020.108342 PMID: 32730788; PubMed Central PMCID: PMC7384403 interest with the contents of this paper.

20. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. Obesity (Silver Spring). 2020; 28(7):1195–9. Epub 2020/04/10. https://doi.org/10.1002/oby.22831 PMID: 32271993; PubMed Central PMCID: PMC7262326.

21. Kuk JL, Rotondi M, Sui X, Blair SN, Ardern CI. Individuals with obesity but no other metabolic risk factors are not at significantly elevated all-cause mortality risk in men and women. Clin Obes. 2018; 8(5):305–12. Epub 2018/07/13. https://doi.org/10.1111/cob.12263 PMID: 29998631; PubMed Central PMCID: PMC6175472.

22. Javed AA, Aljied R, Allison DJ, Anderson LN, Ma J, Raina P. Body mass index and all-cause mortality in older adults: A scoping review of observational studies. Obes Rev. 2020; 21(8):e13035. Epub 2020/04/23. https://doi.org/10.1111/obr.13035 PMID: 32319198.

23. Anderson MR, Geleris J, Anderson DR, Zucker J, Nobel YR, Freedberg D, et al. Body Mass Index and Risk for Intubation or Death in SARS-CoV-2 Infection: A Retrospective Cohort Study. Ann Intern Med. 2020; 173(10):782–90. Epub 2020/07/30. https://doi.org/10.7326/M20-3214 PMID: 32726151; PubMed Central PMCID: PMC7397550.

24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009; 42(2):377–81. Epub 2008/10/22. https://doi.org/10.1016/j.jbi.2008.08.010 PMID: 18929686; PubMed Central PMCID: PMC2700030.

25. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019; 95:103208. Epub 2019/05/13. https://doi.org/10.1016/j.jbi.2019.103208 PMID: 31078660; PubMed Central PMCID: PMC7254481.

26. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005; 43(11):1130–9. Epub 2005/10/15. https://doi.org/10.1097/01.mlr.0000182534.19832.83 PMID: 16224307.

27. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: R package for causal mediation analysis. 2014.

28. Goyal P, Ringel JB, Rajan M, Choi JJ, Pinheiro LC, Li HA, et al. Obesity and COVID-19 in New York City: A Retrospective Cohort Study. Ann Intern Med. 2020; 173(10):855–8. Epub 2020/07/07. https://doi.org/10.7326/M20-2730 PMID: 32628537; PubMed Central PMCID: PMC7384267.

29. Azar KMJ, Shen Z, Romanelli RJ, Lockhart SH, Smits K, Robinson S, et al. Disparities In Outcomes Among COVID-19 Patients In A Large Health Care System In California. Health Aff (Millwood). 2020; 39(7):1253–62. Epub 2020/05/22. https://doi.org/10.1377/hlthaff.2020.00598 PMID: 32437224.

30. Labgold K, Hamid S, Shah S, Gandhi NR, Chamberlain A, Khan F, et al. Estimating the Unknown: Greater Racial and Ethnic Disparities in COVID-19 Burden After Accounting for Missing Race and Ethnicity Data. Epidemiology. 2021; 32(2):157–61. Epub 2020/12/17. https://doi.org/10.1097/EDE.0000000000001314 PMID: 33323745.