Association between Obesity-related Comorbidities and COVID-19-related Adverse Outcomes

Tong, Ling; MS; University of Wisconsin-Milwaukee, Department of Health Informatics and Administration, Milwaukee, WI, USA

Khani, Masoud; MS; University of Wisconsin-Milwaukee, Department of Engineering and Applied Science, Milwaukee, WI, USA

Lu, Qiang; Ph.D.; China University of Petroleum, Department of Computer Science and Technology, Beijing, China

Taylor, Bradley; MS; Medical College of Wisconsin, Clinical and Translational Science Institute of Southeastern Wisconsin, Milwaukee, WI, USA

Osinski, Kristen; MS; Medical College of Wisconsin, Clinical and Translational Science Institute of Southeastern Wisconsin, Milwaukee, WI, USA

Luo, Jake; Ph.D.; University of Wisconsin-Milwaukee, Department of Health Informatics and Administration, Milwaukee, WI, USA

Keywords: Obesity, COVID-19, Hypertension, Diabetes

Acknowledgements:

All authors declared no conflict of interest. The project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, Award Number UL1TR001436. The content is solely the responsibility of the author(s) and does not necessarily represent the official views of the NIH.

This project is also funded by the Research and Education Program Fund, a component of the Advancing a Healthier Wisconsin Endowment at the Medical College of Wisconsin.

This is an observational study. No human or animal subjects were involved during the study.

Ling, Jake and Masoud participated in study design. Bradley and Kristen acquired data from electronic health records. Qiang contributed essential tools of coding platform. Ling performed all statistical analyses. Ling, Jake and Masoud drafted the manuscript draft. All authors revised the paper and approved the final manuscript submission.

Corresponding Author:

Jake Luo, PhD

Associate Professor

Department of Health Informatics and Administration

College of Health Sciences

University of Wisconsin, Milwaukee

Email: jakeluo@uwm.edu

Postal Address: 2025 E Newport Ave 6469, WI, 53211, Milwaukee, USA

Response to Reviewer's Comments:

We thank the reviewer for their careful reading of the manuscript and their constructive comments. We carefully considered and incorporated the comments to improve and clarify the manuscript. Because we revised the manuscript substantially, we summarized the major changes for the convenience of reading. We also track changes and underlined the modified texts of the manuscript.

Major Changes of the Revised Manuscript

1. We stated the odds ratio and hazard ratios of adverse outcomes with different comorbidities in the abstract. We did not report odds ratios of BMI in the abstract because the effect of BMI factor is not statistically significant.
2. We modified the design of Figure 2: The flow diagram of patients and outcomes. This modification follows Clinical Obesity Journal's publication guidelines.
3. We added an ethnicity description to the first paragraph of the results.
4. We added details about how we calculated the hazard ratio and how the model is adjusted by demographic variables to the method - statistical analysis section.
5. We updated Table 2: Controlled cross-group comparison of comorbidity and adverse outcomes. We re-analyzed the cross-group comparison from the obesity population to all weight populations, as suggested by the reviewer.
6. We updated Table 3 and rebuilt the multiple logistic regression model. We included age as a covariate in our model in this revision, as suggested by the reviewer. All odds ratios and p-values have been appropriately adjusted. As we updated Table 3 odds ratios, we updated all reported odds ratios throughout the manuscript main text.

7. We updated Figures 3 and 4 to provide a comprehensive visual representation of Tables 1 and Table 2. The goal is to demonstrate (1) the association between BMI and adverse outcomes; (2) the association between comorbidity and adverse outcomes for each BMI group.
8. We added a new Table 4, a calculation of hazard ratios of clinical outcomes, BMI, and comorbidity factors.
9. We discussed two additional topics in the discussion section as suggested. The first topic is the importance of the study with recent variants and vaccination. The second subject is a comparison with other studies on comorbidities and obesity.
10. We made substantial grammatical and phrase changes to use more precise words and make the manuscript easier to read. Please see the underlined text to track changes.

Also, please see below for a detailed point-by-point response to all comments.

1. Was age a covariate in the models? If not, it should be included as it affects comorbidities and COVID-19 outcomes.

No, age was not a covariate of the multiple logistic regression model in table 3. In previous manuscript, the result was adjusted by patients' race, ethnicity, and gender. Thank you for pointing out we missed the age as a covariate. In this revision, we added the age as a covariate. We modified and updated the logistic regression model's results in table 3.

2. Is ethnicity data available?

Yes, ethnicity data is available. In this revision, we added an ethnicity summary in the demographic population description. Among 2109 patients, 1972 (93.5%) out of 2109 were non-Hispanic. 98 (4.6%) were Hispanic. 39 (1.9%) were unidentified.

3. In the results section, please state in the main text, the hazard ratio for hospitalization, ICU admission, need for mechanical ventilation and death after adjustment for covariates including age, hypertension, and diabetes for normal weight (comparator), overweight, BMI 30-40 and >40 groups.

We calculated the hazard ratio based on the logistic regression model. The model included the following variables: patient's race, ethnicity, gender, age, BMI categories, and four clinical outcomes (hospitalization, ICU stay, need for mechanical ventilation, and death). In "Results" Section, Table 4 presents the hazard ratios, showing how comorbidities and BMI categories are associated with increased risk of clinical outcomes. In the "Statistical Analysis" section, we elaborated on how we computed the hazard ratio.

4. If the sample size permits: do comorbidities increase adverse effects in overweight and normal weight groups? If so, please comment.

In the last manuscript, table 2 only explained the effect on patients of obesity (BMI > 30). We examined the data and check sample sizes on other weight groups. We find comorbidities significantly increase the risk of adverse effects in overweight and normal weight groups, too. Therefore, we revised Table 2 and explained the positive association between comorbidity factors and adverse clinical outcomes among all weight groups. In this revision. Table 2 shows comorbidities increases the odds of adverse effects among patients of BMI>40, BMI 30-40, BMI 25-30, and BMI 18-25. The associations are statistically significant. Therefore, we conclude that the positive association between comorbidity and the increased risk of adverse outcomes applies to all weight groups. Your revision suggestion helped us discover the comorbidity effects on all weight groups, we are very thankful for your constructive comments that expanded our study's scope.

5. Please elaborate on how your findings compare to other studies that have assessed comorbidities and obesity in COVID-19 and why there may be differences.

Thank you for your suggestion, we have introduced more recent publications. We compared our results with similar findings. Please find the new discussions below in section named "Comparison with other studies regarding the comorbidities and obesity." The comparison has highlighted the need for future studies on other comorbidity effects to COVID-19 severity.

6. What are the significance of the findings with more recent variants and vaccination? Please add to discussion.

We added a section named "Study significance with recent variants and vaccination." In this section, we discussed the Vaccine, Omicron and Delta variants, and how they change the COVID-19 outcomes in populations. Although new vaccine decreased the severity. They cannot protect unvaccinated population. The absolute number of infections remains high, making populations in high risk of clinical outcomes. Therefore, our study focused on comorbidity will continue to explore comorbidity factors and how they affect the severity of COVID-19 outcomes.

7. Please update abstract to clearly state the HR for adverse events among weight categories unadjusted after adjustment.

We updated the abstract and reported the adjusted hazard ratio to the abstract.

Minor: Please replace 'we believe' in intro to 'we hypothesize.'

We have replaced all "we believe" with "we hypothesize" in the manuscript.

Again, we thank the reviewer for their careful reading of the manuscript and their constructive comments. Your suggestion helped us to significantly improve the manuscript.

What is already known about this subject?

- The prevalence of obesity in the US population continues to surge.
- Obesity is associated with an increased risk of severe COVID-19 outcomes.
- Controlling obesity rates can reduce comorbidity risks.

What are the new findings?

- Obesity alone does not significantly increase the risk of severe COVID-19 outcomes.
- Obesity-related comorbidities, including primary hypertension and type 2 diabetes, are associated with significantly worse outcomes.

How might your results change the direction of research or the focus of clinical practice?

- Obesity-related comorbidities, including primary hypertension and type 2 diabetes, should be considered more important risk factors than obesity alone in clinical practice.
- Controlling comorbidities in clinical practice improves care quality.

Abstract:

Objective: To analyze associations between body mass index, hypertension, diabetes, and clinical outcomes in COVID-19 patients.

Methods: Between March and December 2020, we chose patients who tested positive for COVID-19. A logistic regression model was used to measure the independent association between comorbidity and outcomes. The hospitalization rate, intensive care unit (ICU) stay rate, mechanical ventilation rate, and mortality rate were clinical outcomes.

Results: Among 2,109 patients, the median body mass index (BMI) was 30.6, the median age was 41.5, and 1,527 (72.4%) of the patients were female. A total of 634 (30.0%) patients were diagnosed with primary hypertension, and 314 (14.9%) with type 2 diabetes mellitus. There were 382 (18.1%) inpatients, with 76 (19.9%) admitted to the intensive care unit. Forty-three (11.3%) were treated with mechanical ventilation, and 33 (8.6%) died. Patients with obesity were more likely to be diagnosed with primary hypertension (Odds Ratio: 3.68, 95% CI:[3.02,4.48]) and Type 2 diabetes (4.14[3.18,5.39]). Obesity-related comorbidities contributed more strongly to clinical outcomes of COVID-19 than obesity alone. The adjusted hazard ratios for hospitalization for primary hypertension (HR:1.27,95% CI:[1.10, 1.43]), secondary hypertension (1.59 [1.24,1.86]), type 1 diabetes (1.29 [1.02,1.47]) and type 2 diabetes (1.19 [1.06,1.30] are all significant.

Conclusion: Patients with obesity and comorbidities have a higher risk of poor outcomes. Obesity is not independently associated with poor clinical outcomes. Obesity-related comorbidities, including hypertension and diabetes, are independently associated with poorer clinical outcomes among COVID-19 patients. Future research is needed to determine the risk of other types of comorbidities.

Introduction

The COVID-19 pandemic has had a global impact on health-care systems, with 308 million cases and 5.5 million deaths as of January 11, 2022[1]. People's lifestyles were altered as a result of the pandemic. Social isolation resulted in more time spent at home, increased social anxiety, and increased screen time, all of which led to an increase in the consumption of highly processed foods and fewer outdoor activities[2]. Obesity is becoming more common because of these factors. Changing dietary habits, as well as environmental and physical activity factors, have all contributed to the rise in obesity rates since the 1980s[3-5]. As a result, obesity will continue to be the leading risk factor affecting people's quality of life.

Obesity can lead to a number of comorbidities, including cardiovascular disease, hypertension, and diabetes[5,6]. Association analyses[2,6–13] showed that obesity is a critical risk factor for COVID-19 outcomes, such as a higher hospital admission rate, longer inpatient stay, and higher risk of comorbidities. These comorbidities are likely to be predisposing factors for adverse outcomes of COVID-19[14]. Investigating differences between obesity and obesity-related comorbidities can help better understand adverse outcomes.

Recent studies[6,12,13] have investigated the association between obesity and adverse COVID-19 outcomes. Obesity-related comorbidities, on the other hand, may be more important. In contrast to obesity, it is possible to manage obesity-related comorbidities in the short term to avoid potentially severe outcomes. No study has examined obesity-related comorbidities as an independent factor in COVID-19 outcomes. We hypothesize that common obesity-related comorbidities can predict COVID-19 outcomes more accurately than obesity alone. To improve care quality, patients with related comorbidities should be treated first.

Methods

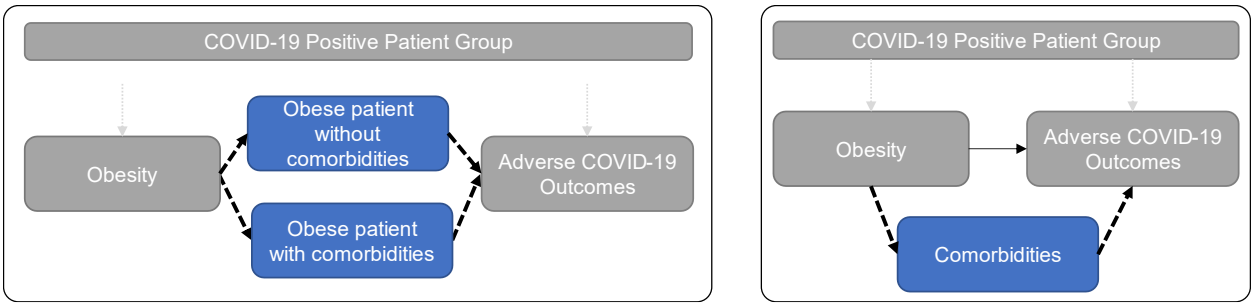


Figure 1: Design of the study. The first model (left) compares the effect of comorbidities. The second model (right) uses logistic regression to evaluate the independent comorbidity effect of obesity.

Figure 1 shows the study design. We created two statistical models to measure the effect of comorbidities. The first model compared two patient groups with similar BMIs and socioeconomic status. The comorbidity group was the experimental group, and the non-comorbidity group was the comparison group. The first model investigates whether comorbidity is an independent factor of adverse outcomes. The second model employed a logistic regression model to assess the independent association between predictors and adverse outcomes.

Data source and study cohort

This retrospective cohort study used electronic health records from the Clinical Research Data Warehouse. The Clinical Research Data Warehouse is a component of the Clinical and Translational Science Institute of Southeast Wisconsin, which maintains a monthly updated mirror of the entire Froedtert and Medical College Electronic Health Record System. Some demographic data fields have been shifted for the protection of patient privacy. The Froedtert and Medical College of Wisconsin Institutional Review Boards reviewed and approved this study.

Patient inclusion and variable extraction

We included all patients who tested positive between March 1 and December 31, 2020. COVID-19 antigen test records are identified by the diagnostic codes of the International Classification of

Diseases. We identified obesity using body mass index (BMI) ranges: healthy weight (BMI 18-25), overweight (25-30), obesity (30–40), and morbid obesity (>40). We identified hypertension and diabetes through ICD-10 codes as comorbidity records for patients with obesity. For adverse outcomes, we extracted hospital admission, ICU stay, mechanical ventilation, and death records for each patient. Patients' ICU stays were identified from hospitalized patients with recorded current procedural terminology (CPT) codes. Patients with mechanical ventilation are identified through the same CPT code system. Patient death records were extracted from the demographic records.

Outcomes

The primary outcomes are descriptive patient data, including obesity rate, obesity-related-comorbidities rate, and COVID-19 adverse outcomes. Furthermore, we evaluated hypertension and diabetes as comorbidities. Hospital admission, ICU stay, mechanical ventilation and mortality were COVID-19 outcome variables. We presented the result in two statistical models to measure the association of comorbidity and adverse outcomes: (1) a cross-controlled group comparison; (2) a logistic regression model. For each weight group, we calculated the odds ratio of clinical outcomes for patients with or without comorbidity. We also calculated the odds ratio and hazard ratio of weight groups, hypertension, and diabetes for each adverse outcome.

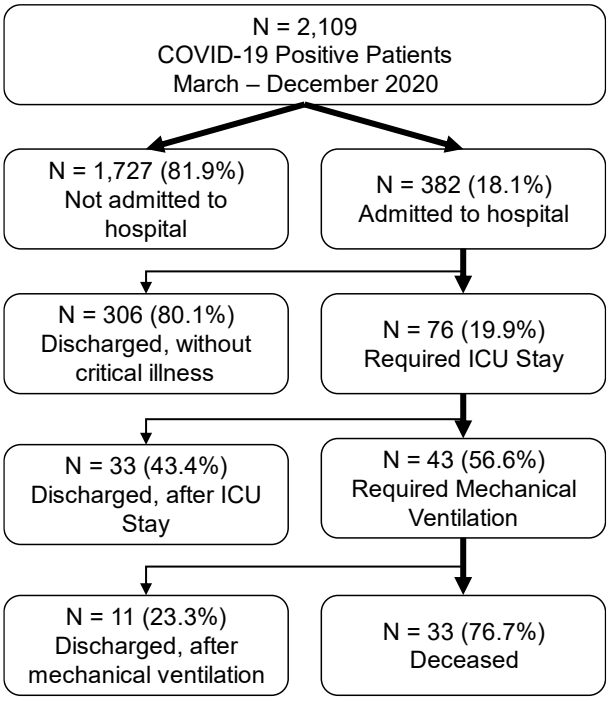
Statistical analysis

We performed all statistical analyses in R programming language. A two-by-two contingency table was used to calculate odds ratio, which measures the strength of the association between two groups. The 95% confidence interval (CI) quantifies the difference between two groups. A P value < 0.05 indicates significance.

We categorized BMI range, hypertension (none, primary hypertension, secondary hypertension) and diabetes (no diabetes, type 1, type 2) as risk factors. logistic regression model was developed to examine the association between adverse outcomes and risk factors. This logistic regression model excluded the confounding effect of multivariate model to evaluate the association independently. The adjusted model excluded the effect of age, gender, race, and ethnicity; therefore, we can measure the independent association between BMI, comorbidities, and adverse outcomes. We examined the association between these predictors and four common adverse outcomes. Each model is represented as an odds ratio and 95% confidence interval. In addition, we calculated the adjusted hazard ratio for each clinical outcomes, BMI and comorbidity factors based on the baseline hazard of a healthy weight, no hypertension, and no diabetes condition.

Results

Patient characteristics



(REVISED) Figure 2: Flow diagram of patients and adverse outcomes.

Figure 2 shows the flow diagram of this study. A total of 2109 patients tested positive and were included. The median BMI was 30.6, the median age was 41.5, and 72.4% were female. Non-Hispanics made up 93.5 percent of the population in 1972. Ninety-eight people (4.6%) were Hispanic. 39 (1.9%) were unidentified. A total of 913 were identified as having obesity (BMI > 30), 634 were diagnosed with primary hypertension, and 314 were diagnosed with type 2 diabetes. A total of 382 were admitted to the hospital, and the remaining 1727 were treated as outpatients. Among 382 patients admitted to the hospital, seventy-six were admitted to the ICU. Forty-three patients proceeded with mechanical ventilation, and thirty-three died.

Association between obesity, comorbidity, and increased risk of adverse outcomes

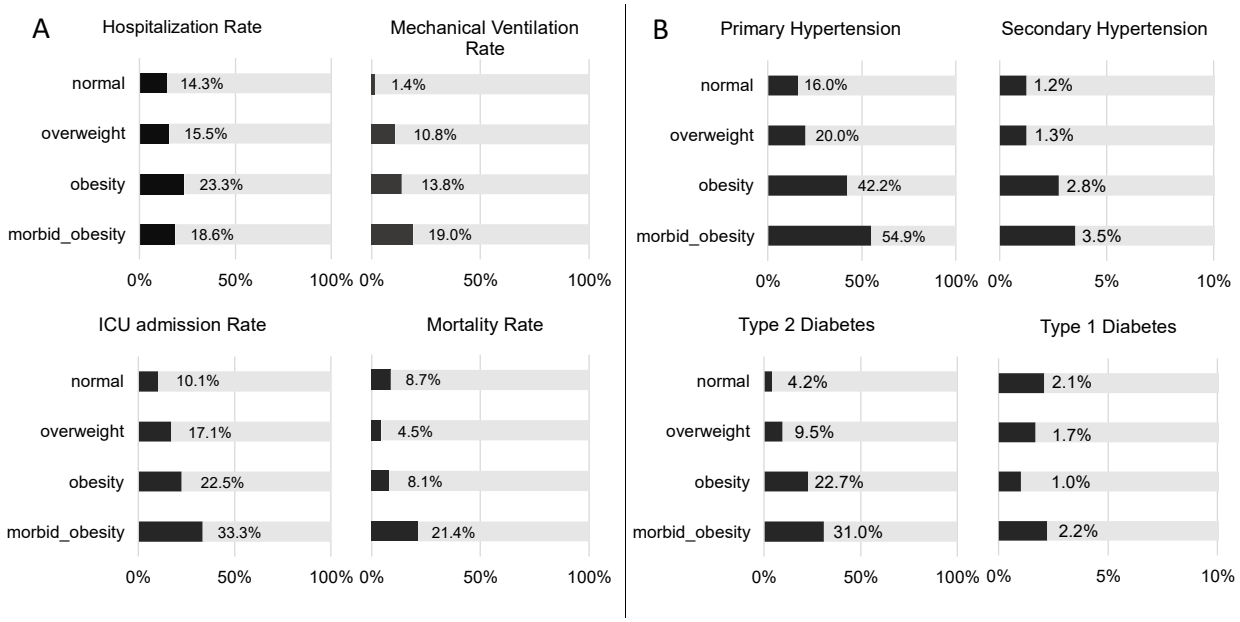
Obesity is a major risk factor for essential hypertension and diabetes. Table 1 shows the prevalence of hypertension and diabetes among different BMI groups. We observe that hypertension and diabetes are more prevalent in populations with a higher BMI. We observe that hypertension and diabetes are more prevalent in higher BMI populations. A total of 16.0% of healthy weight patients were diagnosed with primary hypertension, whereas the percentage increased to 20.0% for overweight patients. The prevalence of primary hypertension among patients with obesity and morbid obesity rose to 42.2% and 54.9%, respectively. The odds ratio indicates that patients with obesity have a 3.68-fold likelihood of being diagnosed with hypertension (95% CI = 3.03, 4.48, $p<0.001$). A similar risk existed between BMI and secondary hypertension, with an odds ratio of 2.40 (OR = 2.40, 95% CI = 1.27, 4.54, $p = 0.006$) and type 2 diabetes (OR = 4.14, 95% CI = 3.18, 5.39, $p<0.001$).

Obesity is associated with a higher risk of adverse outcomes. The odds ratio of hospitalization for patients with obesity was 1.60 (95% CI: 1.28, 2.00, $p<0.001$). The mean length of stay for healthy weight hospitalized patients was 2.11 days. The length of stay increased to 2.56 days for

overweight patients, 3.84 days for patients with obesity, and 4.39 days for patients with morbid obesity. The obesity factor was also associated with a higher risk of ICU stay (OR = 2.52, 95% CI =1.58, 4.02, p <0.001), mechanical ventilation rate (OR = 2.97, 95% CI = 1.57, 5.61, p<0.001) and mortality rate (OR = 2.66, 95% CI = 1.28, 5.51, p=0.006). Obesity is an effective predictor of adverse outcomes.

Table 1: Patient's Comorbidity factors associated with BMI category											
			Patients Above Normal BMI						OR	95% CI	P-value
	Healthy weight (BMI 18 - 25)		Overweight (BMI 25 - 30)		Obesity (BMI 30 - 40)		Morbid Obesity (BMI > 40)		(BMI 18 - 30 vs BMI > 30)		
# Of patients	481		715		687		226				
Comorbidity Factors:											
Hypertension											
Primary Hypertension	77	16.0%	143	20.0%	290	42.2%	124	54.9%	3.68	(3.03, 4.48)	<0.001
Secondary Hypertension	6	1.2%	9	1.3%	19	2.8%	8	3.5%	2.4	(1.27, 4.54)	0.0055
Diabetes											
Diabetes, Type 1	10	2.1%	12	1.7%	7	1.0%	5	2.2%	0.71	(0.35, 1.44)	0.3428
Diabetes, Type 2	20	4.2%	68	9.5%	156	22.7%	70	31.0%	4.14	(3.18, 5.39)	<0.001
Adverse outcomes:											
Hospitalization, #	69	14.3%	111	15.5%	160	23.3%	42	18.6%	1.6	(1.28, 2.00)	<0.001
Length of stay, mean	2.11		2.56		3.84		4.39				<0.001
ICU stay	8	1.7%	20	2.8%	37	5.4%	15	6.6%	2.52	(1.58, 4.02)	<0.001
Mechanical Ventilation	2	0.4%	12	1.7%	23	3.3%	8	3.5%	2.97	(1.57, 5.61)	<0.001
Death	6	1.2%	5	0.7%	13	1.9%	9	4.0%	2.66	(1.28, 5.51)	0.0063

Figure 3 shows that a higher BMI is not only with associated increased risk of clinical adverse event (3.A), but also associated with increased risk of comorbidities, including primary hypertension and type 2 Diabetes.



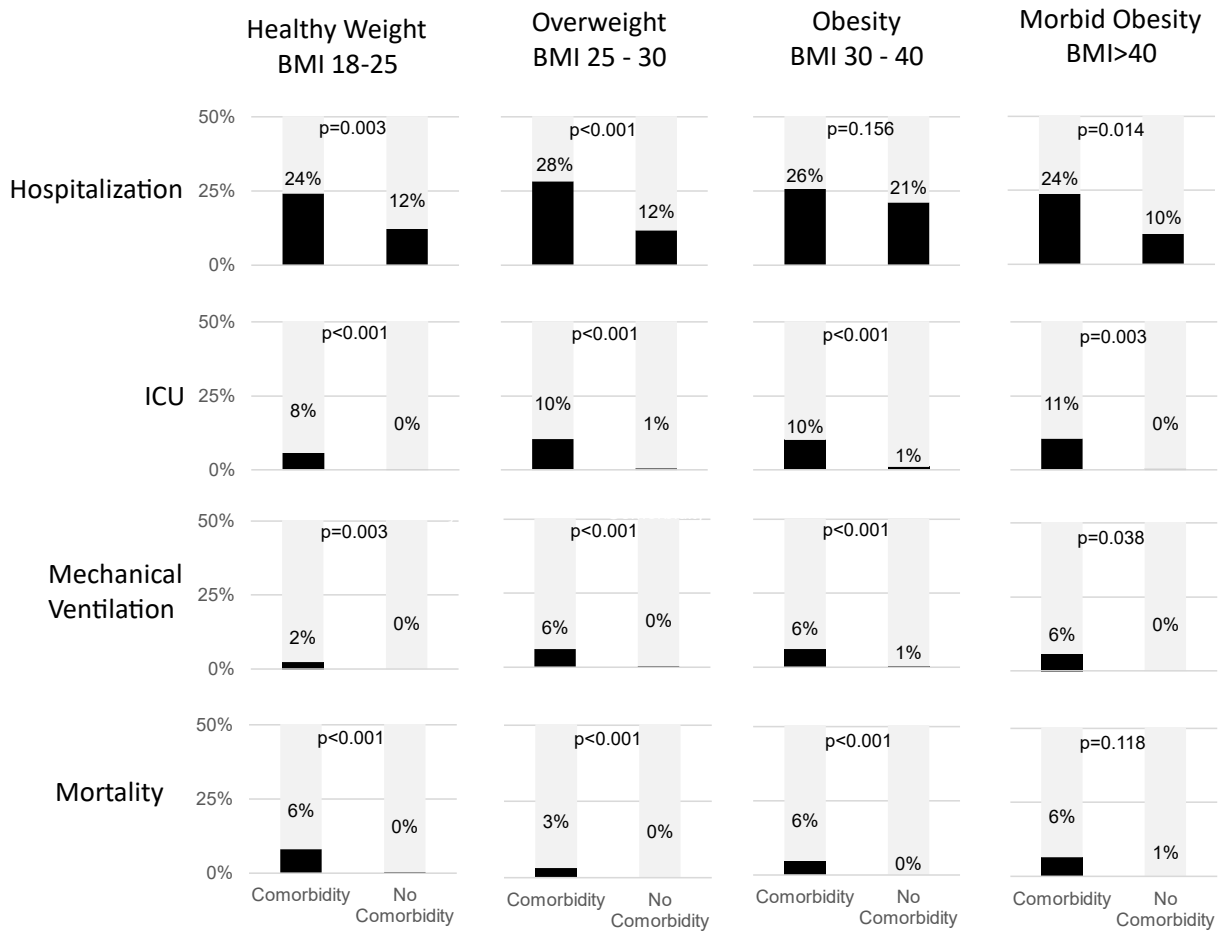
(REVISED) Figure 3: Association between obesity, diabetes, and hypertension. (A): An Increased BMI is associated with increased risk of clinical outcomes. (B): a higher percentage of patients with obesity and patients with morbid obesity are diagnosed with hypertension and diabetes.

Association between comorbidity and outcome variables

To explore the independent risk factor of comorbidity to adverse outcomes, we split the weight variable into four weight categories. The purpose is to control the BMI effect to the adverse outcomes. The variable-controlled association between comorbidity and adverse outcomes is shown in Table 2 for each weight group, showing that worse outcomes were more prevalent among comorbidity groups. Therefore, obesity-related comorbidity is an independent factor of outcomes. When we exclude the possible effect of obesity and other socioeconomic variables, we observe a significantly higher risk for the comorbidity group. For patients with obesity (BMI 30 - 40), the patient group with comorbidities was 1.29 times more likely to be admitted to the

hospital (95% CI: 0.91, 1.84; p = 0.156). The odds ratio for ICU stay was 9.01 (95% CI: 3.33, 24.41, p<0.001). The odds ratio for mechanical ventilation was 10.06 (95% CI: 2.69, 37.61, p<0.001). The odds ratio for death was 30.96 (95% CI: 1.83, 522.9), p<0.001). Figure 4 shows the association between comorbidity and clinical outcomes when controlling for patient BMI and social factors. Patients without comorbidities have a significantly lower risk of adverse outcomes.

(REVISED RESULTS) Table 2: Controlled cross-group Comparison: The independent association of comorbidity and Adverse outcomes										
Adverse outcomes	with comorbidity		Primary Hypertension	Secondary Hypertension	Type 1 Diabetes	Type 2 Diabetes	without comorbidity		Odds Ratio	(95% CI)	P-value
Patient with BMI >40	139		124	8	5	70	87				
Hospitalization, #	33	24%	28	3	3	22	9	10%	2.59	(1.19, 5.65)	0.014
ICU stay	15	11%	12	3	3	13	0	0%	21.75	(1.28, 368.4)	0.003
Mechanical Ventilation	8	6%	6	3	1	7	0	0%	11.29	(0.64, 198.1)	0.038
Death	8	6%	8	1	1	8	1	1%	3.72	(0.64, 21.56)	0.118
BMI 30-40	327		290	19	7	156	360				
Hospitalization, #	84	26%	73	11	4	48	76	21%	1.29	(0.91, 1.84)	0.156
ICU stay	33	10%	29	7	4	22	4	1%	9.01	(3.33, 24.41)	<0.001
Mechanical Ventilation	21	6%	20	5	1	13	2	1%	10.06	(2.69, 37.61)	<0.001
Death	13	5%	12	3	0	9	0	0%	30.96	(1.83, 522.9)	<0.001
BMI 25 - 30:	163		143	9	13	68	552				
Hospitalization, #	46	28%	44	5	3	20	65	12%	2.95	(1.93, 4.53)	<0.001
ICU stay	17	10%	17	2	1	11	3	1%	18.80	(5.88, 60.1)	<0.001
Mechanical Ventilation	10	6%	10	2	1	8	2	0%	15.10	(3.76, 60.67)	<0.001
Death	5	3%	5	0	1	2	0	0%	38.43	(2.11, 698.8)	<0.001
BMI 18 - 25	87		77	6	10	20	394				
Hospitalization, #	21	24%	18	2	4	5	48	12%	2.32	(1.31, 4.12)	0.003
ICU stay	7	8%	6	1	2	3	1	0%	24.56	(4.19, 144.1)	<0.001
Mechanical Ventilation	2	2%	2	0	0	0	0	0%	23.18	(1.1, 487.2)	0.003
Death	5	6%	4	2	0	1	1	0%	17.57	(2.84, 108.6)	<0.001



(REVISED) Figure 4: Association between comorbidity and clinical outcomes after controlling for patient BMI and association factors. Adjusted adverse outcome rates in the comorbidity group were significantly higher than those of non-comorbidity group.

Evaluating comorbidity factors in multiple logistic regression models

The effect of comorbidity can be a direct predictor of adverse outcomes. We verified this hypothesis in the following logistic regression model. In this model, we added BMI and comorbidity factors to predict adverse outcomes. Patients with healthy weight and without comorbidities were defined as the baseline group. Two comorbidity factors were used. BMI ranges were defined to evaluate the effect size separately.

Among 2109 patients with COVID-19, the association between BMI range and adverse outcomes was not significant when excluding comorbidity factors. On the other hand, an

independent association was observed between comorbidity factors and various adverse outcomes. Compared with patients with no hypertension, patients with primary hypertension were 1.63 times more likely to be admitted to the hospital, 3.53 times more likely to stay in the ICU, 3.65 times more likely to go on mechanical ventilation and 3.24 times more likely to die due to COVID-19 outcomes. Compared with patients with no hypertension, patients with secondary hypertension were 3.05 times more likely to be admitted to the hospital, 4.16 times more likely to have an ICU stay, 6.25 times more likely to proceed with mechanical ventilation, and 2.64 times more likely to die due to COVID-19 outcomes. The odds ratio for Type 2 diabetes was 1.64 for hospitalization, 2.61 for ICU stay, 2.21 for mechanical ventilation, and 2.41 for mortality. The odds ratios for type 1 diabetes were 2.26 for hospitalization and 5.68 for ICU stay. The association between type 1 diabetes and mechanical ventilation and mortality was not significant due to a small sample size; only twelve patients were diagnosed with type 1 diabetes, and seven of them were admitted.

When the comorbidity factors were controlled in our multiple logistic regression model, obesity failed to show the same level of association between obesity and outcomes, with p values larger than 0.05. Therefore, comorbidity factors play a dominant role in predicting outcomes when BMI and comorbidity factors coexist in the model. Table 4 shows the adjusted hazard ratio of clinical outcomes for patients with varied BMI and Comorbidity factors with similar increased hazard ratios for increased BMI and comorbidities to worse outcomes.

(REVISED RESULTS) Table 3: Multiple Logistic Regression model: BMI, Comorbidities and Adverse Outcomes								
	Hospitalization		ICU stay		Mechanical Ventilation		Mortality	
	Adjusted OR, 95% CI	P-value	Adjusted OR, 95% CI	P-value	Adjusted OR, 95% CI	P-value	Adjusted OR, 95% CI	P-value
Body mass Index (BMI)								
Overweight	1.14 (0.82, 1.60)	0.444	1.15 (0.48, 2.97)	0.765	2.92 (0.73, 19.6)	0.179	0.31 (0.08,1.14)	0.077
Obese (BMI > 30)	1.50 (1.08, 2.10)	0.016	1.51 (0.66, 3.83)	0.353	3.35 (0.88, 22.1)	0.121	0.50 (0.17,1.63)	0.228
Morbidly obese (BMI>40)	0.98 (0.62, 1.55)	0.942	1.66 (0.62, 4.69)	0.321	3.05 (0.66, 21.9)	0.19	1.13 (0.33,4.11)	0.842
Comorbidity Factors:								
Hypertension								
Primary Hypertension	1.63 (1.20, 2.19)	0.001	3.53 (1.82, 7.17)	<0.001	3.65 (1.51, 9.96)	0.006	3.24 (1.12, 11.8)	0.045
Secondary Hypertension	3.05 (1.55, 6.01)	0.001	4.16 (1.80, 9.27)	<0.001	6.25 (2.45, 15.2)	<0.001	2.64 (0.85, 7.26)	0.073
Diabetes								
Diabetes, Type 1	2.26 (1.04, 4.82)	0.035	5.68 (2.09, 15.2)	<0.001	1.73 (0.35, 6.43)	0.447	2.14 (0.29, 9.93)	0.377
Diabetes, Type 2	1.64 (1.16, 2.31)	0.005	2.61 (1.47, 4.67)	0.001	2.21 (1.07, 4.66)	0.034	2.41 (1.42, 5.84)	0.046

(REVISED RESULTS) Table 4: Adjusted Hazard Ratio for clinical outcomes, BMI, and comorbidity factors				
Adjusted HR, 95% CI	Hospitalization	ICU stay	Mechanical Ventilation	Mortality
Body mass Index (BMI)				
Overweight	1.12 (0.84, 1.47)	1.15 (0.48, 2.88)	2.90 (0.73, 18.19)	0.31 (0.08, 1.14)
Obese (BMI > 30)	1.40 (1.07, 1.81)	1.50 (0.66, 3.66)	3.32 (0.88, 20.32)	0.50 (0.17, 1.62)
Morbidly obese (BMI>40)	0.98 (0.66, 1.44)	1.64 (0.62, 4.42)	3.02 (0.66, 20.15)	1.13 (0.33, 3.96)
Comorbidity Factors				
Hypertension				
Primary Hypertension	1.27 (1.10, 1.43)	3.32 (1.78, 6.21)	3.55 (1.50, 9.11)	3.21 (1.12, 11.3)
Secondary Hypertension	1.59 (1.24, 1.86)	3.86 (1.76, 7.68)	5.93 (2.41, 13.24)	2.62 (0.85, 7.08)
Diabetes				
Diabetes, Type 1	1.29 (1.02, 1.47)	4.36 (1.95, 7.94)	1.69 (0.36, 5.39)	2.08 (0.30, 8.00)
Diabetes, Type 2	1.19 (1.06, 1.30)	2.36 (1.43, 3.78)	2.12 (1.07, 4.13)	2.37 (1.41, 5.51)

Discussion

The prevalence of obesity is a major worldwide problem. Patients with obesity are at a higher risk of poor COVID-19 outcomes. We discovered that patients with obesity had significantly higher rates of adverse outcomes than patients without obesity in this COVID-19 cohort. Patients with obesity have a higher risk of hospitalization, ICU stay, mechanical ventilation, and death.

More importantly, we found that obesity-related comorbidities were independently associated with worse COVID-19 outcomes. More importantly, we discovered that obesity-related comorbidities were associated with poorer COVID-19 outcomes. This finding contradicts some previous research findings, which suggested that obesity is a significant risk factor for COVID-19 severity. Instead, we found that obesity-related comorbidities are a better predictor of negative COVID-19 outcomes than obesity alone.

Significance of the Study

This study explores the association of obesity-related comorbidity and COVID-19 adverse outcomes. Some studies investigated the association between obesity and COVID-19 outcomes but did not consider the impact of obesity-related comorbidities as covariates. We examined the risk factors for various types of adverse outcomes. More importantly, we separated out the obesity-related comorbidity factors from obesity. Obesity-variable controlled chi-square test and logistic regression model show that both common types of obesity comorbidity, hypertension, and type 2 diabetes, are independently associated with an increased risk of COVID-19 severity.

Study significance with recent variants and vaccination

The Delta variant was downgraded from a variant of concern to a variant being monitored by the Centers for Disease Control and Prevention (CDC) in April 2022[27]. Although research in Scotland[28] and Canada[29] suggests that the Delta variant is associated with a higher risk of hospitalization, it is unclear whether the variant causes more severe disease in adults. To answer the question, the CDC's COVID-19-Associated Hospitalization Surveillance Network examined trends in disease severity among 7615 COVID-19 patients hospitalized between January 1 and August 20, 2021[33]. The study found no difference in intensive care unit admissions, the need for invasive mechanical ventilation, or deaths between July and August when the Delta variant was

not the dominant strain. The CDC concluded that the delta variant posed no significant public health risks.

The omicron (B.1.1.529) variant had a significantly higher contagious rate than the original virus that causes COVID-19 and the delta variant in both vaccinated and unvaccinated populations[35]. Fortunately, research indicates[34] that omicron causes less percentage of severe outcomes. Despite the proportion of the population with severe outcomes has decreased[30] due to the increased coverage and effectiveness of recent COVID-19 vaccines, the unvaccinated population is constantly at risk of serious illnesses.[31] In the meantime, the absolute number of deaths remains high[32]. Our study confirm that primary hypertension and type 2 diabetes are two of mediating effects of severe COVID-19 outcomes. Therefore, our findings emphasize the importance of comorbidity-focused care.

Obesity may contribute to adverse COVID-19 outcomes via comorbidity

Evidence[7,10,11,15,16] shows that obesity is a risk factor for greater COVID-19 severity. To date, the role of the comorbidity effect is still unknown. We explored the association between BMI and comorbidities and the association between comorbidities and COVID-19 severity. We discovered that increasing BMI levels increased the risk of primary and secondary hypertension. High BMI levels increase the risk of type 2 diabetes. These findings suggest that obesity-related comorbidity may play a larger role in COVID-19 outcomes.

In addition, hospitalized patients are more likely to suffer from hypertension and diabetes. Primary hypertension had a 1.98 increased odds ratio, secondary hypertension had a 4.73 increased odds ratio, type 1 diabetes had a 3.25 increased odds ratio, and type 2 diabetes had a 2.28 increased odds ratio. Comorbidity and COVID-19 severity have a significant correlation. A higher BMI is associated with an increased risk of hospitalization, ICU admission, mechanical

ventilation, and death. Patients who have had a poor outcome have a higher proportion of Obesity. As a result, comorbidity plays an important role in mediating the relationship between obesity and COVID-19 severity. We believe that obesity, in the form of comorbidities, contributes to the severity of COVID-19.

Our findings on the positive association between obesity and the risk of adverse outcomes are consistent with previous research. Several studies[9,11,16] used a similar approach to associate obesity to severe COVID-19 illness. A study conducted in New York city[9] showed that severe obesity (BMI > 40) is a risk factor for hospital admission. The odds ratio of hospital admission was 2.5 for patients with obesity compared with patients without obesity. A study conducted in a French health center[11] showed that the risk of invasive mechanical ventilation for patients with obesity (BMI>35) was 7.36-fold higher than that for patients in healthy weight range (BMI 18 - 25). A study conducted in a large academic hospital system[16] also revealed that the odds ratio of ICU admission rate was 1.8 for patients with BMI 30-35 and 3.6 for patients with BMI > 35 compared with patients with BMI < 30. A study[8] including many COVID-19 cases suggested a nonlinear relationship between BMI and COVID-19 severity, with the lowest risks at BMIs near the threshold between healthy weight and overweight in most instances and then increasing with higher BMI. Other known risk factors for COVID-19 and obesity include obesity being linked to impaired immune function[17,18]. Obesity decreases lung capacity reserve and can make ventilation more difficult[19], which is linked with COVID-19 severity. All discoveries demonstrated that the patient's disease severity increased with BMI, and obesity is a direct risk factor for COVID-19 severity. The obesity rate increased from 30.5% to 42.4% from 1999-2000 through 2005–2008[3]; therefore, we suggest prioritizing therapy for patients with obesity and COVID-19 infections to control serious patient comorbidities.

Cross-controlled group comparison: independent factor of comorbidity variables

Table 2 shows the variable-controlled association between comorbidity and adverse outcomes. For population of obesity, there was a significantly higher risk of adverse outcomes for the comorbidity group. The patient group with comorbidities was 1.29 (95% CI 0.91, 1.84) times more likely to be admitted to the hospital. The length of stay was significantly longer, and the odds ratio for other adverse outcomes was also significantly higher. The odds ratio for ICU stay was 9.01 (95% CI: 3.33, 24.4). The odds ratio for mechanical ventilation was 10.1 (95% CI: 2.69, 37.6), and the odds ratio for death was 30.96 (95% CI: 1.83, 522.9). The association is also significant in healthy-weight and overweight groups. This result indicates that hypertension and diabetes are independent factors of adverse outcomes regardless of obesity factors.

Logistic Regression Model: The Comorbidity Effects

A logistic regression model compares the probability of adverse outcomes of COVID-19 with or without specific risk factors. Table 3 shows a logistic regression model of adverse outcomes for all patients diagnosed with COVID-19. The quantifiable odds ratios from risk factors indicated the risk of adverse outcomes. For adverse outcomes of COVID-19, including ICU stay, mechanical ventilation and mortality, the impact of primary hypertension was larger, with an ICU stay odds ratio of 3.53, mechanical ventilation odds ratio of 3.65, and mortality odds ratio of 3.24. Other obesity-related comorbidities, including secondary hypertension and type 2 diabetes, are also independent risk factors for COVID-19 outcomes.

An interesting observation is that BMI shows a lower impact when comorbidity factors and BMI factors coexist in the model. The independent association between BMI and adverse outcomes was not significant. In other words, obesity-related comorbidities were a stronger predictor or adverse outcomes than obesity alone in a multiple regression model. This result shows that

obesity-related comorbidities is a higher risk factor for adverse outcomes than obesity alone. The larger impact of comorbidity factors is consistent with our obesity-controlled two-group comparisons.

Comparison with other studies about the association between obesity and adverse outcomes

A cohort of 150 patients in an early-stage study conducted in three hospitals in China[15] showed a clear dose-effect relationship between increasing BMI values and the percentage of patients with severe COVID-19. Each 1-unit increase in BMI was associated with a 12% increase in the risk of severe COVID-19 outcomes (unadjusted OR 1.12, 95% CI 1.01–1.23). The association was also observed after controlling for gender, age, and other comorbidities deemed relevant to the study. An meta-analysis[13] incorporated 75 clinical association studies between COVID-19 and obesity. Obesity is associated with a higher risk of COVID-19 adverse outcomes, including 46.0% higher odds of testing positive (OR = 1.46; 95% CI, 1.30-1.65; $p<0.0001$), 113% higher odds of hospitalization (OR = 2.13; 95% CI, 1.74-2.60; $p<0.0001$), 74% higher odds of ICU admission (OR = 1.74; 95% CI, 1.46-2.08, $p<0.001$). Our study shows a lower risk of hospitalization (OR our study:1.50 vs pooled studies: 2.13) and ICU stay (1.51 vs 1.74). We are unable to measure the risk of death due to insufficient samples. Considering the surging trend of individuals with obesity, it is critical to understand how being an individual with obesity increases the risk for severe COVID-19. Understanding the mechanism ensures that the novel coronavirus receives appropriate interventional therapies. Other viral infectious diseases, such as influenza and epidemiological diseases, provide insights into how obesity raises the risk of COVID-19 severity. Other studies [12,13,15] have investigated the mechanisms of pulmonary, endocrine, and immune dysfunction in obese people. These physiological effects can help to direct future research. These multiple potential mechanisms may explain why comorbidity has a greater

impact than obesity alone. As a result, we believe that people with severe obesity, particularly those with obesity-related comorbidities, should be considered a high-risk group for negative COVID-19 outcomes.

Comparison with other studies regarding the comorbidities and obesity

Obesity is a risk factor for co-morbidities, including primary hypertension and type 2 diabetes[21]. Early COVID-19 studies[22,23,24] discovered that hypertension and diabetes mellitus are associated with a severe clinical course of COVID-19 and increased mortality. However, the early studies' findings did not control for obesity as a correlated factor. For example, a review[25] summarized fifty-five clinical studies to determine the relationship between obesity and COVID-19 severity and comorbidities. Hypertension was a comorbidity in thirty-one of the fifty-five studies, and diabetes was a comorbidity in thirty of the fifty-five studies. Despite these studies frequently show a positive correlation between obesity and COVID-19 severity. They often ignored a variety of comorbidity factors. Because hypertension and diabetes are more common in obese patients, the conclusion that obesity is a risk factor for the severity of COVID-19 may be distorted by comorbidity factors as confounding variables. To address this problem, Wang, Li, Lu, and Huang[26] conducted a pooled study on comorbidity factors and COVID-19 severity risks, finding an odds ratio of 2.29 (95% CI: 1.69-3.10, $p < 0.001$) for hypertension and 2.47 (95% CI: 1.67-3.66, $p < 0.001$) for diabetes. Because the six studies in this meta-analysis were not adjusted for BMI, they may favor the obese population and result in an overestimation of the odds ratio. Therefore, we adjusted the model by BMI values. Our study shows a slightly lower odds ratio for hypertension (1.63 from our results vs 2.29 from the pooled study[26].) and diabetes (1.64 vs 2.47). As a result, it is possible that the adverse effects of obesity are mediated in part by hypertension and type 2 diabetes. It is likely other types of obesity-related comorbidity factors may go

undetected. These undetected comorbidity factors may suggest possible clinical mechanisms that how obesity contributes to COVID-19 severity.

Clinical mechanisms: Pathways explaining how comorbidity can cause COVID-19 severity

Comorbidity is a well-known risk for health-care providers. Obesity's role in contributing to severe COVID-19 can be explained pathologically[7,20]. Obesity, on the other hand, is a well-known risk factor for common chronic diseases such as diabetes, hypertension, and cardiovascular disease. Obese patients are more likely to develop chronic diseases, which may contribute to the poor COVID-19 outcomes. Excess ectopic fat, on the other hand, may have an impact on the cardiovascular and respiratory systems. The underlying impairments reduce the reserve and ability to deal with COVID-19 infection, resulting in secondary immune reactions. Excess adipose tissue may enhance immune response. As a result, an impaired metabolic response can result in severe COVID-19 infection. Furthermore, an impaired immune response may result in respiratory dysregulation. The increased volume of inhalation may increase viral exposure through breathing from a respiratory standpoint. Patients with obesity are frequently exposed to a basal inflammatory state in terms of their immune systems. Inflammation may suppress the immune response and play a synergistic role in COVID-19 severity. Admission to the ICU for patients with severe obesity (BMI > 40) is frequently hampered, as patients with severe obesity are more difficult to ventilate, nurse, image, and rehabilitate, resulting in higher rates of mortality. When obesity progresses to a severe level, a patient is more likely to develop a comorbidity.

Limitations

This research has limitations. The study is based on a single clinical practice at Froedtert Health in Milwaukee, which may result in inaccurate measurements influencing negative outcomes. We

only looked at hypertension and diabetes-related comorbidities. More research is needed to confirm the impact of other obesity-related comorbidities. Some patients' rapid test results at the first few weeks of onset of COVID-19 were not included, which may cause underestimation of the COVID-19 patient population. The data for 2021 is currently unavailable for analysis. Smoking, performance status, laboratory results, COVID-19-directed treatment, or recent surgical procedures were not included as important risk factors. Also, the new COVID-19 variants and vaccinations may significantly change the proportions of adverse outcomes. These risk factors could lead to potential bias in our logistic regression model.

Conclusion

Obesity increases the risk of common comorbidities, such as hypertension and type 2 diabetes. We demonstrated that comorbidity is an independent risk factor for COVID-19 adverse outcomes. Obesity-related comorbidity, according to our model, is a more important risk factor for adverse outcomes than obesity alone. Patients with obesity-related comorbidities have significantly worse outcomes than patients with obesity alone. Obesity's association with comorbidities, and comorbidity's association with worse outcomes, may explain why obesity is a significant risk factor for COVID-19 prognosis. Our findings highlight the significance of care for patients suffering from obesity-related comorbidities. As a result, it is critical to provide care for patients with obesity-related comorbidities during the pandemic to improve care quality.

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