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Impact Of body Mass Index on Cardiopulmonary Outcomes of COVID-19 Hospitalizations Complicated by Severe Sepsis

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ABSTRACT

Background: Body Mass Index (BMI) has a significant impact on Coronavirus disease (COVID-19) patient outcomes; however, major adverse cardiac and cerebrovascular outcomes in patients with severe sepsis have been poorly understood. Our study aims to explore and provide insight into its association.

Methods: This is an observational study looking at the impact of BMI on COVID-19-severe sepsis hospitalizations. The primary outcomes are adjusted odds of all-cause in-hospital mortality, respiratory failure, and major adverse cardiac and cerebrovascular events (MACCE), which include acute myocardial infarction, cardiac arrest, and acute ischemic stroke. The secondary outcome was healthcare resource utilization. Coexisting comorbidities and patient features were adjusted with multivariable regression analyses.

Results: Of 51,740 patients with severe COVID-19-sepsis admissions, 11.4% were overweight, 24.8% had Class I obesity (BMI 30–34.9), 19.8% had Class II obesity (BMI 35–39.9), and 43.9% had the categorization of Class III obesity (BMI >40) cohorts with age>18 years. The odds of MACCE in patients with class II obesity and class III obesity (OR 1.09 and 1.54; 95CI 0.93–1.29 and 1.33–1.79) were significantly higher than in overweight ($p < 0.001$). Class I, Class II, and Class III patients with obesity revealed lower odds of respiratory failure compared to overweight (OR 0.89, 0.82, and 0.82; 95CI 0.75–1.05, 0.69–0.97, and 0.70–0.97), but failed to achieve statistical significance ($p = 0.079$). On multivariable regression analysis, all-cause in-hospital mortality revealed significantly higher odds in patients with Class III obesity, Class II, and Class I (OR 1.56, 1.17, and 1.06; 95CI 1.34–1.81, 0.99–1.38, and 0.91–1.24) vs. overweight patients ($p < 0.001$).

Conclusions: Patients with Class II and Class III obesity had significantly higher odds of MACCE and in-hospital mortality in COVID-19-severe sepsis admissions.

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1. Introduction

The pandemic caused by SARS-CoV-2, also known as COVID-19, has resulted in a significant number of cases with various symptoms. Those affected can experience a wide range of clinical outcomes and post-sequelae, including cardiometabolic complications, which can lead to morbidity and mortality. To date, around 700 million COVID-19 cases have been diagnosed worldwide; the number of deaths exceeds 6 million, as reported to the WHO [48]. Type 2 diabetes (T2DM), obesity, and age in patients with COVID-19 are strong predictors of hospitalization and mortality, with 30% of patients with COVID-19-related hospitalizations having type 2 diabetes and around 35% of deaths occurring in individuals with diabetes [47]. The prevalence of obesity is increasing worldwide, reaching epidemic proportions, leading to significant public health problems defined by a body mass index (BMI) of ≥30 kg/m2, affecting 4 in 10 adults in the United States [1–3]. Obesity is also associated with an increased risk of diabetes, heart failure, and morbidity and mortality related to cardiovascular disease (CVD) [1–3]. Several research studies in the past have shown that obesity is associated with a higher risk of severe pneumonia in hospitalized patients with COVID-19 [4]. Some other studies have shown an increased risk of COVID-19 severity and/or death in a population with obesity [5–7]. The association between obesity and worsening outcomes in COVID-19 patients is still controversial, although many studies show clear evidence [49–54] but lacking a definitive association in other clinical studies [55–57]. Additionally, obesity is known to be an independent risk factor for poor in-hospital outcomes in patients infected with COVID-19, with excess complications including respiratory failure and death [8,9]. Hypertension and coronary artery disease have been well-documented to exhibit significant increases in morbidity and mortality in such patients. Hypertension has been associated with severe disease manifestations leading to acute respiratory distress syndrome (ARDS), disease progression, and the need for ICU admissions in patients with COVID-19 [40]. There have been a few studies in the past that have shown that cardiovascular diseases co-occurring with COVID-19 increase the odds of hospitalizations and death by sixfold. A few of the cardiac complications associated with COVID-19 sepsis during the hospitalization stay, including myocarditis, pericarditis, and cardiac arrest, had an overall worse survival rate [10,11]. Several studies in the past had looked at major cardiac and cerebrovascular events and respiratory failure in ICU patients, however; outcomes in patients admitted with severe sepsis have been poorly understood, and there have not been any comprehensive reviews based on this association. Our study aimed to assess the association of body mass index on cardiovascular outcomes in patients admitted with severe COVID-19 sepsis by conducting a comprehensive analysis using a large national representative database.

2. Methods

2.1. Design and data source

We conducted our analysis using the national inpatient sample year 2020, which is available through the Healthcare Cost and Utilization Project (HCUP). National Inpatient Sample (NIS) is a large publicly available database representing 95% of hospitalizations in the US, covering 48 states and the District of Columbia. We utilized the Internal Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM) coding system to identify the principle of COVID-19-severe sepsis admissions. This is an observational study, looking at the impact of BMI on severe sepsis COVID-19 hospitalizations.

2.2. Study population and characteristics

We included hospitalized patients with a diagnosis of COVID-19 severe sepsis using the ICD-10 codes in the year 2020. We restricted our sample size to overweight (BMI 25–29.9), Class I obesity (BMI 30–34.9), Class II obesity (BMI 35–39.9), and Class III obesity (BMI >40) cohorts; they were identified in the NIS using obesity diagnostic ICD-10-CM codes.

2.3. Outcome measures

The primary outcome of this study is to assess in-hospital mortality, major adverse cardiac and cerebrovascular events (MACCE), and respiratory failure in patients who were admitted with COVID-19 sepsis.

Secondary outcomes included heart care utilization and length of hospitalization stay. Patient confounders were adjusted with multivariable regression analyses, which are known to have prognostic implications for our outcomes.

2.4. Statistical analysis

Patient characteristics and in-hospital outcomes were compared among overweight, Class I, Class II, and Class III patients with obesity who were admitted with severe COVID-19 sepsis. Continuous variables are expressed as mean ± standard deviation and categorical variables are presented as percentages. Odds ratios [OR] along with their 95% confidence intervals (CI) were obtained using multivariable logistic regression for in-hospital mortality and outcomes. All reported P-values are two-sided, with a value of <0.05 considered significant.

3. Results

3.1. Baseline characteristics

A total of 51,740 COVID-19-severe sepsis admissions were identified in the year 2020; 24.8% had Class I obesity (BMI 30–34.9), 19.8% had Class II obesity (BMI 35–39.9), and 43.9% had the categorization of Class III obesity (BMI >40). The median age of patients admitted with COVID-19 sepsis was 62 years (58–66 years), with 53.4% being male patients. The majority of patients admitted to the hospital were Caucasians (44.5%), followed by Hispanics (28.2%), and African Americans (23.4%). Most of the hospitalized

patients with COVID-19 sepsis were admitted primarily to southern hospitals (41.6%), followed by western hospitals (22.4%). These hospitalized patients were primarily Medicare patients (46.6%), with 36.6% of them from low-income quartiles. Patients with class III obesity were mostly white females from low-income quartiles in urban hospitals. Of total admissions, patients with class III obesity were the youngest (median age 58 years vs. patients with Class II obesity 62 years, Class I obesity 64 years, and overweight 68 years).

Patients with class III obesity were also more likely to have hypertension as compared to patients with overweight (70% vs. 69.3%). diabetes (56.8% vs. 48.9%), chronic pulmonary disease (29.6% vs. 19.5%), acute respiratory distress syndrome (32% vs. 25.4%), mechanical ventilation (62.8% vs. 57.4%), chronic kidney disease (25% vs. 25.4%), and acute kidney injury (66.7% vs. 60.1%). Table 1 describes the distribution of co-morbidities among the patients.

3.2. Primary outcomes

In the study of 51,740 COVID-19-severe sepsis admissions, the multivariable regression analysis showed that all-cause in-hospital mortality had higher odds in patients with Class III, Class II, and Class I individuals with obesity. (OR 1.56, 1.17, and 1.06; 95% CI 1.34–1.81, 0.99–1.38, and 0.91–1.24) with $p < 0.001$. Major adverse cardiac and cerebrovascular events (MACCE) were highly prevalent in patients with Class II and Class III obesity (OR 1.09, 1.54; 95% CI 0.93–1.17, 1.33–1.79) compared to patients with overweight ($p < 0.001$).

While patients with Class I, Class II, and Class III obesity revealed lower odds of respiratory failure compared to patients with overweight (OR 0.89, 0.82, and 0.82; 95% CI 0.75–1.05, 0.69–0.97, and 0.70–0.97),

Table 1
Baseline characteristics, comorbidities, and in-hospital outcomes of COVID-19 admissions with severe sepsis stratified by body mass index.

	OVERWEIGHT (5915)	BMI 30–34.9 (12850)	BMI 35–39.9 (10250)	BMI 40 and more (22725)	TOTAL COVID-19 with Severe Sepsis (52740)	P Value
Median Age at admission, years	68	64	62	58	62	<0.001
Max % and Age group in years	59.3% (>/ = 65)	48.7%(>/ = 65)	45.5%(45–64)	47.3%(45–64)	43.9%(45–64)	
Sex	Male > Female	Male > Female	Male > Female	Female > Male	Male > Female	<0.001
Male	65.3%	61.5%	56%	44.6%	53.4%	
Female	34.7%	38.5	44%	55.4%	46.6%	
Race						
White	45.8%	44.1%	43.6%	44.7%	44.5%	<0.001
Hispanic	31.4%	32.3%	30.7%	23.9%	28.2%	
Black	16.8%	18.5%	22.4%	28.3%	23.4%	
Asia/PI	4.7%	3.7%	2.1%	1.5%	2.6%	
Native American	1.2%	1.3%	1.2%	1.5%	1.4%	
Median Income quartile for patients' zipcode						
0-25th	34.7%	33%	34.9%	39.6%	36.4%	
26-50th	24.3%	26.2%	27.4%	27.9%	27%	
51–75	23.9%	24.4%	22.5%	19.8%	21.9%	
76-100th	17.2%	16.4%	15.3	12.8%	14.7%	<0.001
Payer status						
Medicare	59.2%	49%	44.1%	43.1%	46.6%	
Private	23.1%	33%	34.5%	34.1%	32.6%	
Medicaid	14.1%	14.6%	16.2%	18.1%	16.4%	
Self-pay	3.6%	3.3%	5.1%	4.3%	4.1%	<0.001
Hospital region						
South	39%	39%	40.1%	44.6%	41.6%	<0.001
West	25.5%	24.4%	23%	19.8%	22.4%	
Midwest	19.9%	21.5%	22.5%	21.1%	21.3	
Northeast	15.6%	15.1%	14.3%	14.4%	14.7	
Comorbidities						
Hypertension	69.3%	69.3%	71.6%	70%	70%	<0.001
Diabetes Mellitus	48.9%	52.6%	56.3%	56.8%	54.7%	<0.001
Hyperlipidemia	42.7%	44.7%	44.2%	37.2%	41.1%	<0.001
Tobacco use disorder	20.4%	21.4%	20.2%	15.4%	18.4%	<0.001
Chronic pulmonary disease	19.5%	19.2%	21.9%	29.6%	24.3%	<0.001
Peripheral vascular disease	4.6%	3.9%	3.5%	2.7%	3%	<0.001
CKD	25.4%	23.3%	22.1%	25.8%	24.4%	<0.001
In-hospital Outcomes						
Primary						
All-cause mortality	41.9%	40.4%	41.2%	45%	42.7%	<0.001
MACCE	48.3%	45%	45.6%	50.7%	47.9%	<0.001
Acute kidney injury	61.6%	58.2%	60.1%	66.7%	62.7%	<0.001
Acute respiratory distress syndrome	25.4%	29.9%	31.3%	32.9%	30.9%	<0.001
Acute respiratory Failure	67.5%	65.5%	64%	64.4%	64.9%	<0.001
Acute Ischemic stroke	2.5%	1.4%	1%	1.6%	1.5%	<0.001
Cardiac arrest	9.7%	10%	11.9%	11.3%	10.9%	<0.001
Acute myocardial infarction	10.1%	7.5%	7.2%	8.8%	8.3%	<0.001
MACCE_ACM_AMI_CA_AIS	48.3%	45%	45.6%	50.7%	48%	<0.001
Secondary						
Disposition of patients						<0.001
Routine	18.9%	26.2%	29.5%	21.2%	23.9%	<0.001
Transfer to Short-Term Hospital	4.0%	4.4%	3.4%	3.7%	3.8%	<0.001
Transfer Other: SNF, ICF, etc.	25.8%	17.4%	16.4%	20.8%	19.7%	<0.001
Home Health Care	8.8%	11.3%	9.1%	8.8%	9.4%	<0.001
Against Medical Advice	0.6%	0.3%	0.4%	0.4%	0.4%	<0.001
Length of stay (days), median	13	12	12	13	13	<0.001
Cost (USD), median	$1,64,819	$158248	$160369	$189355	$171623	<0.001
Death during hospitalization	41.9%	40.4%	41.2%	45%	42.8%	<0.001

$P < 0.05$ indicates statistical significance.
MACCE major adverse cardiovascular and cerebrovascular events.
Multivariate logistic regression was adjusted for: Age, Sex, Race, Median income quartile, Payer status, Hospital region, Hypertension, Diabetes Mellitus, Hyperlipidemia, Tobacco use disorder, Chronic pulmonary disease, PVD, Chronic kidney disease.

this failed to achieve statistical significance ($p = 0.079$). Table 2 describes the multivariable odds of outcomes.

3.3. Secondary outcomes

Patients with Class II and Class III obesity, hospitalizations are associated with higher costs compared to patients with overweight (median $171,623 and $189,355, respectively, vs. $164,819) without any change in length of stay, while respiratory failure showed no significant difference among the cohorts. In contrast, patients with overweight were more frequently transferred to skilled nursing facilities compared to patients with Class II and Class III obesity (25.8% vs. 16.4% and 20.8%). Table 1 describes the cost outcomes.

4. Discussion

This large population-based outcomes study explored the association between cardiopulmonary outcomes including major adverse cardiac and cerebrovascular events (MACCE) and respiratory failure, associated with body mass index in patients admitted with severe COVID-19 sepsis.

Table 2
Multivariable odds of outcomes as per severity of obesity vs overweight.

All-Cause In-Hospital Mortality	aOR	95% C.I. LL	95% CI UL	P-value
Class 1 vs Overweight	1.06	0.91	1.24	<0.001
Class 2 vs Overweight	1.17	0.99	1.38	
Class 3 vs Overweight	1.56	1.34	1.81	
MACCE				
Class 1 vs Overweight	0.86	0.86	1.17	<0.001
Class 2 vs Overweight	0.93	0.93	1.29	
Class 3 vs Overweight	1.33	1.33	1.79	

BMI Obesity Classes - Overweight, class 1 - 30–34.9, class 2 - 35–35.9, class 3–40 and greater.
Multivariate logistic regression was adjusted for Age, Sex, Race, Median income quartile, Payer status, Hospital region, Hypertension, Diabetes Mellitus, Hyperlipidemia, Tobacco use disorder, Chronic pulmonary disease, PVD, and Chronic kidney disease.
MACCE major adverse cardiac and cerebrovascular events – composite events of all-cause mortality, acute myocardial infarction, cardiac arrest, and acute ischemic stroke.

We showed that the patients with Class III obesity (BMI >40) and overweight (BMI 25–30) have higher mortality risks compared to other population, which suggests a J-shaped association between body mass index and risk of death, as shown in previous studies [12,13]. In our study, who were hospitalized with severe COVID-19 sepsis, patients with Class III obesity were younger with an average age of 58 compared to patients with overweight with an average age of 68 years. Obesity was independently associated with increased hospitalizations in patients with several comorbidities, including type 2 diabetes mellitus, hypertension, coronary artery diseases, and chronic kidney diseases. There is limited research available on COVID-19 patients who have been hospitalized and have experienced MACCE outcomes. However, none of the existing studies have been conducted on cohorts of severe COVID-19 sepsis patients. To our knowledge, this is the first large population-based study that shows major adverse cardiac and cerebrovascular events in cohorts hospitalized with severe COVID-19 sepsis. Both univariate and multivariate logistic regression models have been used to analyze the association between body mass index and cardiopulmonary outcomes in cohorts hospitalized with severe COVID-19 sepsis. Our study supports of findings of previously published large population-based studies showing obesity as a predictor of increased hospitalizations, ICU admissions, mechanical ventilation, and increased death in patients with COVID-19 [14–16] also, with similar findings and associations in major adverse cardiac and cerebrovascular events (MACCE). These results in contrast to a few of the studies published in the last few years, showed no association between obesity and mortality in patients admitted with COVID-19 infection [17–19]. As per the Centers for Disease Control and Prevention (CDC), the prevalence of obesity in the United States from 2017 to 2020 was 41.9%, with class III obesity reaching approximately 9.2% [20]. In the last decade, the prevalence of obesity has risen significantly from 30.5% to 41.9%, along with Class III obesity, which rose from 4.7% to 9.2%. Obesity is often an insulin-resistant state characterized by adipocyte insulin resistance, inflammation, and release of inflammatory and insulin-provoking adipocytokines and is a strong prediction of hospitalization and mortality in COVID-19 patients. Although the precise mechanism remains unclear, there has been some evidence that obesity may impact COVID-19 severity through several different mechanisms: including, diminished functions of both adaptive and innate immune responses, endothelial dysfunction, release of inflammatory markers by changing cytokine responses, and by reducing antigen response [21–25]. Immune responses in patients with obesity are altered which can be explained by several mechanisms; one of the mechanisms is the deposition of adipocytes into lymphoid tissue leading to altered secretion of adipocytokines by adipose tissue, including leptin, adiponectin, and resistin levels [26,27]. The implications of leptin dysregulation in COVID-19 are not fully understood. However, there is a hypothesis that higher levels of leptins can have pro-inflammatory functions by increasing cytokine storm in plasma by stimulating the production of Interleukin (IL)-2 and tumor necrosis factor-alpha (TNF-α) in COVID-19 patients leading to multi-organ dysfunction and respiratory failure, especially in patients with obesity [41]. In contrast, adiponectin was reduced in patients in COVID-19 cohorts which exerts anti-inflammatory actions [28]. Resistin has been linked to numerous inflammatory disorders and was found to have increased levels of COVID-19 infection which might predict the need for invasive mechanical ventilation [42]. Another mechanism is by angiotensin-converting enzyme-2 (ACE-2) involvement. It was shown that the COVID-19 virus uses ACE-2 enzymes to bind and enter host cells. Adipose tissue has a higher expression of ACE-2, since the population with obesity has an increase in adipose tissue, leading to an increase in the level of ACE-2 expression, which in turn increases susceptibility to COVID-19 infection [29]. There is also some evidence that increased lipoproteins and adipose tissue will bind to bacterial toxins and inactivate lipopolysaccharides [30,31]. Insulin resistance is a fundamental flaw associated with obesity [43]. Furthermore, metabolic disorders have been found to have a significantly higher prevalence in patients with COVID-19, which can lead to an increased need for ventilatory support and mortality. There have been no studies so far which examined the presence of insulin resistance in COVID-19 patients. However, the COVID-19 virus has been associated with the activation of innate immune response and causing the cytokine storm leading to the production of inflammatory cytokines which can induce insulin resistance [44–46]. Obesity is also associated with an increased risk of several comorbidities, including sleep apnea, hypertension (HTN), non-alcoholic fatty liver disease, and cardiovascular risks. These coexisting conditions are considered to increase the likelihood of severe illness from COVID-19 in the population with obesity [36–38]. Obesity is associated with increased activation of the renin-angiotensin system, contributing to high blood pressure, which may be a protective mechanism for hospitalized individuals due to less utilization of fluids and vasopressors [39]. Hyperglycemia and diabetes are considered one of the worse risk factors for COVID-19 hospitalizations and have been found to increase hospitalizations and deaths. According to a recent analysis, patients with diabetes and high levels of fasting plasma glucose are the earliest predictors of poor outcomes and mortality in COVID-19 patients, as opposed to patients without diabetes [32,33]. In our current study, 54.7% of the patient population have diabetes, most prevalent in the population with obesity. The exact mechanism is unknown, but some of the possible mechanisms include increasing proinflammatory cytokines, decreasing immunity, insulin resistance, and the destruction of beta cells [34]. Elevated glucose levels are also considered an independent risk factor for COVID-19 [35]. The mechanism of obesity affecting the MACCE, and pulmonary complications is mentioned in Fig. 1.

4.1. Limitations

The limitations of our study are as follows: Firstly, we confined our study to hospitalized critically ill COVID-19 sepsis patients, which helped us reduce selection bias by narrowing down the study population. Our analysis was conducted using the National Inpatient Sample for the year 2020, utilizing ICD-10 codes to identify cohorts admitted with COVID-19 sepsis. This approach might introduce the possibility of misclassification, particularly regarding height and weight measurements. However, this potential misclassification should be consistent among both survivors and non-survivors, thus not significantly affecting the interpretation of the results. We did not account for different strains of the COVID-19 virus, which could potentially impact the population in varying ways. Additionally, we lack information about the vaccination status of the cohorts, which could act as a confounding factor, especially in the context of mortality among population with obesity, immunocompromised, and elderly. Our study also did not compare outcomes

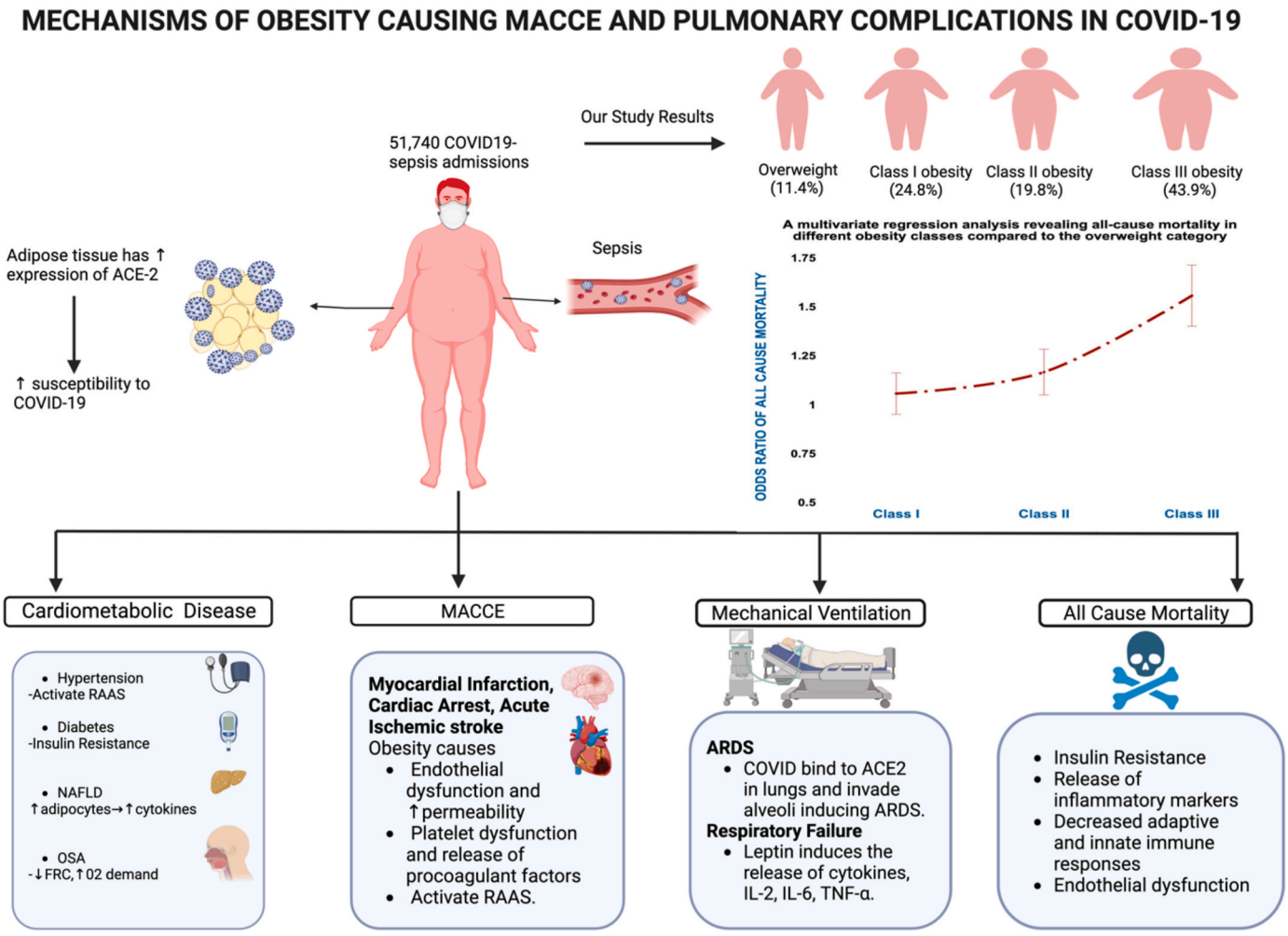

Fig. 1. Mechanism of obesity causing MACCE and pulmonary complications of COVID-19.
Abbreviations: Body Mass Index (BMI), Coronavirus disease (COVID-19), Major adverse cardiac and cerebrovascular events (MACCE), Angiotensin-converting enzyme-2 (ACE-2), Interleukins (IL-2, IL-6), Tumor necrosis factor (TNF), Non-alcoholic fatty liver disease (NAFLD), Obstructive sleep apnea (OSA), Renin-angiotensin-aldosterone system (RAAS), Acute respiratory distress syndrome (ARDS), Overweight (BMI 25–29.9), Class I obesity (BMI 30–34.9), Class II obesity (BMI 35–39.9), and Class III obesity (BMI >40).

with visceral obesity; we solely utilized BMI due to the absence of information regarding adipose tissue. Nevertheless, the substantial sample size of our study enhances its statistical power, helping to mitigate the aforementioned limitations.

5. Conclusions

Our study has revealed that patients with Class II and Class III obesity, who are also suffering from COVID-19 severe sepsis, are at a higher risk of experiencing MACCE (OR 1.09 and 1.54) and in-hospital mortality (OR 1.56, 1.17), compared to patients with overweight.

- Obesity may affect immune function, which makes it necessary to monitor such patients closely and provide them with targeted interventions.
- Hospitalizations of patients with obesity in severe COVID-19 sepsis can result in higher costs. However, the study's limitations prevent us from establishing causality or assessing long-term outcomes using administrative data.
- Therefore, more research is needed to study the long-term outcomes of these populations.

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Author contribution

Dr. Sivaram Neppala and Dr. Himaja Dutt Chigurupati share equal contributions in manuscript writing. The remaining authors contributed equally to analyzing the data and writing this manuscript. We gratefully acknowledge the expert assistance of Dr. Sai Prasanna Lekkala in the development of the graphical abstract for this manuscript.

Declaration of the potential use of AI

Artificial intelligence was not used in preparing this manuscript.

Ethical approvals

Not Applicable.

Patient consent

No written consent has been obtained from the patients as there is no

patient-identifiable data included in this observational study from the NIS database.

IRB approval

None required. This is an observational study from the NIS database.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet 2006;368:666–78. https://doi.org/10.1016/S0140-6736(06)69251-9.

[2] Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018NCHS Data Brief. 2020. p. 18.

[3] Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013;309(1):71–82.

[4] Cai Q, Chen F, Wang T, et al. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. Diabetes Care 2020;43:1392–8.

[5] Copin MC, Parmentier E, Duburcq T, Poissy J, Mathieu D, Lille C-I, et al. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection. Intensive Care Med 2020;46:1124–6.

[6] Lavie CJ, Sanchis-Gomar F, Henry BM, Lippi G. COVID-19 and obesity: links and risks. Expet Rev Endocrinol Metabol 2020:1–2.

[7] Sanchis-Gomar F, Lavie CJ, Mehra MR, Henry BM, Lippi G. Obesity and outcomes in COVID-19: when an epidemic and pandemic collide. Mayo Clin Proc 2020;95:1445–53.

[8] de Leeuw A, Oude Luttikhuis M, Wellen AC, Müller C, Calkhoven CF. Obesity and its impact on COVID-19. J Mol Med 2021;99(7):899–915. Berlin, Germany.

[9] Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, Southern WN, Mantzoros CS. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx. New York. Metabolism 2020:108.

[10] Block JP, Boehmer TK, Forrest CB. Cardiac complications after SARS-CoV-2 infection and mRNA COVID-19 vaccination PCORnet, United States, January 2021 January 2022. MMWR Morb Mortal Wkly Rep 2022;71:517–23. https://doi.org/10.15585/mmwr.mm7114e1.

[11] Miles JA, Mejia M, Rios S, Sokol SI, Langston M, Hahn S, Leiderman E, Salgunan R, Soghier I, Gulani P, Joshi K, Chung V, Morante J, Maggiore D, Uppal D, Friedman A, Katamreddy A, Abittan N, Ramani G, Irfan W, Liaqat W, Grushko M, Krouss M, Cho HJ, Bradley SM, Faillace RT. Characteristics and outcomes of in-hospital cardiac arrest events during the COVID-19 pandemic: a Single-Center experience from a New York City public hospital. Circ Cardiovasc Qual Outcomes 2020 Nov;13(11):e007303. https://doi.org/10.1161/CIRCOUTCOMES.120.007303. Epub 2020 Sep 25. PMID: 32975134; PMCID: PMC7673640.

[12] Gao M, Piernas C, Astbury NM, Hippisley-Cox J, O'Rahilly S, Aveyard P, Jebb SA. Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study. Lancet Diabetes Endocrinol 2021 Jun;9(6):350–9. https://doi.org/10.1016/S2213-8587(21)00089-9. Epub 2021 Apr 28. PMID: 33932335; PMCID: PMC8081400.

[13] Dana R, Bannay A, Bourst P, et al. Obesity and mortality in critically ill COVID-19 patients with respiratory failure. Int J Obes 2021;45:2028–37. https://doi.org/10.1038/s41366-021-00872-9.

[14] Ikhapery A, Abdelhay A, Boppana HK, et al. Higher BMI is strongly linked to poor outcomes in adult COVID-19 hospitalizations: a national inpatient sample study. Obes Sci Pract 2023.

[15] Huang Y, Lu Y, Huang YM, Wang M, Ling W, Sui Y, et al. Obesity in patients with COVID-19: a systematic review and meta-analysis. Metabolism 2020;113:154378.

[16] Nationwide analysis of the outcomes and mortality of hospitalized COVID-19 patients. Curr Probl Cardiol 2023;48(2):101440.

[17] Biscarini S, Colaneri M, Ludovisi S, Seminari E, Pieri TC, Valsecchi P. The obesity paradox: analysis from the SMAtteo COvid-19 REgistry (SMACORE) cohort. Nutr Metabol Cardiovasc Dis 2020;30(11):1920–5.

[18] Zahid M, Leung V, Nayudu SK, Galiveeti S, Mantri N, Sun H, et al. Role of body mass index in outcomes of patients hospitalized with COVID-19 illness. Obes Sci Pract 2022;8(6):748–56.

[19] Wolf M, Alladina J, Navarrete-Welton A, Shoults B, Brait K, Ziehr D. Obesity and critical illness in COVID-19: respiratory Pathophysiology. Obesity 2021;29(5):870–8.

[20] Lavie CJ, Sanchis-Gomar F, Henry BM, Lippi G. COVID-19 and obesity: links and risks. Expet Rev Endocrinol Metabol 2020;15:215–6.

[21] Sanchis-Gomar F, Lavie CJ, Mehra MR, Henry BM, Lippi G. Obesity and outcomes in COVID-19: when an epidemic and pandemic collide. Mayo Clin Proc 2020;95:1445–53.

[22] Kang Z, Luo S, Gui Y, Zhou H, Zhang Z, Tian C, et al. Obesity is a potential risk factor contributing to clinical manifestations of COVID-19. Int J Obes 2020.

[23] Bustamante A, Repine J. Adipose-lung cell crosstalk in the obesity-ARDS paradox. J Pulm Respir Med 2013;3:144.

[24] COVID-19 infection: multiple potential mechanisms. Circulation 2020;142:4–6.

[25] Rebello CJ, Kirwan JP, Greenway FL. Obesity. the most common comorbidity in SARS-CoV-2: is leptin the link? Int J Obes 2020;44:1810–7.

[26] Messina G. Functional Role of Dietary intervention to Improve the outcome of COVID-19: a hypothesis of Work. Int J Mol Sci 2020;21(9):3104. https://doi.org/10.3390/ijms21093104.

[27] Salvator H, Grassin-Delyle S, Naline E, Brollo M, Fournier C, Couderc LJ, Devillier P. Contrasting effects of Adipokines on the cytokine production by primary human bronchial epithelial cells: inhibitory effects of adiponectin. Front Pharmacol 2020;11:56. https://doi.org/10.3389/fphar.2020.00056.

[28] Ali AN, Sood A. Leptin, adiponectin and pulmonary diseases. Biochimie 2012;94(10):2180–9. https://doi.org/10.1016/j.biochi.2012.03.006.

[29] Kassir R. Risk of COVID-19 for patients with obesity. Obes Rev 2020;21(6):e13034. https://doi.org/10.1111/obr.13034.

[30] Ulevitch RJ, Johnston AR, Weinstein DB. New function for high density lipoproteins. Their participation in intravascular reactions of bacterial lipopolysaccharides. J Clin Invest 1979;64(5):1516–24.

[31] Wu A, Hinds CJ, Thiemermann C. High-density lipoproteins in sepsis and septic shock: metabolism, actions, and therapeutic applications. Shock 2004;21(3):210–21.

[32] Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, Zhao L, Fan H, Luo S, Hu D. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020:e3319.

[33] Yang JK, Jin JM, Liu S, Bai P, He W, Wu F, Liu XF, Han DM. Blood glucose is a representative of the clustered indicators of multi-organ injury for predicting mortality of COVID-19 in Wuhan, China. SSRN 2020:28.

[34] Sen S, Chakraborty R, Kalita P, Pathak MP. Diabetes mellitus and COVID-19: understanding the association in light of current evidence. World J Clin Cases 2021 Oct 6;9(28):8327–39. https://doi.org/10.12998/wjcc.v9.i28.8327. PMID: 34754842; PMCID: PMC8554438.

[35] Zhang P, Wang M, Wang Y, Li T, Zeng J, Wang L, Li C, Gong Y. Risk factors associated with the progression of COVID-19 in elderly diabetes patients. Diabetes Res Clin Pract 2021;171:108550.

[36] Muscogiuri G, Pugliese G, Barrea L, Savastano S, Colao A. Commentary: obesity: the "Achilles heel" for COVID-19? Metabolism 2020;108:154251. https://doi.org/10.1016/j.metabol.2020.154251.

[37] Zhou Y, Yang Q, Chi J, Dong B, Lv W, Shen L. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: a systematic review and meta-analysis [published online ahead of print, 2020 Jul 25]. Int J Infect Dis 2020;99:47–56. https://doi.org/10.1016/j.ijid.2020.07.029.

[38] Hussain A, Vasas P, El-Hasani S. Letter to the editor: obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. Metabolism 2020;108:154256. https://doi.org/10.1016/j.metabol.2020.154256.

[39] Pepper DJ, Sun J, Welsh J, Cui X, Suffredini AF, Eichacker PQ. Increased body mass index and adjusted mortality in ICU patients with sepsis or septic shock: a systematic review and meta-analysis. Crit Care 2016;20:181.

[40] Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. J Renin-Angiotensin-Aldosterone Syst JRAAS: J Renin-Angiotensin-Aldosterone Syst JRAAS 2020;21(2).

[41] Perrotta F, Scialò F, Mallardo M, Signoriello G, D'Agnano V, Bianco A, Daniele A, Nigro E. Adiponectin, leptin, and resistin are dysregulated in patients infected by SARS-CoV-2. Int J Mol Sci 2023 Jan 6;24(2):1131. https://doi.org/10.3390/ijms24021131. PMID: 36674646; PMCID: PMC9861572.

[42] Perpinan C, Bertran L, Terra X, Aguilar C, Binetti J, Lopez-Dupla M, Rull A, Reverte L, Yeregui E, Gomez-Bertomeu F, Peraire J. Resistin and IL-15 as predictors of invasive mechanical ventilation in covid-19 pneumonia irrespective of the presence of obesity and metabolic syndrome. J Personalized Med 2022;12(3):391.

[43] Goldstein BJ. Insulin resistance as the core defect in type 2 diabetes mellitus. Am J Cardiol 2002 Sep 5;90(5A):3G–10G. https://doi.org/10.1016/s0002-9149(02)02553-5. PMID: 12231073.

[44] Fizelova M, Jauhiainen R, Kangas AJ, Soininen P, Ala-Korpela M, Kuusisto J, Laakso M, Stancáková A. Differential associations of inflammatory markers with insulin sensitivity and secretion: the prospective METSIM study. J Clin Endocrinol Metab 2017 Sep 1;102(9):3600–9. https://doi.org/10.1210/jc.2017-01057. PMID: 28911155; PMCID: PMC5587063.

[45] Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006 Jul;116(7):1793–801. https://doi.org/10.1172/JCI29069. Erratum in: J Clin Invest. 2006 Aug;116(8):2308. PMID: 16823477; PMCID: PMC1483173.

[46] Festa A, D'Agostino Jr R, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000 Jul 4;102(1):42–7. https://doi.org/10.1161/01.cir.102.1.42. PMID: 10880413.

[47] Li R, Shen M, Yang Q, Fairley CK, Chai Z, McIntyre R, Ong JJ, Liu H, Lu P, Hu W, Zou Z, Li Z, He S, Zhuang G, Zhang L. Global diabetes prevalence in COVID-19 patients and contribution to COVID-19- related severity and mortality: a systematic review and meta-analysis. Diabetes Care 2023 Apr 1;46(4):890–7. https://doi.org/10.2337/dc22-1943. PMID: 36826982; PMCID: PMC10090902.
[48] World Health Organization. WHO coronavirus (COVID-19) dashboard in *WHO health emergency dashboard*. World Health Organization; 2022.
[49] Gil-Rodrigo Adriana, Miró Òscar, Pascual Pinera, Burillo-Putze Guillermo, Jimenez Sonia, Martin Alfonso, Martin-Sanchez Francisco Javier. Analysis of clinical characteristics and outcomes in patients with COVID-19 based on a series of 1000 patients treated in Spanish emergency departments. Emerge: revista de la Sociedad Espanola de Medicina de Emergencias 2020:233–41.
[50] Yang Jun, Tian Congmin, Chen Ying, Zhu Chunyan, Chi Hongyu, Li Jiahao. Obesity aggravates COVID-19: an updated systematic review and meta-analysis. J Med Virol 2021;93(5):2662–74.
[51] Du Yanbin, Yuan Lv, Zha Wenting, Zhou Nan, Hong Xiuqin. Association of body mass index (BMI) with critical COVID-19 and in-hospital mortality: a dose-response meta-analysis. Metabolism 2021;117:154373.
[52] Pranata Raymond, Lim Michael A, Yonas Emir, Vania Rachel, Lukito Antonia A, Siswanto Bambang B, Meyer M. Body mass index and outcome in patients with COVID-19: a dose–response meta-analysis. Diabetes & metabolism 2021;47(2):101178.
[53] Popkin Barry M, Du Shufa, Green William D, Beck Melinda A, Algaith Taghred, Herbst Christopher H, Alsukait Reem F, Alluhidan Mohammed, Alazemi Nahar, Shekar Meera. Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. Obes Rev 2020;21(11):e13128.
[54] Ho Jamie SY, Fernando Daniel I, Chan Mark Y, Sia Ching-Hui. Obesity in COVID-19: a systematic review and meta-analysis. Ann Acad Med Singapore 2020;49(12):996–1008.
[55] Abumayyaleh Mohammad, Iván J Núñez Gil, El-Battrawy Ibrahim, Estrada Vicente, Manuel Becerra-Muñoz Víctor, Aparisi Alvaro, Fernández-Rozas Inmaculada. Does there exist an obesity paradox in COVID-19? Insights of the international HOPE-COVID-19-registry. Obes Res Clin Pract 2021;15(3):275–80.
[56] Rodriguez-Gonzalez, Guadalupe Carmen, Chamorro-de-Vega Esther, Valerio Maricela, Angel Amor-Garcia Miguel, Tejerina Francisco, Sancho-Gonzalez Milagros, Narrillos-Moraza Alvaro. COVID-19 in hospitalised patients in Spain: a cohort study in Madrid. Int J Antimicrob Agents 2021;57(2):106249.
[57] Thakur Bhaskar, Dubey Pallavi, Joseph Benitez, Torres Joshua P, Reddy Sireesha, Shokar Navkiran, Aung Koko, Mukherjee Debabrata, Kumar Dwivedi Alok. A systematic review and meta-analysis of geographic differences in comorbidities and associated severity and mortality among individuals with COVID-19. Sci Rep 2021;11(1):8562.