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Diabesity Associates with Poor COVID-19 Outcomes among Hospitalized Patients

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Background: Although numerous studies have investigated obesity's negative effect on coronavirus disease 2019 (COVID-19) outcomes, only a limited number focused on this association in diabetic patients. In this study, we analyzed the association between obesity and COVID-19 outcome (death, intensive care unit [ICU] admission, mechanical ventilation needs, quick Sequential Organ Failure Assessment [qSOFA] score, and confusion, urea, respiratory rate, blood pressure [CURB-65] scores) for hospitalized diabetic patients.

Methods: In this prospective hospital-based registry of patients with COVID-19 in East Azerbaijan, Iran, 368 consecutive diabetic patients with COVID-19 were followed from admission until discharge or death. Self-reported weight and height were used to calculate body mass index (kg/m^2) upon admission. Our primary endpoint was analyzing obesity and COVID-19 mortality association. Assessing the associations among obesity and disease severity, ICU admission, and mechanical ventilation was our secondary endpoint.

Results: We analyzed data from 317 patients and found no significant difference between obese and non-obese patients regarding frequency of death, invasive mechanical ventilation, ICU admission, CURB-65, or qSOFA scores ($P>0.05$). After adjusting for confounding factors, obese diabetic COVID-19 patients were 2.72 times more likely to die than non-obese patients. Moreover, ventilator dependence (adjusted odds ratio [aOR], 1.87; 95% confidence interval [CI], 1.03–4.76) and ICU admission (aOR, 2.41; 95% CI, 1.11–5.68) odds were significantly higher for obese patients than non-obese patients.

Conclusion: The results of the present study indicated that obesity worsens health outcomes for diabetic COVID-19 patients.

Key words: COVID-19, Death, Diabetes mellitus, Intensive care units, Obesity

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak originated in Wuhan, China, spread rapidly, and was declared a global pandemic in March 2020. In Iran, the first official COVID-19 death was February 19, 2020. Between then and August 4, 2020, approximately 312,035 more cases have been diagnosed.[1] COVID-19 is associated with high morbidity and mortality rates[2] and a 6.0% global fatality rate.[3] In Iran, there is a 24.4% 30-day cumulative risk for in-hospital mortality[4] with a 3.6% average COVID-19 mortality rate.[5] Different factors affect COVID-19's morbidity and mortality rates including age, sex, obesity, and comorbidities such as diabetes mellitus, hypertension, cardiovascular disease, kidney disease, and liver disease.[6]

After hypertension, diabetes mellitus is the most prevalent comorbid disease affecting COVID-19 patients.[7] The COVID-19 morbidity rate is significantly higher in diabetic patients than non-diabetic patients.[8] In this regard, studies have attempted to investigate factors contributing to diabetic patients' poor health outcomes. Thus far, reports show that age and comorbid hypertension are

contributors.[9] Obesity is a risk factor for infectious diseases such as pneumonia, surgical-site infections, nosocomial infections, periodontitis and skin infections.[10] Numerous studies have also shown obesity's negative effect on COVID-19 severity and critical conditions.[3,11,12] Mechanisms such as increased proinflammatory cytokines, decreased immunity and decreased lung function may play a role in poor COVID-19 health outcomes among obese patients.[13]

In addition, obesity may contribute to the COVID-19 health outcomes in patients with underlying diseases such as diabetes mellitus. Diabetic patients often have impaired immune function, low-grade chronic systemic inflammation, and impaired lung function.[14-16] This is similar to the comorbidities observed in obese patients. In this study, we postulated that obese diabetic patients with COVID-19 may have worse disease outcomes than non-obese diabetic patients. There have been few studies on the relationship between obesity and COVID-19 outcomes in diabetic patients. In this study, we analyzed the association between obesity and COVID-19 outcomes (death, intensive care unit [ICU] admission, mechanical ventilation, quick Sequential Organ Failure Assessment [qSOFA] scores, and confusion, urea, respiratory rate [RR], blood pressure [CURB-65] scores) in hospitalized diabetic patients.

METHODS

Data were obtained from the AzarCoRe (East Azar Covid-19 Registry) study. Briefly, patients were included in this registry if COVID-19 was confirmed by reverse transcription-polymerase chain reaction of throat and nose swab specimens from the upper respiratory tract or clinically diagnosed based on lung imaging like chest computed tomography scans showing ground glass pathognomonic features consistent with coronavirus pneumonia. All registered cases were given a unique code to prevent duplication.

For data collection, a questionnaire that included demographic characteristics, vital signs, drug history, laboratory parameters, COVID-19-related symptoms, medication, and outcomes was designed. We also collected lifestyle information such as smoking and physical activity levels. During anamnesis, we collected information on comorbidity diagnoses. The COVID-19 nurses completed the questionnaires and a trained researcher transferred the information to the statistical software. We ascertained diabetes mellitus status through self-reporting.

The patients were followed until they were discharged. Trained nurses recorded all clinical and laboratory parameters daily. Body mass index (BMI; kg/m^2) was calculated using self-reported weight and height upon hospital admission. We considered a person with a BMI higher than 30 kg/m^2 to be obese. In the AzarCoRe, approximately 338 diabetic patients registered at Imam Reza Hospital. Twenty-one patients did not complete the questionnaire's request for anthropometric information or disease outcomes, so we only analyzed data from 317 patients.

Tabriz University of Medical Sciences' Ethics Committee approved this study (Ethics code: IR.TBZMED.REC.1398.1274). Informed consent was obtained from the patients or their next of kin.

Outcomes

The primary endpoint of this study was analyzing the association between obesity and mortality from COVID-19 after adjusting for demographics and comorbidities in diabetic patients. Assessing the association between obesity and COVID-19 severity using the qSOFA score, the CURB-65 score, ICU admission, and mechanical ventilation at any point were our secondary endpoints. The qSOFA score is a validated ICU mortality prediction score. It helps clinicians identify patients with suspected infections that are at high risk for poor outcomes.[17] We calculated qSOFA by awarding one point each for the Glasgow Coma Scale <15, RR ≥ 22, and systolic blood pressure (SBP) ≤ 100. A qSOFA score ≥ 2 was used as the cutoff based on a higher risk of mortality.[18] The CURB-65 score was used to evaluate pneumonia severity.[19] It classifies mortality risk for pneumonia patients.[20,21] CURB-65 was calculated by awarding 1 point each for Glasgow Coma Scale <15, blood urea nitrogen >19 mg/dL, RR ≥ 30, SBP <90 mmHg or diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 years. A CURB-65 score ≥ 3 was used as the cutoff based on a higher risk of mortality.[22]

Statistical analysis

For statistical analysis, IBM SPSS version 25 (IBM Corp., Armonk, NY, USA) was used. The normality of the data distribution was analyzed by the Kolmogorov-Smirnov test. The quantitative and qualitative values are reported as the mean and frequency (%), respectively. To compare data between obese and non-obese patients, we

used the independent test. Between-group comparisons for qualitative data were performed by the chi-square test. Logistic regression was used to analyze univariate and multivariate models. The multivariate model considered demographic, lifestyle, and on-admission clinical factors significant in the univariate model. We adjusted the multivariate model for age, sex, smoking, and comorbidities. For all analyses, a *P*-value < 0.05 was considered significant.

RESULTS

The data of 317 diabetic COVID-19 patients were included in the present study. Table 1 shows demographic characteristics and comorbidity prevalence stratified by obesity status. The participants' mean age was 65.09 ± 13.29 years and 51.4% was male. There were significant differences between obese and non-obese participants regarding sex ($P < 0.01$).

Table 2 presents outcome according to BMI. There were no significant differences between obese and non-obese patients regarding the frequency of death, mechanical ventilation, ICU admission, CURB-65 score, or qSOFA score. Table 3 summarizes the COVID-19 outcomes and obesity status logistic regression analyses. There was no significant association between obesity and COVID-19 outcome in the unadjusted model. However, after adjusting for confounding factors (age, sex, smoking, and comorbidities), obese diabetic COVID-19 patients had a 2.72 times higher death rate than non-obese patients. Moreover, ventilator dependence

Table 1. The demographic characteristics of diabetic patients with COVID-19

Demographic variable	Total (n = 317)	Non-obese patient (BMI < 30 kg/m^2, n = 241)	Obese patient (BMI ≥ 30 kg/m^2, n = 76)	*P*
Age (yr)	65.09 ± 13.29	65.99 ± 12.97	62.89 ± 13.93	0.14*
Sex				< 0.01†
Male	163 (51.4)	133 (55.1)	30 (39.5)	
Female	155 (48.8)	108 (44.8)	46 (60.5)	
Comorbidity				
CVD	111 (35.0)	86 (35.6)	25 (32.8)	0.49†
Respiratory disease	48 (15.1)	37 (15.3)	11 (14.4)	0.55†
HTN	200 (63.1)	151 (62.6)	49 (64.4)	0.39†
Kidney disease	58 (16.0)	46 (19.1)	12 (15.8)	0.44†
Carcinoma	19 (5.9)	14 (5.8)	5 (6.5)	0.50†
Liver disease	8 (2.5)	4 (1.6)	4 (5.2)	0.15†
Autoimmune disease	5 (1.5)	2 (0.8)	3 (3.9)	0.21†
Smoker	17 (5.4)	14 (5.8)	3 (3.9)	0.43†
Antidiabetic agent use				0.34†
Insulin	107 (33.7)	76 (31.5)	31 (40.7)	
Oral agent	196 (61.8)	155 (64.3)	41 (53.9)	
Combination insulin/oral agent	14 (4.4)	10 (4.1)	4 (5.2)	
SBP (mmHg)	125.55 ± 17.26	125.30 ± 17.01	125.67 ± 17.68	0.88*
FBG (mg/dL)	170.40 ± 26.37	169.30 ± 23.47	186.70 ± 24.21	0.07*
ALT (IU/L)	25.90 ± 18.27	24.41 ± 20.55	26.55 ± 13.82	0.57*
AST (IU/L)	35.93 ± 12.70	30.32 ± 11.67	37.96 ± 14.92	0.04*
Creatinine (mg/dL)	1.89 ± 1.81	1.97 ± 1.85	1.77 ± 1.84	0.49*
hs-CRP	5.30 ± 1.28	6.30 ± 1.41	6.66 ± 2.73	0.63*
GCS < 15	105 (33.1)	82 (34.4)	23 (30.2)	0.45†
RR ≥ 22	60 (18.9)	46 (19.5)	14 (18.4)	0.76†
SBP < 100 mmHg	33 (10.7)	21 (8.2)	12 (15.7)	0.06†
BUN > 19	197 (62.1)	147 (60.9)	50 (65.7)	0.47†

Values are presented as mean ± standard deviation or number (%).
*Independent t-test; †Chi-square test.
COVID-19, coronavirus disease 2019; BMI, body mass index; CVD, cardiovascular disease; HTN, hypertension; SBP, systolic blood pressure; FBG, fasting blood glucose; ALT, alanine amino transferase; AST, aspartate amino transferase; hs-CRP, high sensitive-C reactive protein; GCS, Glasgow Coma Scale; RR, respiratory rate; BUN, blood urea nitrogen.

Table 2. The frequency of COVID-19 outcomes in diabetic patients

Outcome	Total (n=317)	Obese patient (BMI <30 kg/m^2, n=241)	Non-obese patient (BMI ≥30 kg/m^2, n=76)	*P**
Death	67 (21.1)	47 (19.5)	20 (26.3)	0.19
Mechanical ventilation	71 (22.3)	49 (20.33)	22 (28.9)	0.29
ICU admission	89 (28.07)	69 (28.6)	20 (26.3)	0.17
CURB-65 score				0.38
0–1	76 (23.9)	57 (23.6)	19 (25.0)	
2	117 (36.9)	92 (38.1)	25 (32.8)	
3–5	124 (39.1)	92 (38.1)	32 (42.1)	
qSOFA score				0.45
0	33 (10.4)	31 (12.8)	2 (4.5)	
1	255 (80.4)	193 (80.08)	62 (81.8)	
2	29 (9.1)	17 (7.05)	12 (13.6)	

Values are presented as number (%).
*Chi-square test.
COVID-19, coronavirus disease 2019; BMI, body mass index; ICU, intensive care unit; CURB-65, confusion, urea, respiratory rate, blood pressure; qSOFA, quick Sequential Organ Failure Assessment.

Table 3. Logistic regression analysis of obesity and COVID-19 outcomes in diabetic patients

Outcome	OR (95% CI)	*P*	aOR* (95% CI)	*P*
Death	1.47 (0.70–3.04)	0.30	2.72 (1.13–7.44)	0.01
Requirement for mechanical ventilation	1.51 (0.72–3.15)	0.26	1.87 (1.03–4.76)	0.04
ICU admission	1.27 (0.64–2.53)	0.48	2.41 (1.11–5.68)	0.03
CURB-65	1.31 (0.60–2.85)	0.48	1.68 (0.32–4.57)	0.57
qSOFA	2.12 (0.66–6.72)	0.20	1.47 (0.33–10.72)	0.23

Dependent variables: death, mechanical ventilation, ICU admission, CURB-65 score, qSOFA score; Independent variable: obesity status (BMI >30 kg/m^2).
*Adjusted OR for age, sex, smoking status, comorbidities (CVD, respiratory diseases, hypertension, kidney diseases, carcinoma, liver diseases, and autoimmune diseases), glucose concentration and hs-CRP.
COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; aOR, adjusted OR; ICU, intensive care unit; CURB-65, confusion, urea, respiratory rate, blood pressure; qSOFA, quick Sequential Organ Failure Assessment; CVD, cardiovascular disease; hs-CRP, high sensitive-C reactive protein.

(adjusted odds ratio [aOR], 1.87; 95% confidence interval [CI], 1.03–4.76) and ICU admission (aOR, 2.41; 95% CI, 1.11–5.68) were significantly higher in obese patients than non-obese patients.

DISCUSSION

Our study shows that mortality, ICU admission, and mechanical ventilation odds for hospitalized diabetic COVID-19 patients are significantly higher for obese patients than non-obese patients. Obesity is a risk factor for severe COVID-19.[23] In Iran, obesity is a community health problem affecting 24% of the Iranian population.[24] Various studies have shown a significant association between obesity and poor COVID-19 outcomes.[23,25,26] In a systematic review, Földi et al.[25] reported that obesity is a significant risk factor for COVID-19 ICU admission and invasive mechanical ventilation. Another systematic review and meta-analysis showed the dose-response association between BMI and COVID-19 mortality and severity.[27]

Our results are likely related to the negative effect of both obesity and diabetes mellitus on immune function,[28,29] which can result in poor COVID-19 outcomes. The higher inflammatory factors found in both obese and diabetic patients may make them susceptible to poor COVID-19 outcomes.[13] Obesity causes systemic inflammation[30] and diabetes mellitus is associated with low-grade chronic systemic inflammation.[31,32] These two conditions may synergically affect COVID-19 outcomes.[33,34] A cytokine storm immune response may cause multiorgan failure.[3] Lung mechanics may also play a significant role in the link between obesity and COVID-19 outcomes in diabetic patients. Earlier studies indicate that obesity is associated with poor mechanical ventilation due to limiting diaphragm and chest wall movement.[35,36] Diabetes mellitus also affects lung function.[14,15] These two comorbid conditions (obesity and diabetes mellitus) could result in impaired lung function. Moreover, both obesity and diabetes mellitus are associated with increased plasminogen activator inhibitor-1 levels, which increases COVID-19 virulence,[16,37] and increased reactive oxygen species levels and hypoxia-inducible factor 1α activation, which sustains severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication.[13,38-40]

This study was limited by the small number of patients with simultaneous diabetes mellitus and COVID-19. Moreover, we used self-reported height and weight for BMI calculations. Studies have shown, however, that BMI computed from self-reported weight and height is a valid measure in men and women across different sociodemographic groups. This study's strengths include its prospective nature and the large number of confounding factors analyzed. In conclusion, our results support the hypothesis that obesity is a risk factor for poor health outcomes in diabetic COVID-19 patients. Further studies with larger sample sizes and measured anthropometric indices are needed to confirm these results.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Study concept and design: MHS, ZN, MFD; acquisition of data: LM, ZN, AT; analysis and interpretation of data: ZN, MFD, MHS, AT; drafting of the manuscript: ZN; critical revision of the manuscript: ZN, MHS, MFD; statistical analysis: ZN; obtained funding: MHS; administrative, technical, or material support: MFD; and study supervision: MHS.

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