DOI: http://dx.doi.org/10.18502/cjn.v22i1.???

Current Journal of Neurology

Original Paper

Curr J Neurol 2023; 22(1): 23-9

The effect of body mass index on the morbidity and outcomes of COVID-19 in Iranian patients with multiple sclerosis

Received: 05 Sep. 2022
Accepted: 11 Nov. 2022

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Keywords
Body Mass Index; COVID-19; Multiple Sclerosis; Obesity; Symptom Assessment; Risk

Abstract

Background: It seems that patients with multiple sclerosis (MS) are at a higher risk for coronavirus disease 2019 (COVID-19) implications due to being subjected to immunomodulatory or immunosuppressive treatments. Besides, obesity as a risk factor may lead to more adverse consequences. The relationship between obesity and COVID-19 morbidity and outcomes in Iranian patients with MS still remains unclear.

Methods: A cross-sectional study was conducted in Sina Hospital, Tehran, Iran. Patients with MS were asked to complete an online questionnaire in the Google Form format. Demographic information, clinical information including MS disease-related factors, COVID-19-related factors, and anthropometric information were recorded. Totally, 492 patients filled the questionnaire during two weeks in November 2021, by the response rate of 21.6%. Body mass index (BMI) was categorized based on the standard classification of the World Health Organization (WHO). The logistic regression was used to examine the risk of morbidity and chi-square test/one-way analysis of variance (ANOVA) was employed to determine the difference regarding severity and symptoms among groups.

Results: In the fully adjusted model**,** the odds ratio (OR) of COVID-19 morbidity in class II obese participants was significantly 5.41 times higher than that in the normal BMI group [OR: 5.41, 95% confidence interval (CI): 1.00-29.09]. COVID-19 severity was significantly different among BMI groups ($P = 0.024$). Respiratory symptoms ($P = 0.05$) as well as gastrointestinal (GI) symptoms ($P < 0.01$) of COVID-19 were more prevalent among class I and class II obese patients compared with overweight, normal weight, and underweight groups.

How to cite this article: Rezaeimanesh N, Abbasi N, Sahraian MA, Azimi A, Razeghi-Jahromi S, Naser Moghadasi A. The effect of body mass index on the morbidity and outcomes of COVID-19 in Iranian patients with multiple sclerosis. Curr J Neurol 2023; 22(1): 23-9.

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Moreover, no one in the class I and class II obesity groups reported COVID-19 morbidity without any symptoms (P = 0.04).

Conclusion: The results of the current study support the view that obesity could play a key role in susceptibility to COVID-19 morbidity and severity of the symptoms in patients with MS. The findings recommended that neurologists pay more attention to patients' BMI during this pandemic.

Introduction

Coronavirus disease 2019 (COVID-19) elicited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has recently resulted in a pandemic outbreak.[1]

Centers for Disease Control and Prevention (CDC) announced that patients with underlying medical conditions such as neurological diseases, those consuming immunosuppressive medications, and patients with overweight or obesity might be at a greater risk for serious infections.[2] It also mentioned that increases in the number of comorbidities would raise COVID-19 death risk ratio.[2]

Previous studies have illuminated the relationship between obesity and the risk of severe outcomes in reaction to other viruses like influenza A (H1N1) during 2009 pandemic.[3] Obesity seems to be a potent risk factor for breathing difficulties such as elevated need for ventilation, higher work of breathing, respiratory muscle inefficiency, and reduced respiratory compliance.[4] Furthermore, metabolic equivalents and obesity may cause a state of chronic inflammatory reactions. It also leads to disturbances in innate and adaptive immune responses.[5] Consequently, the probable role of body mass index (BMI) in COVID-19 outcomes is increasingly considered.

Findings of the recent studies during the COVID-19 pandemic exhibited that obesity resulted in more severe clinical sequences of COVID-19, higher mortality rate, greater amount of hospitalization, need for mechanical ventilation,[6] and greater chance of developing COVID-19.[7]

According to CDC, overweight and obesity raise the risk of severe COVID-19 outcomes. Obesity was reported to triple COVID-19 hospitalization risk.[8]

Multiple sclerosis (MS), as a neurological autoimmune inflammatory disease, may increase the risk of adverse outcomes of COVID-19 due to the use of immunomodulatory or immunosuppressive medications.[9] Some MS medications such as rituximab, an immunosuppressive drug, have been reported to elevate the risk of hospitalization, admission to the intensive care unit (ICU), and requirement for artificial ventilation among MS patients with COVID-19.[10] The findings of a recently published observational study among patients with MS revealed age and obesity as the risk factors for COVID-19 severity,[10] which have also been mentioned as the factors increasing the risk of SARS-CoV-2 infection in people with MS.[11] Therefore, assessment of related risk factors for COVID-19 is of great importance in decreasing mortality rates in these patients. However, although many studies have already focused on the percentage of obese patients' excess risk of severity in the general population, the relation between obesity and COVID-19 risk consequences in patients with MS in Iran still remains unclear. In this regard, the present study was conducted to explore the association between BMI and COVID-19 morbidity risk and outcomes (i.e., the onset, severity, and symptoms of the infection, and the number of infected cases) in Iranian patients with MS.

Materials and Methods

Study design and participants: A cross-sectional study was conducted among Iranian patients with MS in Multiple Sclerosis Research Center, Tehran University of Medical Sciences, Tehran, Iran, in November 2021.

Inclusion criteria were being a definite patient with MS diagnosed by an expert neurologist and based on revised McDonald criteria,[12] being over 18 years old, having access to the study Google Form link in the social media, and ability to fill online forms.

Ethical approval: Project objectives and voluntary participation in the study were described for participants in the beginning of the questionnaire and they were asked to sign the consent form before starting the questions.

The project protocol has been confirmed by the Ethics Committee of Tehran University of Medical Sciences with the ethics code of "IR.TUMS.NI.REC.1399.052".

Data collection: An online questionnaire was developed in the Google Form format in three sections including: 1) demographic information (i.e., age, gender, education, marital status, underlying diseases, smoking status, alcohol

consumption, and physical activity), 2) clinical information consisting of MS disease-related factors [i.e., MS type, current disease-modifying therapy (DMT), disability status, and onset year] and COVID-19-related factors (i.e., onset, rate, severity and symptoms of morbidity, vaccination status, and the type of vaccine), and 3) anthropometric information (i.e., height and weight). The COVID-19 morbidity verification was based on polymerase chain reaction (PCR) test or chest computed tomography (CT) scan corresponding COVID-19 infection according to infectious disease specialist confirmation. The study Google Form link was shared through the MS patients' channels in social media.

BMI was calculated using weight (kg)/height^2 (m^2) formula and categorized considering the standard classification of the World Health Organization (WHO) as underweight (BMI < 18.5), normal weight (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30), obesity class I (30 ≤ BMI < 35), and obesity class II (BMI ≥ 35).[13]

SPSS software (version 26, IBM Corporation, Armonk, NY, USA) was used for analyses. Descriptive statistics were reported as mean ± standard deviation (SD) and number (percentage) for quantitative and qualitative variables, respectively.

Binary logistic regression methods in three models were adopted to assess the associations between BMI and COVID-19 odds. The first model was unadjusted, the second model was adjusted for age, gender, and COVID-19 vaccination, and the last one was additionally adjusted for comorbidities, Expanded Disability Status Scale (EDSS), MS type, smoking status, alcohol consumption, as well as light and heavy physical activities. For assessing the differences in terms of COVID-19 symptoms, severity, and rate of morbidity among BMI categories, the study employed chi-square test and one-way analysis of variance (ANOVA), respectively. P-value of less than 0.05 was considered statistically significant.

Results

Totally, 492 patients with MS participated in this study which was conducted in two weeks by the response rate of 21.6%. Demographic data and clinical characteristics of participants are presented in table 1. The mean age of respondents was 36.70 ± 8.26 years and 395 (80.3%) of them were women. Among the participants, 350 (71.1%) suffered from relapsing-remitting MS (RRMS), 63 (12.8%) from primary progressive MS (PPMS), and 49 (10.0%) from secondary progressive MS (SPMS). Three of the mostly received MS drugs by the attendances were rituximab [177 (36.0%)], interferon beta-1a [81 (16.5%)], and fingolimod [69 (14.0%)]. The mean BMI was 24.33 ± 4.54 kg/m^2. According to the findings, 234 (47.6%) of the participants experienced COVID-19 morbidity during the pandemic. It was revealed that 465 (94.5%) of them had received two doses of vaccine and 15 (3.0%) had received only one dose. Among them, 439 (92.0%) had received the Sinopharm COVID-19 vaccine.

Odds ratios (ORs) and 95% confidence intervals (CIs) for COVID-19 morbidity according to the BMI categories are reported in table 2**.** Normal BMI was considered to be the reference category and three regression models were run. The results of analyses indicated that the OR of COVID-19 morbidity was higher in overweight and obese participants compared to the normal group in all three models (OR > 1). In the fully adjusted model, which was controlled for age, gender, vaccination, comorbidities, EDSS, MS type, MS treatment, smoking status, alcohol consumption, as well as light and heavy physical activities as confounder factors, the OR of COVID-19 morbidity was significantly 5.41 times more than that of the normal group in class II obese participants (OR: 5.41, 95% CI: 1.00-29.09).

As highlighted in table 3, the COVID-19 morbidity rate did not differ significantly among the BMI groups (P = 0.250). However, COVID-19 severity was significantly different among the BMI groups. While no one in underweight group reported hospitalization in the ward or ICU, 8.6%, 7.9%, and 13.6% of participants in normal BMI, overweight, and obesity class I groups, respectively, reported hospitalization. Hospitalization percentage in class II obese participants was 50.0% (37.5% were inward patients and 12.5% were in ICU) and no one in this group experienced COVID-19 morbidity without treatment.

Further analyses revealed that the symptoms of COVID-19 morbidity varied according to the BMI of patients with MS (Table 4). Respiratory symptoms including shortness of breath and cough (P = 0.050) and gastrointestinal (GI) symptoms including nausea, vomiting, stomachache, and diarrhea (P < 0.01) were more prevalent among class I and class II obese participants compared to the other groups. Moreover, no one in the class I and class II obesity groups reported COVID-19 morbidity without any symptoms (P = 0.040).

Table 1. Basic characteristics of the participants

Variable	Value	Variable	Value
Age (year)	36.70 ± 8.26	BMI (kg/m^2)	24.33 ± 4.54
Gender		Past COVID-19 morbidity	
Male	395 (80.3)	No	258 (52.4)
Female	97 (19.7)	Yes	234 (47.6)
Education		COVID-19 vaccine	
High school	5 (1.0)	No	12 (2.4)
Diploma	95 (19.3)	Yes, the first dose	15 (3.0)
Bachelor	220 (44.7)	Yes, two doses	465 (94.5)
Master of Science	137 (27.8)	COVID-19 vaccine type	
PhD	35 (7.1)	Sinopharm	439 (92.0)
Marital status		AstraZeneca	10 (2.1)
Single	161 (32.7)	COVIran Barekat	7 (1.5)
Married	305 (62.0)	Sputnik	14 (2.9)
Divorced	25 (5.1)	Others	10 (2.0)
Widow	1 (0.2)	Smoking status	
MS type		No	418 (85.0)
RRMS	350 (71.1)	Yes	74 (15.0)
PPMS	63 (12.8)	Alcohol drinking	
SPMS	49 (10.0)	No	360 (73.2)
CIS	25 (5.1)	Yes	132 (26.8)
RIS	5 (1.0)	Light physical activity (minute per week)	148.95 ± 275.32
MS duration (year)	9.50 ± 7.22	Heavy physical activity (minute per week)	53.06 ± 117.18
EDSS	2.94 ± 1.73	Underling diseases	
MS treatment		Hypertension	77 (15.7)
Rituximab	177 (36.0)	Diabetes mellitus	63 (12.8)
Fingolimod	69 (14.0)	Hyperlipidemia	75 (15.2)
Interferon beta-1a	81 (16.5)	Cancer	61 (12.4)
Dimethyl fumarate	54 (11.0)	Heart disease	60 (12.2)
Glatiramer acetate	25 (5.1)	Pulmonary disease	62 (12.6)
Ocrelizumab	20 (4.1)	Liver disease	63 (12.8)
Natalizumab	14 (2.8)	Renal disease	60 (12.2)
Teriflunomide	13 (2.6)	Hypothyroidism	114 (23.2)
Interferon beta-1b	10 (2.0)	Autoimmune disease	18 (3.7)
Azathioprine	2 (0.4)	Migraine	4 (0.8)
Mitoxantrone	1 (0.2)	Huntington	1 (0.2)
None	16 (3.3)	Myopathy	1 (0.2)
Others	10 (2.0)	Human T-lymphotropic virus type 1	1 (0.2)

Quantitative variables are presented as mean ± standard deviation (SD), whereas qualitative variables are reported as number (%)

MS: Multiple sclerosis; EDSS: Expanded Disability Status Scale; BMI: Body mass index; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; PPMS: Primary progressive multiple sclerosis; CIS: Clinically isolated syndrome; RIS: Radiologically isolated syndrome; COVID-19: Coronavirus disease 2019

Discussion

The results of this study support the view that obesity could play a key role in susceptibility to COVID-19 morbidity in patients with MS.

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for coronavirus disease 2019 (COVID-19) morbidity according to the body mass index (BMI) categories

	BMI categories				P
	18.5 ≤ BMI < 25	25 ≤ BMI < 30	30 ≤ BMI < 35	≥ 35	
No. of infected/not infected	129/147	63/69	22/20	8/3	
Model 1	Reference	1.040 (0.687-1.576)	1.253 (0.654-2.401)	3.039 (0.789-11.696)	0.17
Model 2	Reference	1.078 (0.704-1.650)	1.430 (0.735-2.782)	3.447 (0.883-13.463)	0.08
Model 3	Reference	1.276 (0.778-2.093)	1.727 (0.745-4.002)	5.410 (1.006-29.093)	0.03

1: Crude regression model; 2: Regression model adjusted for age, gender, and COVID-19 vaccine; 3: Fully adjusted regression model controlled for age, gender, vaccination, comorbidities, Expanded Disability Status Scale (EDSS), multiple sclerosis (MS) type, smoking status, alcohol consumption, and light and heavy physical activity

BMI: Body mass index

Table 3. Number and severity of coronavirus disease 2019 (COVID-19) morbidities according to the body mass index (BMI) categories

	BMI					P
	Underweight	Normal	Overweight	Type 1 obesity	Type 2 obesity	
COVID-19 severity						0.024*
No treatment	6 (46.2)	33 (25.6)	17 (26.6)	3 (13.6)	0 (0)	
Outpatients	7 (53.8)	85 (65.9)	42 (65.6)	16 (72.7)	4 (50.0)	
Hospitalization in COVID-19 ward	0 (0)	9 (7.0)	4 (6.3)	3 (13.6)	3 (37.5)	
Hospitalization in ICU	0 (0)	2 (1.6)	1 (1.6)	0 (0)	1 (12.5)	
Number of COVID-19 infections	1.27 ± 0.47	1.19 ± 0.54	1.19 ± 0.39	1.47 ± 0.80	1.43 ± 0.79	0.250**

COVID-19 severity was presented as number (%) in each group and number of COVID-19 morbidity as mean ± standard deviation (SD)
*P-value is calculated using chi-square test; **P-value is calculated using one-way analysis of variance (ANOVA) test
BMI: Body mass index; COVID-19: Coronavirus disease 2019; ICU: Intensive care unit

Furthermore, COVID-19 severity was totally associated with BMI which is in agreement with the results of a study conducted among patients with MS[14] and also other studies in the general population.[6,15]

It is almost certain that obesity is an important factor in decreasing lung compliance, more airway resistance, and increased work of breathing that result in the increased need for more energy to control the chest wall compliance. Therefore, recovery from severe illnesses that detrimentally involve respiratory function, like COVID-19, is a challenge for these patients and may cause more severe symptoms,[6] that are in line with our findings.

Petrilli et al. proposed that individuals with obesity were twice as probable to be hospitalized due to COVID-19 as those under the age of 60,[16] which is confirmed by our results. It was also reported that higher degree of obesity increased the risk of death.[14]

A systematic review demonstrated that obesity increased the risk for COVID-19 incidence. This correlation may be due to immunological impairments in these patients.[17]

Moreover, obesity could cause an increase in inflammatory reactions. Several levels of innate and adaptive immune responses are affected in obese patients. Hypertrophic lipid-engorged adipocytes in this group are more probable to be exposed to induced endoplasmic reticulum and mitochondrial stress responses. These factors result in the stimulation of a potential chronic, pro-inflammatory state within the adipose tissue which may be worsened by an alternative virus such as COVID-19.[6]

Table 4. Coronavirus disease 2019 (COVID-19) symptoms according to body mass index (BMI) categories

Symptoms		BMI					P*
		Underweight	Normal	Overweight	Obesity type 1	Obesity type 2	
Fever, chills, body aches	No	7 (53.8)	53 (40.5)	29 (45.3)	5 (22.7)	1 (12.5)	0.132
	Yes	6 (46.2)	78 (59.5)	35 (54.7)	17 (77.3)	7 (87.5)	
Fatigue	No	5 (38.5)	58 (44.3)	27 (42.2)	6 (27.3)	1 (12.5)	0.282
	Yes	8 (61.5)	73 (55.7)	37 (57.8)	16 (72.7)	7 (87.5)	
Respiratory symptoms	No	11 (84.6)	89 (67.9)	47 (73.4)	11 (50.0)	3 (37.5)	0.057
(cough and shortness of breath)	Yes	2 (15.4)	42 (32.1)	17 (26.6)	11 (50.0)	5 (62.5)	
Smell loss	No	8 (61.5)	66 (50.4)	42 (65.6)	15 (68.2)	4 (50.0)	0.226
	Yes	5 (38.5)	65 (49.6)	22 (34.4)	7 (31.8)	4 (50.0)	
Taste loss	No	8 (61.5)	86 (65.6)	45 (70.3)	17 (77.3)	5 (62.5)	0.791
	Yes	5 (38.5)	45 (34.4)	19 (29.7)	5 (22.7)	3 (37.5)	
GI symptoms	No	12 (92.3)	113 (86.3)	57 (89.1)	13 (59.1)	5 (62.5)	0.004
(nausea/vomiting/stomachache /diarrhea)	Yes	1 (7.7)	18 (13.7)	7 (10.9)	9 (40.9)	3 (37.5)	
Headache/dizziness	No	9 (69.2)	94 (71.8)	41 (64.1)	15 (68.2)	4 (50.0)	0.645
	Yes	4 (30.8)	37 (28.2)	23 (35.9)	7 (31.8)	4 (50.0)	
None	No	11 (84.6)	129 (98.5)	60 (93.8)	22 (100)	8 (100)	0.043
	Yes	2 (15.4)	2 (1.5)	4 (6.3)	0 (0)	0 (0)	

Data are presented as number and percentage. *P-value is calculated using chi-square test
BMI: Body mass index; GI: Gastrointestinal

Karlsson et al. found a decrease in influenza-specific $CD8^+$ memory T cells in obese mice.[18] Furthermore, prior studies have noted the effect of obesity on impaired memory $CD8^+$ T cell responses to influenza virus infections that lead to excess mortality and higher viral titers in lung. In fact, the lack of adequate $CD8^+$ memory T cell responses to virus poses a challenge in immunity. Hence, we assumed that there was a correlation between the number of COVID-19 infections and BMI; nevertheless, this relationship was not significant in our study.[6]

Obesity may increase viral shedding period; it has been mentioned that virus shedding among symptomatic obese patients is 42% longer than others.[19] Adipose tissue can provide a storage for several viruses like influenza A virus, human adenovirus 36 (Adv-36), Mycobacterium tuberculosis, and human immunodeficiency virus (HIV).[20] In comparison, adipose tissue, if infected by COVID-19, can facilitate virus spread to other tissues.[21]

It is also important to determine clinical manifestations of COVID-19 among obese patients with MS to control the symptoms.

In the general population, obesity increases COVID-19 symptoms including cough and breath difficulties.[22] These results match with those obtained in our study confirming that patients with lower BMI are more non-symptomatic. It was also found that respiratory symptoms among patients with MS were associated with higher BMI ($P = 0.057$). Moreover, this study found a correlation between obesity and COVID-19 GI symptoms which was clarified by findings from a meta-analysis that revealed a relation between gastroesophageal reflux and higher BMI.[23]

It can, therefore, be concluded that such connections exist between BMI and COVID-19 outcomes among patients with MS.

Conclusion

The results suggest that patients with MS who are suffering from obesity are more prone to COVID-19 incidence and severity. Hence, it is recommended that neurologists pay more attention to patients' BMI during this pandemic and avoid prescribing inappropriate supplements affecting BMI.

Further investigations and experimentations into the effects of BMI on COVI-19 among patients with MS are strongly recommended.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

We thank the patients with MS for participating in this study.

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