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Original Article

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Is Obesity a Potential Risk factor for Poor Prognosis of COVID-19?

Meltem Agca [1], Eylem Tuncay [2], Elif Yıldırım [1], Reyhan Yıldız [1], Tülin Sevim [1], Dilek Ernam [1], Nermin Ozer Yılmaz [3], Nazlı Huma Teke [1], Simge Yavuz [1], Zuhal Karakurt [1], COVID-19 Team*, and Ipek Ozmen [1]

[1]Department of Pulmonology, University of Health Sciences, Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
[2]Department of Respiratory Intensive Care Unit, University of Health Sciences, Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
[3]Department of Infectious Diseases, University of Health Sciences, Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey

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Corresponding Author:
Meltem Agca, MD
Department of Pulmonology, University of Health Sciences, Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Barbaros cad. Ihlamur sok. Uphıll Court, A8/14, Batı Atasehir/ Istanbul, Turkey.
Tel: 0090-505-284-48-18
E-mail: agcameltem@yahoo.com

*COVID-19 Team
Sibel Arinc[1], Selma Aydogan[1], Baran Gundogus[1], Ozlem Sogukpinar[1], Aysem Oztin Guven[1], Dildar Duman[1], Nagihan Durmus Kocak[1], Ulku Aka Akturk[1], Esin Sonkaya[1], Sumeyye A.Bekir[1], Murat Kavas[1], Lale Sertcelik[1], Fatma Ozbaki[1], Dilem Anıl Tokyay[1], Feride Yaman[1], Gul Erdal Donmez[1], Makbule Akbay[1], Sibel Boga[1], Selahattin Oztas[1], Tulay Torun[1], Ozlem Oruc[1], OzlemYazıcıoglu Mocin[2], Emine Aksoy[1], Birsen Ocakli[1], Hakan Gunen[1], Nalan Adıguzel[2], Gokay Gungor[2], Barış Yılmaz[2], Hilal Altinoz[1], Sinem Gungor[2], Tekin Yıldız[1], Huriye Berk Takir[1]

ORCID iDs
Meltem Agca
https://orcid.org/0000-0001-9694-7909

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) continues to cause major mortality and morbidity worldwide even after a year of its emergence. In its early days, hypertension, diabetes, and cardiovascular diseases were noted as poor prognostic factors, while obesity gained attention at a later stage. In the present study, unfavorable clinical outcomes (transfer to the intensive care unit, invasive mechanical ventilation, and mortality) were investigated in obese patients with COVID-19.
Materials and Methods: In this retrospective study we analyzed patients with positive polymerase chain reaction test in tertiary care hospital between March-May 2020. They were divided into 3 groups according to body mass index (BMI) as normal, overweight, and obese (BMI: 18.5 - 24.99 kg/m^2, 25 - 29.99 kg/m^2, and ≥ 30 kg/m^2, respectively). We compared clinical features and laboratory findings of these groups and recorded adverse clinical outcomes. Multivariate logistic analysis was performed for unfavorable outcomes.
Results: There were 99 patients (35%), 116 (41%), and 69 patients (24%) in the normal-weight, overweight, and obese group, respectively. Among all patients, 52 (18%) patients were transferred to the intensive care unit (ICU), 30 (11%) patients received invasive mechanical ventilation (IMV), and 22 patients (8%) died. Obese patients had minimum 1 more comorbidity than normal BMI patients (73% *vs.* 50%, $P = 0.002$), and a longer median (interquartile range [IQR]) duration of hospitalization (8 [5 - 12] *vs.* 6 [5 - 9]) days, $P = 0.006$). Obese participants had higher concentrations of serum C-reactive protein, procalcitonin, ferritin than non-obese patients ($P < 0.05$ in all). In a multivariate analysis, obesity was associated with ICU admission (adjusted odds ratio [aOR]: 2.99, 95% confidence interval [CI]: 1.26 - 7.04, $P = 0.012$). Moreover, IMV requirement was associated with obesity (aOR: 8.73, 95% CI: 2.44 - 31.20, $P = 0.001$). Mortality occurred in 16%, 9%, and 1% of the obese group, overweight group, and normal-weight group, respectively (Chi-square trend analysis, $P = 0.002$).
Conclusion: Obesity is a risk factor for adverse outcomes and caused increased mortality, hence requiring close follow-up.

Keywords: Body mass index; COVID-19; Intensive care unit; Obesity, SARS-CoV-2

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Eylem Tuncay
https://orcid.org/0000-0002-5046-1943
Elif Yıldırım
https://orcid.org/0000-0001-9614-5754
Reyhan Yıldız
https://orcid.org/0000-0002-6770-3937
Tülin Sevim
https://orcid.org/0000-0003-4989-8168
Dilek Ernam
https://orcid.org/0000-0001-9008-4508
Nermin Ozer Yılmaz
https://orcid.org/0000-0001-5440-8261
Nazlı Huma Teke
https://orcid.org/0000-0003-2380-5410
Simge Yavuz
https://orcid.org/0000-0003-3194-9983
Zuhal Karakurt
https://orcid.org/0000-0003-1635-0016
Ipek Ozmen
https://orcid.org/0000-0002-3448-3675

Conflict of Interest
No conflicts of interest.

Informed Consent
All participants signed an informed consent form before participating in the study.

Ethical Statement
Approval was obtained from the Ethics Committee of Health Sciences University Sureyyapasa Pulmonary Disease and Pulmonary Surgery Training and Research Hospital. The procedures used in this study adhere to the tenets of the Declaration of Helsinki (No: 2020.41.172).

Author Contributions:
Conceptualization: AM, OI, TE. Data curation: ST, ED, YE, YS, TNH. Formal analysis: AM, OI. Investigation: AM. Methodology: AM, OI, YE. Resources: AM, TE. Software: AM, OI. Supervision: OI, TE, YE, ED. Validation: AM, OI, TE. Writing - original draft: AM, OI, TE. Writing - review & editing: AM, OI, TE, YR, ST, ED.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is the agent causing the new coronavirus disease, started to spread rapidly all over the world after it was first identified in China on January 7, 2020 [1]. After the World Health Organization (WHO) declared the disease as a pandemic on March 11, 2020, the number of confirmed cases worldwide was 98 million as of January 2020, and the number of deaths was 2 million [2]. In Turkey, the total number of patients exceeded 2 million and the total number of deaths exceeded 25,000 as of end of January 2020 since March 11, 2020 (the date at which the country's first case was reported) [3].

In the early days of the pandemic; advanced age, hypertension, diabetes, chronic heart, and lung diseases were included in the risk group, while obesity began to be included in this group at a later stage [4-7]. Indeed, obesity was previously demonstrated to be a risk factor for disease severity and mortality in viral infections during the H1N1 Influenza A outbreak [8].

Obesity is defined as the accumulation of abnormal or excessive fat tissue that can impair health [9]. The body mass index (BMI) is used for its definition and grading, however, different cut-off values were used for BMI in coronavirus disease 2019 (COVID-19) studies according to characteristics of the geographical region in question [6, 9-11]. In the majority of these studies, obesity has been demonstrated to be an independent risk factor that adversely affects the prognosis in COVID-19. Obesity has been shown to increase the rate of hospital admissions, the severity of the disease, and the need for intensive care and invasive mechanical ventilation (IMV), and lead to a longer duration of hospitalization and higher mortality rates [6, 7, 11-13]. On the contrary, there are few studies which reported that obesity is not an independent risk factor for COVID-19 and does not increase mortality [14, 15].

The prevalence of obesity is gradually increasing worldwide in the adult population over the age of 18. According to WHO estimates, 39% of adults were overweight and 13% were obese in 2016 [9]. Given the increasing prevalence of obesity and persistence of COVID-19, the impact of obesity on the course of COVID-19 is worthy of attention.

The aim of this study was to investigate whether obesity is a poor prognostic factor in COVID-19 and to examine the factors of obesity that may be associated with poor clinical outcome.

MATERIALS AND METHODS

This single-center observational, cross-sectional, and retrospective study was conducted between March 11, 2020 and May 31, 2020 in patients hospitalized with suspected and confirmed COVID-19 diagnosis at Sureyyapasa Thoracic Diseases and Thoracic Surgery Training and Research Hospital. The data of all the patients were retrieved from the electronic medical database of the hospital.

Patients with positive real-time polymerase chain reaction (RT-PCR) test in nasal and/or oropharyngeal swabs used for the diagnosis of COVID-19 were included in the study [16]. Swab samples were evaluated at the General Directorate of Public Health Microbiology Reference Laboratory and designated Public Health Laboratories.

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1. Study population

BMI was calculated by dividing body weight (kg) by the square of height (m^2) [9].
Patients were divided into 3 groups based on BMI;
Normal weight (BMI: 18.5 - 24.99 kg/m^2)
Overweight (BMI: 25 - 29.99 kg/m^2)
Obese (BMI ≥ 30.00 kg/m^2)

Patients' vital signs (heart rate, heart rhythm, respiratory rate, blood pressure, body temperature, and oxygen saturation), radiological images, and laboratory values were recorded starting from their admission to the ward. The disease was classified as mild, moderate, and severe according to the guidelines of the Ministry of Health, and treatment was given according to their classification [17].

2. Mild

1) Symptoms of fever, muscle/joint pain, cough, and a sore throat without respiratory distress (respiratory rate <24, saturation of percutaneous oxygen (SpO_2) >93% at room air).
2) No underlying co-morbid disease (mainly cardiovascular disease, diabetes mellitus, hypertension, cancer, chronic pulmonary disease, and other immunosuppressive conditions), and patients under 50 years old.
3) A normal chest X-ray and/or thorax tomography.

3. Moderate

1) Symptoms such as fever, muscle/joint pain, cough, and a sore throat without respiratory distress (respiratory rate ≤30, SpO_2 >90% at room air).
2) Evidence of bilateral pneumonia on chest-X ray or thorax tomography.

4. Severe disease

Patients with severe pneumonia, acute respiratory distress syndrome, sepsis, septic shock, myocarditis, arrhythmia, and cardiogenic shock as well as multiple organ failure. These patients were followed up in the intensive care unit (ICU) [17].

5. Indication for Intensive Care Unit admission

COVID-19 treatment was performed in the ICU according to the criteria determined in the guidelines of the Ministry of Health [17].

6. Invasive mechanical ventilation (IMV)

IMV was employed in cases of refractory hypoxemia, tachypnea, aspiration risk, impaired hemodynamics, multiorgan failure, or impaired mental state [17].

7. Inclusion criteria

Patients hospitalised for mild, moderate and severe COVID-19 infection due to positive nasal and/or oranasal swabs PCR test.

8. Exclusion criteria

Age <18 years,
COVİD-19 patients followed up in outpatient clinic,
Patients with negative RT-PCR test,
BMI value not recorded
BMI <18.5 kg/m^2 (**Fig. 1**).

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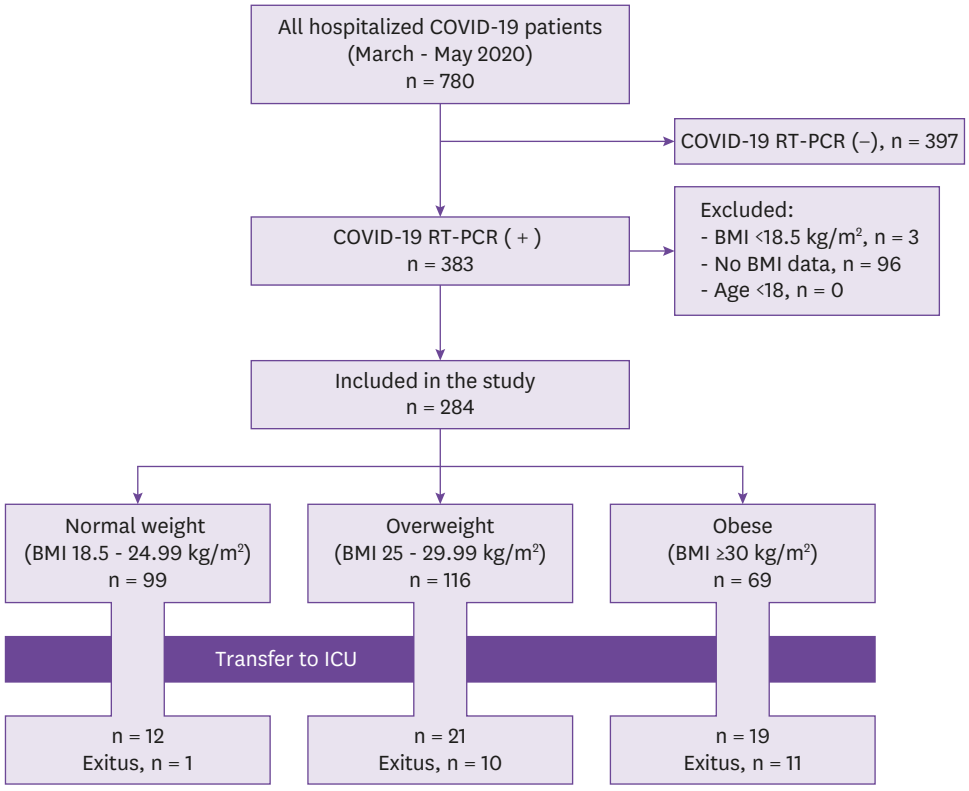

Figure 1. Flow chart.
COVID-19, coronavirus disease 2019; RT-PCR, polymerase chain reaction; BMI, body mass index; ICU, intensive care unit.

Demographic characteristics, comorbidities, symptoms at presentation, length of hospital stay, ICU requirement, in-hospital mortality, laboratory values, and radiological findings of all three groups were compared.

Unfavorable clinical outcomes of all patients, *i.e.*, transfer to ICU, IMV, and in-hospital mortality, were examined and univariate and multivariate logistic regression analyses were performed for possible risk factors such as age, gender, comorbidity, and obesity.

9. Statistical analysis

The IBM SPSS-22 portable package program (IBM Corporation, Chicago, IL, USA) was used to perform the statistical analyses. Data distributions were examined using the Kolmogorov–Smirnov test. Comparisons between two groups were made by using the independent samples t-test, the chi-square test, or the Mann–Whitney *U*-test, as appropriate. When comparing more than two groups, normally distributed data were analyzed using one-way analysis of variance whereas non-normally distributed data were analyzed using the Kruskal–Wallis test. Normally distributed data were expressed as mean (SD) and non-normally distributed data as median (interquartile range [IQR]). Categorical variables were presented as frequency and percentage. Spearman's correlation analysis was performed between BMI and inflammatory markers. Intensive care, IMV, and mortality rates of all three groups were compared with Chi-square trend analysis. Among the possible risk factors for transfer to the ICU and need of IMV; age, gender and presence of comorbidity and obesity were evaluated first by univariate analysis and then by multivariate logistic analysis. The results were

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expressed as odds ratios (ORs) with 95% confidence interval (CI). All statistical tests were 2-tailed, and statistical significance was defined as P <0.05.

10. Ethics statement

Permission was obtained from the scientific committee of the hospital and the Ministry of Health, and approval was obtained from the local ethics committee for the study (No: 2020.41.172).

RESULTS

The data of 284 patients hospitalized at the Chest Diseases clinic and according to inclusion criteria were analyzed.

There were 99 normal-weight patients (35%), 116 overweight patients (41%), and 69 obese (24%) patients according to the BMI classification. Among obese patients, the majority (14%) had class I obesity (BMI: 30 - 34.9 kg/m^2) (n = 40), 7% had class II obesity (BMI: 35 - 39.9 kg/m^2) (n = 19), and 3% had class III obesity (BMI ≥ 40 kg/m^2) (n = 10) (**Fig. 2**).

Table 1 shows the general characteristics of all three groups. In the obese group (BMI ≥ 30), female gender was more common than in the non-obese groups (55% *vs.* 37 - 40%, P = 0.049). Similarly, the presence of any comorbidity including diabetes, hypertension, and chronic lung diseases was more common in the obese group than in the other groups (P = 0.001 - 0.029). In terms of the duration of hospitalization, the duration of hospitalization of obese patients was longer than those with normal weight (median [IQR], 8 [5 - 12] *vs.* 6 [5 - 9] days, P = 0.006) (**Table 1**).

When laboratory values of all three groups were compared, there were significant differences in obese patients compared to non-obese patients. Leucocyte count (median 5.9 *vs.* 5.1) and neutrophil count (median 3.8 *vs.* 3.3) were significantly higher. Median glucose, and lactate dehydrogenase (LDH) values were found to be significantly higher (P = 0.002, P = 0.03, respectively), while albumin and Ca^+ values were significantly lower (P = 0.019, P = 0.012,

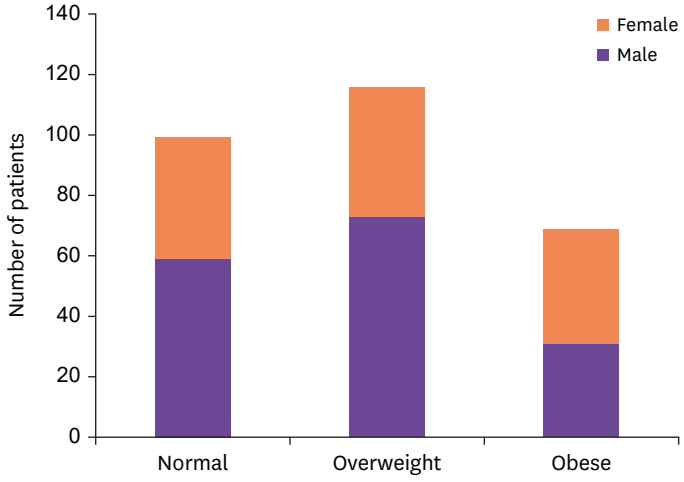

Figure 2. Distribution of BMI classification according to gender.
Normal BMI 18.5 - 24.99 kg/m^2; Overweight 25 - 29.99 kg/m^2; Obese ≥30 kg/m^2.
BMI, body mass index.

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Table 1. Demographic and general characteristics of patients according to BMI categories

	BMI, kg/m²				
	Total (n = 284)	Normal (n = 99, 35%)	Overweight (n = 116, 41%)	Obese (n = 69, 24%)	*P*-value
Age, year	54 (41 - 65)	50 (38 - 65)	54 (41 - 63)	55 (46 - 68)	0.13
Gender, male	163 (57)	59 (60)	73 (63)	31 (45)	0.049
BMI, kg/m²	25.9 (18.8 - 48.8)	23.5 (18.8 - 24.9)	26.6 (25 - 29.8)	33.8 (30.2 - 48.8)	0.001
Comorbidities					
Any	154 (54)	49 (50)	55 (47)	50 (73)	0.002
Diabetes mellitus	60 (2)	21 (21)	16 (14)	23 (33)	0.007
Hypertension	87 (31)	26 (26)	31 (27)	30 (44)	0.029
Chronic cardiac disease[a]	32 (11)	12 (12)	11 (10)	9 (13)	0.71
Chronic respiratory disease[b]	53 (19)	15 (15)	13 (11)	25 (36)	0.001
Chronic renal disease	4 (1)	2 (1)	-	2 (1)	0.79
Symptoms on admission					
Fever	138 (49)	46 (16)	55 (19)	37 (13)	0.56
Dyspnea	112 (39)	35 (12)	44 (16)	33 (12)	0.18
Dry cough	157 (56)	53 (19)	64 (23)	40 (14)	0.79
Diarrhea	19 (7)	8 (2)	10 (4)	1 (0)	0.14
Duration of the symptoms, days	5 (3 - 8)	5 (3 - 7)	5 (3 - 7)	7 (3 - 10)	0.47
Length of hospital stay, days	7 (7 - 11)	6 (5 - 9)	8 (5 - 12)	8 (5 - 12)	0.006
Radiological findins on chest CT					0.09
Bilateral opacity	232 (82)	74 (75)	98 (84)	61 (88)	
Unilateral opacity	26 (9.2)	11 (11)	9 (8)	6 (9)	

[a]Chronic cardiovasculary disease, including diagnoses of coronary artery disease, congestive heart failure, arrhythmias.
[b]Chronic respiratory disease, including diagnoses of asthma, chronic obstructive pulmonary disease, interstitial fibrosis.
Data are expressed as number (%), median (IQR) interquartile range (25th - 75th percentile).
BMI, body mass index; CT, computed tomography.

Table 2. Comparison of the laboratory values of the patients according to BMI categories

	n	Total (n = 284)	Normal (n = 99, 35%)	Overweight (n = 116, 41%)	Obese (n = 69, 24%)	*P*-value
Total blood count						
Leukocyte count, × 10⁹/L	284	5.4 (4 - 7)	5.1 (4.1 - 6.9)	5.4 (3.9 - 6.5)	5.9 (4.5 - 8.5)	0.023
Hemoglobin, g/dL	284	13.1 (12 - 14)	12.9 (11.8 - 14)	13.2 (12.3 - 14.2)	12.9 (11.4 - 13.7)	0.048
Platelet count, × 10⁹/L	284	206 (161 - 260)	203 (158 - 260)	205 (160 - 259)	214 (165 - 269)	0.82
Lymphocyte count, × 10⁹/L	284	1.2 (0.8 - 1.6)	1.2 (0.9 - 1.6)	1.1 (0.8 - 1.5)	1.2 (0.8 - 1.6)	0.38
Eosinophil count, × 10⁹/L	284	0.01 (0 - 0.06)	0.02 (0 - 0.08)	0.01 (0 - 0.04)	0.01 (0 - 0.05)	0.46
Neutrophil count, × 10⁹/L	284	3.4 (2.5 - 4.9)	3.33 (2.4 - 4.7)	3.4 (2.4 - 4.5)	3.78 (2.8 - 6.9)	0.031
Biochemistry						
Glucose, mg/dL	281	108 (96 - 139)	104 (91 - 130)	104 (95 - 132)	127 (99 - 166)	0.002
Albumin, g/dL	276	39 (35 - 42)	39 (35 - 43)	39 (36 - 42)	37 (33 - 41)	0.019
Ca, mmol/L	281	8.72 (0.61)	8.86 (0.53)	8.68 (0.63)	8.5 (0.67)	0.012
LDH, U/L	281	236 (189 - 303)	227 (185 - 299)	228 (183 - 293)	267 (212 - 355)	0.030
D-Dimer, μg/L	257	0.58 (0.4 - 0.9)	0.60 (0.4 - 1.0)	0.57 (0.4 - 0.9)	0.61 (0.3 - 1.2)	0.96
Inflammatory marker						
NLR	284	2.93 (2 - 4.6)	2.59 (2 - 3.8)	3.0 (2 - 4.6)	3.4 (2.2 - 5.5)	0.12
CRP, mg/mL	281	23.5 (7.8 - 7.3)	20.85 (4.8 - 49.9)	21.6 (6.9 - 57.0)	47.7 (10.9 - 111)	0.004
Procalcitonin, μg/L	255	0.067 (0.050 - 0.122)	0.060 (0.047 - 0.097)	0.065 (0.049 - 0.106)	0.089 (0.053 - 0.184)	0.044
Ferritin (ng/mL)	259	161.40 (78.7 - 337.6)	126.50 (65.7 - 239.2)	219.80 (109.3 - 396.6)	190.15 (59.2 - 351.1)	0.007

BMI, body mass index; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.
Data are expressed as mean (SD), median interquartile range (IQR) (25th – 75th percentile).

respectively) in obese patients (**Table 2**). When Ca^{+} was calculated as corrected for blood albumin value, it was found to be normal (Ca^{+}: 10.90 mmol/L).

Similarly, significant differences were found in inflammatory markers. Among the inflammatory markers, C-reactive protein (CRP) (median 47.7 *vs.* 20.85 mg/mL), procalcitonin (median 0.089 *vs.* 0.060 μg/L), ferritin (median 190.15 *vs.* 126.50 ng/mL) were significantly higher in obese patients than in non-obese patients (**Table 2**).

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Table 3. Correlation analysis between BMI and inflammatory markers

	BMI	
	R	*P*-value
Leucocyte count	0.132	0.026
Neutrophil count	0.152	0.010
Lymphocyte %	−0.143	0.016
NLR	0.153	0.010
CRP	0.205	0.001
LDH	0.138	0.021
Albumin	−0.105	0.081
Glucose	0.177	0.003
Procalcitonin	0.150	0.017
Ferritin	0.117	0.060

Correlation analysis of nonparametric Spearman's rho test.
BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Spearman's Rho correlation analysis was performed between BMI and inflammatory markers (**Table 3**). There was a weak but significant positive correlation between BMI and leucocyte count, neutrophil count, neutrophil/lympochyte ratio (NLR), CRP, LDH, glucose and procalcitonin (P = 0.001 - 0.026) and negative between BMI and lymphocyte percentage (P = 0.016). The strongest positive correlation was found between BMI and CRP (R = 0.205, P = 0.001).

Demographic characteristics and the presence of obesity, which are among the possible risk factors for transfer to ICU, were evaluated by univariate and multivariate logistic regression analyses (**Table 4**). Age and obesity (BMI ≥ 30 kg/m^2) posed a significant risk for transfer to ICU both together and independently (adjusted for gender and comorbidity). In multivariate analysis, transfer to the ICU increased by 4% per unit of increase in age (adjusted odds ratio [aOR]: 1.04, 95% CI: 1.02 - 1.07, P <0.001), whereas male gender and obesity increased the risk approximately 3 times (aOR: 2.65, 95% CI: 1.29 - 5.43, P = 0.008; aOR: 2.99, 95% CI: 1.26 - 7.04, P = 0.012, respectively) (**Table 4**).

In **Table 5**, patients' ICU, non-IMV, IMV demand and mortality risk were analyzed using chi-square trend analyses according to BMI classifications. Transfer to ICU was required in 52 (18%) of 284 patients. While 12% of normal-weight patients, 18% of overweight patients, and 28% of obese patients were transferred to ICU, the difference was statistically significant (P = 0.039). In addition, IMV was employed in 4% of normal-weight patients, 9% of overweight patients, and 22% of obese patients, and the difference was significant (P = 0.001). While one patient with normal weight died (1%), 10 patients (9%) died in the overweight group, and 11 patients (16%) died in the obese group (P = 0.002).

When univariate and multivariate regression analyses were performed for IMV, age and obesity were found to be significant risk factors in both analyses. In multivariate analysis

Table 4. Univariate and multivariate analysis for possible risk factors for intensive care unit transfer among all patients

	Univariate		Multivariate	
	Odd ratio (95% CI)	*P*-value	Odd ratio (95% CI)	*P*-value
Age	1.04 (1.02 - 1.06)	<0.001	1.04 (1.02 - 1.07)	<0.001
Male	1.67 (0.89 - 3.16)	0.11	2.65 (1.29 - 5.43)	0.008
Comorbidity	1.96 (1.04 - 3.69)	0.038	1.04 (0.48 - 2.23)	0.93
BMI categories				
Overweight *vs.* normal weight	1.60 (0.75 - 3.45)	0.23	1.56 (0.67 - 3.49)	0.28
Obese *vs.* normal weight	2.76 (1.24 - 6.14)	0.013	2.99 (1.26 - 7.04)	0.012

BMI, body mass index; CI, confidence interval.

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Table 5. NIMV, IMV and mortality rates in patients in need of ICU

	BMI, kg/m²				
	Total (n = 284)	Normal (n = 99, 35%)	Overweight (n = 116, 41%)	Obese (n = 69, 24%)	*P*-value[a]
Hospitalization unit					0.039
Pulmonology ward	232 (82)	87 (88)	95 (82)	50 (72)	
ICU	52 (18)	12 (12)	21 (18)	19 (28)	
Only nasal oxygen therapy	21 (7)	8 (8)	10 (9)	3 (4)	0.53
NIMV	1 (0.4)	-	-	1 (100)	
IMV	30 (11)	4 (4)	11 (9)	15 (22)	0.001
In hospital mortality	22 (8)	1 (1)	10 (9)	11 (16)	0.002

[a]Chi-square trend, by column.
Data are presented as number (%).
NIMV, non invasive mechanical ventilation; IMV, invasive mechanical ventilation; ICU, intensive care unit; BMI, body mass index.

Table 6. Univariate and multivariate analysis for possible risk factors in invasive mechanical ventilation in all patients

	Univariate		Multivariate	
	Odd ratio (95% CI)	*P*	Odd ratio (95% CI)	*P*-value
Age	1.06 (1.04 - 1.10)	<0.001	1.07 (1.03 - 1.10)	<0.001
Male	1.32 (0.60 - 2.89)	0.49	3.09 (1.19 - 8.04)	0.02
Comorbidity	3.09 (1.28 - 7.45)	0.012	1.14 (0.40 - 3.29)	0.80
BMI categories				
Overweight *vs.* normal weight	2.49 (0.77 - 8.08)	0.13	2.70 (0.77 - 9.47)	0.12
Obese *vs.* normal weight	6.60 (2.08 - 20.89)	0.001	8.73 (2.44 - 31.20)	0.001

BMI, body mass index.

(adjusted for gender and comorbidity), while the IMV risk was increased by 7% per unit of increase in age (aOR: 1.07, 95% CI: 1.03 - 1.10, P <0.001), male gender increased the risk three times (aOR: 3.09, 95% CI: 1.19 - 8.04, P = 0.020) and presence of obesity increased the risk approximately 9 times (aOR: 8.73, 95% CI: 2.44 - 31.20, P = 0.001) (**Table 6**).

In **Table 7**, the demographic and laboratory characteristics of the patients who were transferred to ICU (n = 19) and those who were not (n = 50) among patients with obesity (n = 69) were compared. The mean age of the patients who were transferred to ICU was higher than those who were not transferred to ICU (67 *vs.* 51, P <0.001), and also mean neutrophil count and percentage, glucose, urea, creatinine, LDH, pro-brain natriuretic peptide (P-BNP), D-dimer, troponin, and international normalized ratio (INR) values were significantly higher in the ICU group (from P <0.001 to 0.019). On the other hand, mean lymphocyte count, lymphocyte percentage, albumin, and Ca^+ values were significantly lower in the ICU group (from P <0.001 to 0.018). Ca^+ corrected for blood albumin level was normal (Ca^+: 13.53 mmol/L).

In the ICU group, compared with the group not transferred to the ICU, median NLR (8.03 *vs.* 2.46, P <0.001), CRP (117 *vs.* 34 mg/mL, P <0.001), and ferritin (306 *vs.* 146 ng/mL, P = 0.026) values, which are among inflammatory markers, were higher. Median procalcitonin value (0.38 *vs.* 0.20 μg/L, P = 0.278) did not differ significantly between the two groups.

DISCUSSION

In this study, the prevalence of overweight (25 kg/m² ≤ BMI <29.99 kg/m²) and obese (BMI ≥ 30 kg/m²) patients in the PCR positive COVID-19 patient group was 41% and 24%, respectively. Obese patients were found to have more comorbidities (especially hypertension), higher inflammatory markers and longer length of stay in hospital than patients with normal weight. A BMI ≥ 30 kg/m² was shown to increase the risk for transfer

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Table 7. Comparison of demographic and laboratory values of patients transferred to ICU with BMI ≥ 30

	n	Non-ICU (n = 50)	ICU (n = 19)	*P*-value
Age, year	69	51 (13.8)	67 (16.08)	<0.001
Gender	69			0.40
Female	38	26 (52)	12 (63)	
Male	31	24 (48)	7 (37)	
Any comorbidity	69	35 (70)	15 (79)	0.45
Total blood count				
Leukocyte count, × 10^9/L	69	6.43 (3.3)	8.30 (4.7)	0.07
Hemoglobin, g/dL	69	12.9 (11.4 - 13.7)	12.4 (9 - 13.2)	0.18
Platelet count, × 10^9/L	69	222 (165 - 276)	194 (166 - 246)	0.37
Lymphocyte count, × 10^9/L	69	1.36 (1.10 - 1.67)	0.81 (0.50 - 0.98)	<0.001
Lymphocyte, %, mean (SD)	69	25.13 (11.14)	10.33 (5.90)	<0.001
Eosinophil, %	69	0.20 (0.08 - 1.38)	0.08 (0.01 - 0.32)	0.029
Eosinophil, %		0.02 (0 - 0.07)	0 (0 - 0.03)	0.08
Neutrophil count, × 10^9/L	69	3.3 (2.7 - 5.5)	5.9 (4.3 - 9.7)	0.003
Neutrophil, %, mean (SD)	69	63 (13)	82 (8)	<0.001
Biochemistry				
Glucose, mg/dl, mean (SD)	69	134 (59)	195 (94)	0.016
BUN, mg/dL, mean (SD)	69	30 (14)	53.74 (27)	<0.001
Creatinine, mg/dL, mean (SD)	69	0.70 (0.23)	0.89 (0.41)	0.019
ALT, U/L	69	30 (20 - 41)	22 (14 - 47)	0.42
AST, U/L	69	30 (25 - 38)	33 (23 - 57)	0.28
Albumin, g/dl, mean (SD)	68	38.5 (4.6)	33.42 (4)	<0.001
LDH, U/L	69	246 (205 - 301)	365 (254 - 480)	0.004
Calcium, mmol/L, mean (SD)	69	8.7 (0.7)	8.3 (0.5)	0.018
D-Dimer, µg/L	68	0.5 (0.3 - 1)	0.9 (0.5 - 1.9)	0.010
INR	67	1.04 (1.01 - 0.98)	1.08 (1.02 - 1.20)	0.002
Pro BNP, pg/ml	29	43 (19 - 72)	431 (234 - 2,648)	0.001
Troponin, µg/L	67	3.00 (1.55 - 4.95)	11.80 (5.10 - 24.60)	<0.001
Inflammatory markers				
NLR	69	2.4 (1.7 - 4.4)	8.03 (4.3 - 17.9)	<0.001
CRP, mg/mL	69	34 (8 - 70)	117 (79 - 184)	<0.001
Procalcitonin, µg/L, mean (SD)	67	0.20 (0.65)	0.38 (0.32)	0.27
Ferritin, ng/mL	66	146 (56 - 298)	306 (124 - 609)	0.026
Length of hospital stay, day	66	7 (5 - 10)	16 (10 - 26)	<0.001

Data are expressed as mean (SD), number (%), median (IQR) interquartile range (25th – 75th percentile).
ICU, intensive care unit; BMI, body mass index; BUN, blood urea nitrogen; ALT, alanine amino transferase; AST, aspartate amino transferase; LDH, lactate dehydrogenase; INR, international normalized ratio; Pro BNT, pro-brain natriuretic peptide; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

to the ICU by about 3 times and the risk for IMV by 9 times compared with normal BMI, regardless of age, gender, and comorbidities.

It has been reported that obese patients are at risk for infection with the SARS-CoV-2 virus and that COVID-19 has a more severe course in this patient group [6, 11, 12]. The most frequently suggested hypothesis regarding this issue is that the angiotensin converting enzyme (ACE-2), which is used as a receptor by the SARS-CoV-2 virus for entering into the human cell, is found in abundant amounts in adipose tissue as well as in tissues, such as lung, heart, and kidney [18, 19]. ACE-2 receptors in adipose tissue enable the entrance of SARS-CoV-2 into adipocytes, making adipose tissue an important organ for viral reservoir [20]. Turkey is regarded as one of the countries with the highest prevalence of obesity in Europe with an obesity prevalence of 29.5% [9]. The prevalence of obesity in our study was found to be slightly lower than that in the national data (24% *vs.* 29.4%). The missing BMI data of some patients (n = 96) in the study may have affected the prevalence of obesity in the study. In the COVID-19 and obesity studies conducted in other countries, the prevalence of obesity was reported to be 5 - 48% [7, 10, 12, 14, 21]. The lowest prevalence was reported in

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China, the highest prevalence was reported in France, USA, and Italy, and these rates were higher than these countries' own obesity prevalences (6.2% in China, 18% in France, 40% in the USA, and 20% in Italy) [9]. These findings suggest that the prevalence of obesity is higher in hospitalized COVID-19 patients than in the normal population.

In the present study, the presence of at least 1 comorbidity was significantly higher in obese patients than in normal-weight patients with COVID-19 (73% *vs.* 50%). Hypertension was the most common (44%) comorbidity in obese patients, followed by chronic lung diseases (36%), and diabetes (33%). These results were consistent with other similar COVID-19 obesity studies [6, 14]. Indeed, obesity alone is a condition closely associated with comorbidities, and comorbidities have been reported as risk factors for patients with severe COVID-19 [15, 22, 23]. The most frequently suggested hypothesis regarding obesity and comorbidity is the presence of a continuous and low-grade systemic inflammation in the adipose tissue of obese individuals. It is considered that inflammation leads to endothelial damage in the liver, insulin resistance, and consequently many interrelated organ dysfunctions, such as diabetes, cardiovascular disease, and hypertension [22]. In the present study, the presence of comorbidity alone posed a significant risk for transfer to the ICU and use of IMV, but when evaluated independently of age, gender, and categorized BMI, it did not pose a significant risk as in some other studies [6, 12]. These findings should be re-evaluated with a higher number of patients in the future.

Various immunological, hormonal, and physical characteristics in obese patients have been shown to lead to major challenges in the medical management of these patients. These characteristics include, above all, susceptibility to infections due to impaired immunity and high glucose levels, lipo-toxicity, vitamin D deficiency, obesity–hypoventilation syndrome, decreased lung volume due to increased intrabdominal pressure, decreased diaphragm contractility, ventilation/perfusion abnormalities, pulmonary embolism risk, and increased tendency to develop hypoxemia as a result of all these conditions [23-26]. Failure to provide effective drug doses in obese patients, ineffective exercise of care by the personnel due to excessive body weight, and difficulty in prone positions are other challenging physical factors [24, 27, 28]. In a meta-analysis, it was shown that adverse outcomes such as ICU requirement, IMV employment, and in-hospital mortality were approximately twice as high in obese patients with COVID-19 (OR: 1.88; 95% CI: 1.25 - 2.80; $P = 0.002$) [29]. Simonnet et al. [12] reported that obesity increased the risk of IMV in line with its severity; the presence of class II obesity (BMI ≥ 35 kg/m^2) increased this risk by 7 times compared with normal BMI. Lighter et al. [7] reported that younger patients who were obese (BMI 30 kg/m^2) had twice more hospital admissions and 1.8 times higher ICU requirements than non-obese patients in their study, where they classified patients as under 60 and over 60 years of age. They reported that a BMI ≥ 35 kg/m^2 further increased the risk of hospital admissions by 2.2 times and ICU requirement by 3.6 times. Gao et al. [11] showed that the severity of COVID-19 increased by 13% with each unit of increase in BMI. Similar to all these studies, obesity was found to be a significant risk factor in both univariate analysis and multivariate analysis in COVID-19 patients in the present study. In the multivariate analysis, it was shown to lead to an approximately 3-fold increase in risk for transfer to the ICU and a 9-fold increase in risk for IMV, regardless of age, gender, and comorbidity. Social isolation, staying at home, and physical activity limitation, are crucial in reducing COVID-19 transmission, which have been shown to cause significant weight gain and increase in BMI [30]. Since the negative effect of obesity in COVİD-19 infection is recognized, the clinical importance of obesity during pandemic might be the one of the main issue to be considered.

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Different mortality results were defined according to the results of the studies on obesity and COVID-19. In a study by Nakeshband et al. [6], obesity increased the mortality risk by 1.3 times (95% CI: 1.0 - 1.7, $P = 0.04$), while in a study by Moriconi et al. [14], no difference in mortality was found between obese and non-obese patients (16% *vs.* 19%). In our study, 16% of the patients who died were obese, 9% were overweight, and 1% were normal weight, and the difference was significantly higher in favor of obese patients ($P = 0.002$, chi-square trend test).

Studies on inflammatory markers have generally been performed in patients hospitalized with the diagnosis of COVID-19, and laboratory findings such as elevated CRP, LDH, ALT, and AST, decreased albumin, and lymphopenia are non-specific. However, more severely elevated laboratory values have been associated with more severe disease [31]. There are a few studies in the literature that show the relationship between obesity and inflammatory markers in COVID-19. Among these studies, Moriconi et al. [14] reported that they found ferritin, CRP, and TNF-α values to be significantly higher in obese patients compared with non-obese patients with COVID-19. Gao et al. [11] reported that they found lymphopenia and elevated CRP, which are included as predictors for severe disease in the national guidelines, to be more severe in obese patients. In the present study, α-TNF and IL-6 values could not be measured; however, leucocyte, neutrophil, CRP, LDH, ferritin, and procalcitonin values, among other inflammatory markers, were significantly higher in obese patients compared with normal-weight patients. In addition, in our study, a significant increase in neutrophil, LDH, CRP, and ferritin values and a significant decrease in lymphocyte count, lymphocyte percentage, and albumin value were found in the subgroup analysis we performed in obese patients transferred to the ICU. When a correlation analysis was performed between BMI and the aforementioned inflammatory markers, a weak but significant positive relationship was found in all of them except ferritin. Among these markers, CRP showed the highest correlation with BMI. This chronic and low-grade inflammation in obese patients may aggravate the inflammation that develops in COVID-19 patients. In addition, this condition leads to impaired immune response and adverse effects of COVID-19 on lung parenchyma and bronchi in obese patients [18]. Further studies with a higher number of obese patients and inflammatory markers are needed regarding this issue.

The most important limitation of the study is that it is single centered and the sample size is small. Another limitation is that some data are missing due to its retrospective nature. In addition, although BMI that was used for the definition of obesity in the study, is the most common criterion, other anthropometric measurements showing central obesity such as waist/hip ratio are more sensitive measurements for cardiovascular health. Further studies can be performed in the future based on this information. Despite these limitations, to the best of our knowledge, this is the first study in Turkey to investigate the relationship between obesity and COVID-19 and provides important information for clinicians in that it showed the relationship between COVID-19 and obesity.

In our study, overweight and obese patients were found to be more common than normal-weight patients among patients with COVID-19. Comorbidities and inflammatory markers were significantly higher in obese patients than in patients with normal weight. Obesity (BMI ≥ 30 kg/m^2) was identified as an important risk factor both together and independently of age, gender, and comorbidity in admission to the ICU and employment of IMV. Mortality was higher in obese patients than in non-obese patients. In summary, this study showed the clinicians that the obese patient group should be followed more closely in COVID-19. The findings of the study may be re-evaluated with a larger number of patients in the future.

https://doi.org/10.3947/ic.2021.0026

REFERENCES

1. World Health Organization (WHO). Novel coronavirus (2019-nCoV): situation report-11. Available at: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020. Accessed 30 January, 2020.
2. World Health Organization (WHO). Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed 30 January, 2020.
3. Republic of Turkey Ministry: COVID-19 information page. Available at: https://covid19.saglik.gov.tr/?_Dil=2. Accessed 30 January, 2020.
4. Wu Z, McGoogan JM. Characteristics of and Important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239-42.
PUBMED | CROSSREF
5. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020;94:91-5.
PUBMED | CROSSREF
6. Nakeshbandi M, Maini R, Daniel P, Rosengarten S, Parmar P, Wilson C, Kim JM, Oommen A, Mecklenburg M, Salvani J, Joseph MA, Breitman I. The impact of obesity on COVID-19 complications: a retrospective cohort study. Int J Obes (Lond) 2020;44:1832-7.
PUBMED | CROSSREF
7. Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, Stachel A. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. Clin Infect Dis 2020;71:896-7.
PUBMED | CROSSREF
8. Fezeu L, Julia C, Henegar A, Bitu J, Hu FB, Grobbee DE, Kengne AP, Hercberg S, Czernichow S. Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: a systematic review and meta-analysis. Obes Rev 2011;12:653-9.
PUBMED | CROSSREF
9. World Health Organization (WHO). Obesity and overweight. Available at: http:www.who.int/mediacentre/factsheets/fs311/en/. Accessed 30 January, 2020.
10. Cai Q, Chen F, Wang T, Luo F, Liu X, Wu Q, He Q, Wang Z, Liu Y, Liu L, Chen J, Xu L. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. Diabetes Care 2020;43:1392-8.
PUBMED | CROSSREF
11. Gao F, Zheng KI, Wang XB, Sun QF, Pan KH, Wang TY, Chen YP, Targher G, Byrne CD, George J, Zheng MH. Obesity is a risk factor for greater COVID-19 severity. Diabetes Care 2020;43:e72-4.
PUBMED | CROSSREF
12. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, Labreuche J, Mathieu D, Pattou F, Jourdain M; LICORN and the Lille COVID-19 and Obesity study group. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) Requiring invasive mechanical ventilation. Obesity (Silver Spring) 2020l;28:1195-9.
PUBMED | CROSSREF
13. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, Cerfolio RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.
PUBMED | CROSSREF
14. Moriconi D, Masi S, Rebelos E, Virdis A, Manca ML, De Marco S, Taddei S, Nannipieri M. Obesity prolongs the hospital stay in patients affected by COVID-19, and may impact on SARS-COV-2 shedding. Obes Res Clin Pract 2020;14:205-9.
PUBMED | CROSSREF
15. Wu J, Li W, Shi X, Chen Z, Jiang B, Liu J, Wang D, Liu C, Meng Y, Cui L, Yu J, Cao H, Li L. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19). J Intern Med 2020;288:128-38.
PUBMED | CROSSREF
16. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
PUBMED | CROSSREF

17. Republic of Turkey Ministry Public Health. Directorate general of public health. COVID-19 (SARS-CoV-2 infection) guide. Available at: http://www.atuder.org.tr/75/haberler/2372/covid-19-sars-cov2-enfeksiyonu-rehberi-bilim-kurulu-calismasi-t-c-sa. Accessed 11 March 2020.
18. 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.
PUBMED | CROSSREF
19. Ramalingam L, Menikdiwela K, LeMieux M, Dufour JM, Kaur G, Kalupahana N, Moustaid-Moussa N. The renin angiotensin system, oxidative stress and mitochondrial function in obesity and insulin resistance. Biochim Biophys Acta Mol Basis Dis 2017;1863:1106-14.
PUBMED | CROSSREF
20. Kruglikov IL, Scherer PE. The role of adipocytes and adipocyte-like cells in the severity of COVID-19 infections. Obesity (Silver Spring) 2020;28:1187-90.
PUBMED | CROSSREF
21. Sung HK, Kim JY, Heo J, Seo H, Jang YS, Kim H, Koh BR, Jo N, Oh HS, Baek YM, Park KH, Shon JA, Kim MC, Kim JH, Chang HH, Park Y, Kang YM, Lee DH, Oh DH, Park HJ, Song KH, Lee EK, Jeong H, Lee JY, Ko JY, Choi J, Ryu EH, Chung KH, Oh MD; Korea National Committee for Clinical Management of COVID-19. Korea National Committee for clinical management of COVID-19. Clinical course and outcomes of 3,060 patients with coronavirus disease 2019 in Korea, January-May 2020. J Korean Med Sci 2020;35:e280.
PUBMED | CROSSREF
22. León-Pedroza JI, González-Tapia LA, del Olmo-Gil E, Castellanos-Rodríguez D, Escobedo G, González-Chávez A. Inflamación sistémica de grado bajo y su relación con el desarrollo de enfermedades metabólicas: de la evidencia molecular a la aplicación clínica [Low-grade systemic inflammation and the development of metabolic diseases: from the molecular evidence to the clinical practice]. Cir Cir 2015;83:543-51.
PUBMED | CROSSREF
23. Martí A, Marcos A, Martínez JA. Obesity and immune function relationships. Obes Rev 2001;2:131-40.
PUBMED | CROSSREF
24. Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. Int J Obes (Lond) 2013;37:333-40.
PUBMED | CROSSREF
25. Walsh JS, Bowles S, Evans AL. Vitamin D in obesity. Curr Opin Endocrinol Diabetes Obes 2017;24:389-94.
PUBMED | CROSSREF
26. Ashburn DD, DeAntonio A, Reed MJ. Pulmonary system and obesity. Crit Care Clin 2010;26:597-602.
PUBMED | CROSSREF
27. Neidich SD, Green WD, Rebeles J, Karlsson EA, Schultz-Cherry S, Noah TL, Chakladar S, Hudgens MG, Weir SS, Beck MA. Increased risk of influenza among vaccinated adults who are obese. Int J Obes 2017;41:1324-30.
PUBMED | CROSSREF
28. Ryan DH, Ravussin E, Heymsfield S. COVID 19 and the Patient with Obesity - The Editors Speak Out. Obesity (Silver Spring) 2020;28:847.
PUBMED | CROSSREF
29. Malik P, Patel U, Patel K, Martin M, Shah C, Mehta D, Malik FA, Sharma A. Obesity a predictor of outcomes of COVID-19 hospitalized patients-A systematic review and meta-analysis. J Med Virol 2021;93:1188-93.
PUBMED | CROSSREF
30. Kang HM, Jeong DC, Suh BK, Ahn MB. The impact of the coronavirus disease-2019 pandemic on childhood obesity and vitamin D status. J Korean Med Sci 2021;36:e21.
PUBMED | CROSSREF
31. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020;324:782-93.
PUBMED | CROSSREF