






Is obesity paradox valid for critically-ill COVID-19 patients with respiratory failure?

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Abstract

OBJECTIVE: We aimed to analyze the association between body mass index and mortality in patients with coronavirus disease 2019 induced acute respiratory distress syndrome.

MATERIAL AND METHODS: In this retrospective cohort study, we analyzed 108 consecutive patients admitted in the intensive care unit for coronavirus disease 2019-induced lung disease in a single center between March 2020 and February 2021. Coronavirus disease 2019 infection was confirmed by real-time reverse transcription-polymerase chain reaction assay of nasal swabs or lower respiratory tract samples. Acute respiratory distress syndrome was defined using Berlin criteria. Acute respiratory distress syndrome severity was assessed with partial pressure of arterial oxygen/fraction of inspired oxygen ratio. We categorized patients according to the body mass index as underweight, <18.5 kg/m²; normal weight, from 18.5 kg/m² to <25 kg/m²; overweight, from 25 kg/m² to <30 kg/m²; obese, ≥30 kg/m². Clinical characteristics and mortality were compared among groups. Demographic and clinical data were collected from electronic medical records of the hospital system.

RESULTS: The mean age was 67.3 ± 13.3 years. Study participants were predominantly males (66.7%). The mean BMI was 28.2 ± 5.6 kg/m². There were 2 patients (2%), 28 (26%), 42 (39%), and 36 patients (33%) in the underweight, normal-weight, overweight, and obese groups, respectively. The hospital mortality was 40.7%. There was no association between body mass index and mortality (*P* = .09). In multivariate analysis, mortality was associated with the presence of cancer [odds ratio = 7.338 (1.636-32.914), *P* = .009], and time between diagnosis and intubation [odds ratio = 1.318 (1.150-1.509), *P* ≤ .001].

CONCLUSION: Neither acute respiratory distress syndrome severity nor mortality was higher in patients with higher body mass index compared to the ones with normal body mass index.

KEYWORDS: Body mass index, acute respiratory distress syndrome, COVID-19, obesity paradox, mortality

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2), was first detected in Wuhan at the end of December 2019. It has spread rapidly worldwide and soon became a pandemic. To date over 266 million cases of COVID-19 have been reported worldwide with approximately 5.2 million deaths.¹ Turkey was the sixth most affected country in the world.¹

Coronavirus disease 2019 infection may be asymptomatic or causes mild symptoms in the majority of the cases, while bilateral viral pneumonia, acute respiratory distress syndrome (ARDS), cardiac and kidney injury, hypercoagulation, and multiple organ failure may also occur in some patients.² ARDS is a type of respiratory failure characterized by acute onset of diffuse inflammation in the lungs that leads to increased pulmonary vascular permeability, increased lung weight, loss of aerated tissue, and usually the result of infectious or chemical injury. Although lung-protective mechanical ventilation strategies and rescue manoeuvres like prone positioning and neuromuscular blocker agents are applied, the mortality rate of ARDS patients is still around 30-40%.³

Risk factors related to mortality in patients with COVID-19 are age, gender, diabetes mellitus (DM), cardiovascular, pulmonary, and cerebrovascular diseases.⁴⁻⁵ On the other hand, several studies reported that a higher body mass index (BMI) is a risk factor for severe disease in patients with COVID-19.^{6,7} In the USA, it was reported that at least 25% of adults in the intensive care unit (ICU) were overweight, obese, or morbidly obese.⁸ There is conflicting data in the literature, with regards to mortality among critically ill obese patients with ARDS. Some authors have demonstrated that higher BMI was associated with a lower mortality rate in patients with ARDS⁹ and have described this situation as the obesity survival paradox.⁹ It is not clear whether the obesity paradox is true in patients with COVID-19 infection.

In this study, we aimed to find out whether BMI plays a role in the prognosis of COVID-19 related ARDS and whether the mortality is decreased as suggested in cases of ARDS developing due to other conditions in patients with obesity.

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MATERIAL AND METHODS

In this retrospective single-center cohort study, we enrolled consecutive patients over 18 years of age admitted to ICU for COVID-19-induced ARDS between March 15, 2020, and February 15, 2021. Acute respiratory distress syndrome was defined using Berlin criteria; timing (the onset of symptoms within 1 week), chest imaging (presence of bilateral infiltrates), origin of edema (no suspicion of congestive heart failure), and hypoxemia (acute onset of hypoxemia; the ratio of partial pressure of arterial oxygen (PaO₂) to fraction of inspired oxygen (FiO₂) <300 mmHg.¹⁰

Severe acute respiratory syndrome coronavirus-2 infection was confirmed by real-time reverse transcriptase-polymerase chain reaction assay of nasal swabs or lower respiratory tract samples. All of the patients underwent computed tomography imaging of the chest before admission to ICU and, they had typical findings compatible with COVID-19 pneumonia. There were 108 hospitalized patients during that period of time. The institutional ethics review board approved this study (Ethical approval number 2020.371.IRB1.148 with a date of October 27, 2020).

Follow-up data collection was obtained from hospital records. The data of the patients included the following: age, sex, BMI [(recorded weight and height at ICU admission were used to calculate the BMI. Body mass index: ratio of body weight to squared height (kg/m²)], smoking history (non-smokers, current smokers), medical comorbidities (DM, hypertension, hyperlipidemia, cancer, chronic liver disease, chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m²),¹¹ lung disease, coronary artery disease, prior medication use (angiotensin-converting enzyme inhibitor, angiotensin II type-1 receptor blocker and statin), onset of symptoms (day), mode of respiratory support (invasive mechanical ventilation, non-invasive mechanical ventilation), time between diagnosis and intubation (day), days of intubation, severity of ARDS (it was classified by the worst PaO₂/FiO₂ ratio, PaO₂/FiO₂ ratio 200-300 was classified as mild ARDS, 100-200 as moderate ARDS, and <100 as severe ARDS¹⁰), use of vasopressors/interleukin antagonists, prone positioning, complications during ICU stay (acute kidney injury, hepatic failure), need for tracheostomy, ICU length of stay, hospital length of stay and hospital mortality. We categorized BMI according to the definition of the National

Institutes of Health Guideline in 1998 (underweight BMI, <18.5 kg/m²; normal BMI, 18.5 kg/m² to <25 kg/m²; overweight BMI, 25 kg/m² to <30 kg/m²; obese BMI, 30 kg/m² to <40 kg/m²; severe obese BMI, ≥40 kg/m²).¹²

Statistical Analysis

Statistical Package for Social Sciences 24.0 (IBM SPSS Corp.; Armonk, NY, USA) package program was used for data analysis. Descriptive analyzes of dependent and independent variables were performed using frequency, percentage, median and interquartile range for skewed distribution, and mean and standard deviation for normally distributed variables. Compliance of quantitative data to normal distribution was evaluated by Kolmogorov–Smirnov, Shapiro–Wilk test, and graphical evaluations. Non-normal distributed variables were evaluated with the help of non-parametric tests. A chi-square test was applied for the non-comparison of categorical data. Mann–Whitney *U* test was used for the significance of the difference between the 2 mean values in the comparison of the mean values. Kruskal–Wallis test was used to determine for differences between normal, overweight, and obese groups. Post hoc analyzes were evaluated using the Tamhane test. A post hoc power analysis was conducted using the software package, G-Power 3.1. The sample size of 108 was used for the statistical power analyses and the effect of different BMI levels on mortality and ARDS severity was evaluated as the primary outcome. The post hoc analyzes revealed that the statistical power for this study was 0.14 for detecting a small effect, 0.80 for detecting a medium effect, and 0.99 for detecting a large effect. There was more than adequate power at the medium to larger effect size level. Logistic regression analysis was performed to determine the predictors of mortality. Correlation analysis was done by Spearman or Pearson test where appropriate. The level of statistical significance was defined as a *P* < .05.

RESULTS

A total of 108 patients were admitted in ICU for COVID-19 related lung injury during the study period. The mean age was 67.3 ± 13.3 years. Study participants were predominantly males (*n* = 72, 66.7%). The mean BMI was 28.2 ± 5.6 kg/m². There were 2 patients (2%), 28 (26%), 42 (39%), and 36 patients (33%) in the underweight, normal-weight, overweight, and obese group, respectively. The most prevalent comorbidities were hypertension, DM, chronic renal disease (CRD), coronary artery disease (CAD), cancer (predominantly lung and hematologic malignancy), and chronic obstructive pulmonary disease (COPD). Thirteen percent of patients had no comorbidities, 25% had one, 25% had 2, and 37% had 3 or more comorbidities. Eighty-nine patients (82.4%) received non-invasive mechanical ventilation, of which 68 (63%) had non-invasive mechanical ventilation failure and subsequently were intubated. Near 54% of the subjects had severe ARDS. Fifty-six patients (51.9%) with severe ARDS underwent prone positioning for at least 16 hours. Of 108 patients, 26 (20.3%) developed acute kidney injury and 9 (8.3%) had a liver injury during ICU stay. At the time of analysis, 63 (58.3%) patients were discharged alive from the hospital, 44 (40.7%) patients died, and 1 patient is still in ICU with a tracheostomy performed. Clinical characteristics were detailed in Table 1.

MAIN POINTS

- Patients admitted to the intensive care unit (ICU) had moderate to severe acute respiratory distress syndrome.
- The majority of the patients admitted to the ICU consisted of overweight and obese patients.
- The hospital mortality was 40.7%.
- There was no association between body mass index and mortality.
- Presence of cancer and the time between diagnosis and intubation were independent predictors of hospital mortality.

Table 1. Baseline Clinical Characteristics of the Whole Study Population

| Parameters | All patients (n = 108) |
|--|------------------------|
| Age, year, (mean ± SD) | 67.3 ± 13.3 |
| Sex, n (%) | |
| Male | 72 (66.7) |
| Female | 36 (33.3) |
| BMI (kg/m²), (mean ± SD) | 28.2±5.6 |
| BMI (kg/m²), n (%) | |
| Underweight, <18.5 | 2 (1.9) |
| Normal, 18.5-24.9 | 28 (25.9) |
| Overweight, 25-29.9 | 42 (38.9) |
| Obese, ≥ 30-39.9 | 31 (28.7) |
| Severe obese, ≥ 40 | 5 (4.6) |
| Smoking history, n (%) | |
| Present | 4 (3.7) |
| Absent | 88 (81.5) |
| Unknown | 16 (14.8) |
| Comorbid conditions, n (%) | |
| Hypertension | 61 (56.5) |
| DM | 41 (38) |
| CRD | 36 (33.3) |
| CAD | 26 (24) |
| Cancer | 19 (17.6) |
| COPD | 13 (12) |
| Hyperlipidemia | 8 (7.4) |
| Number of comorbid conditions, n (%) | |
| None | 14 (13) |
| 1 | 27 (25) |
| 2 | 27 (25) |
| ≥3 | 40 (37) |
| Prior medications, n (%) | |
| ACE inhibitors | 7 (6.5) |
| ARBs | 10 (9.3) |
| Statins | 11 (10.2) |
| Symptom onset (day), (mean±SD) | 5.0±3.2 |
| IMV, n (%) | 68 (63) |
| Non-IMV, n (%) | 89 (82.4) |
| Time between diagnosis and intubation (day), median (IQR) | 1 (7) |
| Duration of IMV (day), median (IQR) | 5 (15) |
| Duration of Non-IMV (day), median (IQR) | 3 (6) |
| ARDS severity, n (%) | |
| Mild | 12 (11.1) |
| Moderate | 38 (35.2) |
| Severe | 58 (53.7) |
| Therapies, n (%) | |
| Vasopressor | 61 (56.5) |
| Tocilizumab | 41 (38.0) |
| Prone positioning | 56 (51.9) |
| Patients with tracheostomy, n (%) | 12 (11.1) |
| Length of stay in the ICU (day), (mean±SD) | 15.2±12.6 |
| Total hospital length of stay (day), (mean±SD) | 23.0±14.4 |
| Outcome, n (%) | |
| Discharged from hospital | 64 (59.3) |
| Death | 44 (40.7) |

BMI, body mass index; DM, diabetes mellitus; CRD, chronic renal disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ARB, angiotensin II type-1 receptor blocker IMV, invasive mechanical ventilation; IQR, interquartile range; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

When patients were classified according to the severity of ARDS (as shown in Table 2), invasive mechanical ventilation (IMV) requirement was higher ($P < .001$), the median timing of intubation (day) ($P = .001$), and the median duration of IMV day ($P = .001$) were longer in severe ARDS group. Vasopressor ($P = .04$), tocilizumab ($P = .04$), and prone positioning ($P < .001$) were used higher in those developed severe ARDS. The median duration of ICU length of stay ($P < .001$) was longer, and deaths ($P = .007$) were higher in the severe ARDS

group compared to the others. Furthermore, we analyzed the correlation between BMI and PaO₂/FiO₂ ratio, but we found no significant correlation ($r = 0.056$, $P = .56$).

The patients were categorized into 3 groups based on BMI (group 1: ≤ 24.9 kg/m², group 2: 25-29.9 kg/m², and group 3: ≥ 30 kg/m²). Cancer was higher in group 1 than in group 2 and group 3 ($P = .02$). Hypertension and CRD were the highest in group 3 ($P = .003$, $P = .05$, respectively). Compared

Table 2. Comparison of the clinical characteristics of patients according to ARDS severity

| Parameters | Mild (n = 12) | Moderate (n = 38) | Severe (n = 58) | P |
|---|---------------|-------------------|-----------------|---------|
| Age, year, median (IQR) | 67 (17) | 71 (22) | 68 (17) | .71* |
| Sex, n (%) | | | | |
| Male | 6 (50) | 22 (57.9) | 44 (75.9) | .81** |
| Female | 6 (50) | 16 (42.1) | 14 (24.1) | |
| BMI kg/m ² , median (IQR) | 28.6 (10.7) | 26.8 (6.7) | 28.6 (6.4) | .27* |
| BMI (kg/m ²), n (%) | | | | |
| Underweight, <18.5 | 1 (8.3) | 1 (2.6) | 0 (0) | |
| Normal, 18.5-24.9 | 1 (8.3) | 12 (31.6) | 15 (25.9) | .31** |
| Overweight, 25-29.9 | 5 (41.7) | 14 (36.8) | 23 (39.7) | |
| Obese, ≥ 30 -39.9 | 4 (33.3) | 8 (21.1) | 19 (32.8) | |
| Severe obese, ≥ 40 | 1 (8.3) | 3 (7.9) | 1 (1.7) | |
| Comorbid conditions, n (%) | | | | |
| Yes | 12 (100) | 33 (86.8) | 49 (84.5) | .34** |
| None | 0 (0) | 5 (13.2) | 9 (15.5) | |
| Hypertension | 8 (66.7) | 22 (57.9) | 31 (53.4) | .68** |
| DM | 5 (41.7) | 15 (39.5) | 21 (36.2) | .91** |
| CRD | 5 (41.7) | 12 (31.6) | 19 (32.8) | .80** |
| CAD | 1 (8.3) | 12 (31.6) | 13 (22.4) | .23** |
| Cancer | 5 (41.7) | 4 (10.5) | 10 (17.2) | .04** |
| COPD | 1 (8.3) | 5 (13.2) | 7 (12.1) | .90** |
| Hyperlipidemia | 0 (0) | 2 (5.3) | 6 (10.3) | .37** |
| Number of comorbid conditions, n (%) | | | | |
| None | 0 (0) | 5 (13.2) | 9 (15.5) | .34** |
| 1 | 3 (25) | 8 (24.2) | 16 (32.7) | |
| 2 | 5 (41.7) | 8 (24.2) | 14 (28.6) | .64** |
| ≥ 3 | 4 (33.3) | 17 (51.5) | 19 (38.8) | |
| Symptom onset (day), median (IQR) | 3 (7) | 4.5 (5) | 4.5 (5) | .81* |
| IMV, n (%) | 7 (58.3) | 15 (39.5) | 46 (79.3) | <.001** |
| Non-IMV, n (%) | 9 (75) | 31 (81.6) | 49 (84.5) | .72** |
| Time between diagnosis and intubation (day), median (IQR) | 1 (4) | 1 (4) | 5 (8) | .001* |
| Duration of IMV (day), median (IQR) | 2.5 (11) | 1 (7) | 8.5 (16) | .001* |
| Duration of Non-IMV (day), median (IQR) | 1.5 (4) | 4 (6) | 3 (7) | .18* |
| Therapies, n (%) | | | | |
| Vasopressor | 6 (50) | 16 (42.1) | 39 (67.2) | .04** |
| Tocilizumab | 2 (16.7) | 11 (28.9) | 28 (48.3) | .04** |
| Prone positioning | 1 (8.3) | 1 (2.6) | 54 (93.1) | <.001** |
| ICU length of stay (day), median (IQR) | 6.5 (9) | 8 (9) | 16.5 (18) | <.001* |
| Total hospital length of stay (day), median (IQR) | 12 (16) | 20.5 (10) | 23 (17) | .04* |
| Outcome, n (%) | | | | |
| Death | 5 (41.7) | 8 (21.1) | 31 (53.4) | .007** |
| Discharged from hospital | 7 (58.3) | 30 (78.9) | 27 (46.6) | |

*Kruskal–Wallis test.

**Chi-square test.

ARDS, acute respiratory distress syndrome; IQR, interquartile range; BMI, body mass index; DM, diabetes mellitus; CRD, chronic renal disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IMV, invasive mechanical ventilation; ICU, intensive care unit.

with other groups, group 2 was more likely to receive tocilizumab ($P = .001$). There was no significant difference among the groups in terms of mortality ($P = .09$), although seemed to be lower in the overweight group compared to the obese and normal-weight groups. The comparison of clinical parameters of groups is shown in Table 3.

In Table 4, we compared the patients based on mortality (survivors and non-survivors). The non-survivor group was older than the survivor group ($P = .009$). In non-survivors, the incidence of severe ARDS was higher than in survivors

($P = .007$). The lowest mortality rate was found in patients without comorbid conditions, and the highest mortality was found in patients with ≥ 3 comorbid conditions ($P = .01$).

Multivariate analysis conducted taking mortality as the dependent variable and the age, gender, BMI, presence of comorbidities (hypertension, DM, HL, COPD, and cancer), time between diagnosis and intubation revealed only cancer [OR = 7.338 (1.636-32.914), $P = .009$], and time between diagnosis and intubation [OR = 1.318 (1.150-1.509), $P \leq .001$] to be related to increased risk of mortality.

Table 3. Comparison of the clinical characteristics of patients according to their BMI

| Parameters | Group 1 (n = 30) (≤ 24.9 kg/m ²) | Group 2 (n = 42) (25-29.9 kg/m ²) | Group 3 (n = 36) (≥ 30 kg/m ²) | P |
|---|---|--|---|--------|
| Age, year, median (IQR) | 70.5 (15) | 68 (18) | 68 (19) | .79* |
| Sex, n (%) | | | | |
| Male | 19 (63.3) | 33 (78.6) | 20 (55.6) | .08** |
| Female | 11 (36.7) | 9 (21.4) | 16 (44.4) | |
| Comorbid conditions, n (%) | | | | |
| Hypertension | 10 (33.3) | 24 (57.1) | 27 (75.0) | .003* |
| DM | 10 (33.3) | 13 (31.0) | 18 (50.0) | .18** |
| CRD | 10 (33.3) | 9 (21.4) | 17 (47.2) | .05** |
| CAD | 5 (16.7) | 12 (28.6) | 9 (25.0) | .50** |
| Cancer | 10 (33.3) | 4 (9.5) | 5 (13.9) | .02** |
| COPD | 3 (10.0) | 8 (19.0) | 2 (5.6) | .17** |
| Hyperlipidemia | 3 (10.0) | 2 (4.8) | 3 (8.3) | .68** |
| Number of comorbid conditions, n (%) | | | | |
| None | 5 (16.7) | 6 (14.3) | 3 (8.3) | |
| 1 | 6 (20.0) | 13 (31.0) | 8 (22.0) | .58** |
| 2 | 10 (33.3) | 9 (21.4) | 8 (22.0) | |
| ≥ 3 | 9 (30.0) | 14 (33.3) | 17 (47.2) | |
| Symptom onset (day), median (IQR) | 3 (5) | 5.5 (5) | 4 (6) | .57* |
| IMV, n (%) | 19 (63.3) | 26 (61.9) | 23 (63.9) | .98** |
| Non-IMV, n (%) | 21 (70.0) | 39 (92.9) | 29 (80.6) | .40** |
| Time between diagnosis and intubation (day), median (IQR) | 1 (7) | 2 (8) | 1 (6) | 0.90* |
| Duration of IMV (day), median (IQR) | 3.5 (15) | 7 (15) | 6.5 (16) | .83* |
| Duration of Non-IMV (day), median (IQR) | 3 (7) | 4 (7) | 3.5 (6) | .54* |
| ARDS severity, n (%) | | | | |
| Mild | 2 (6.7) | 5 (11.9) | 5 (13.9) | .78** |
| Moderate | 13 (43.3) | 14 (33.3) | 11 (30.6) | |
| Severe | 15 (50.0) | 23 (54.8) | 20 (55.6) | |
| Therapies, n (%) | | | | |
| Vasopressor | 18 (60.0) | 21 (50.0) | 22 (61.1) | .55** |
| Tocilizumab | 7 (23.3) | 25 (59.5) | 9 (25.0) | .001** |
| Prone positioning | 14 (46.7) | 22 (52.4) | 20 (55.6) | .76** |
| ICU length of stay (day), median (IQR) | 11 (17) | 10.5 (15) | 14.5 (14) | .64* |
| Total hospital length of stay (day), median (IQR) | 18 (23) | 21 (15) | 20 (11) | .53* |
| Outcome, n (%) | | | | |
| Death | 13 (43.3) | 12 (28.6) | 19 (52.8) | .09** |
| Discharged from hospital | 17 (56.7) | 30 (71.4) | 17 (47.2) | |

*Kruskal-Wallis test.

**Chi-square test.

BMI, body mass index; IQR, interquartile range; DM, diabetes mellitus; CRD, chronic renal disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IMV, invasive mechanical ventilation; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Table 4. Comparison of Clinical Features of Patients According to the Hospital Mortality

| Parameters | Non-survivors (n = 44) | Survivors (n = 64) | P |
|--|------------------------|--------------------|-------------------|
| Age, year, median (IQR) | 70 (16) | 65.5 (20) | .009* |
| Sex, n (%) | | | |
| Male | 29 (65.9) | 43 (67.2) | .89** |
| Female | 15 (34.1) | 21 (32.8) | |
| BMI kg/m², median (IQR) | 28.2 (7) | 27.8 (5.8) | .71* |
| BMI (kg/m²), n (%) | | | |
| Underweight, <18.5 | 1 (2.3) | 1 (1.6) | |
| Normal, 18.5-24.9 | 12 (27.3) | 16 (25) | |
| Overweight, 25-29.9 | 12 (27.3) | 30 (46.9) | .26** |
| Obese, ≥ 30-39.9 | 17 (38.6) | 14 (21.9) | |
| Severe obese, ≥ 40 | 2 (4.5) | 3 (4.7) | |
| Comorbid conditions, n (%) | | | |
| Yes | 42 (95.5) | 52 (81.3) | .03** |
| None | 2 (4.5) | 12 (18.8) | |
| Hypertension | 28 (63.6) | 33 (51.6) | .20** |
| DM | 18 (40.9) | 23 (35.9) | .60** |
| CRD | 22 (48.9) | 14 (22.2) | .004** |
| CAD | 13 (29.5) | 13 (20.3) | .10** |
| Cancer | 12 (27.3) | 7 (10.9) | .02** |
| COPD | 7 (15.9) | 6 (9.4) | .30** |
| Hyperlipidemia | 5 (11.4) | 3 (4.7) | .19** |
| Number of comorbid conditions, n (%) | | | |
| None | 2 (4.5) | 12 (18.8) | |
| 1 | 7 (15.9) | 20 (31.3) | |
| 2 | 14 (31.8) | 13 (20.3) | .01** |
| ≥3 | 21 (47.7) | 19 (29.7) | |
| Symptom onset (day), median (IQR) | 4.3 (1) | 4.5 (5) | .60* |
| IMV, n (%) | 40 (90.9) | 28 (43.8) | <.001** |
| Non-IMV, n (%) | 31 (70.5) | 58 (90.6) | .007** |
| Time between diagnosis and intubation (day), median (IQR) | 6 (9) | 1 (3) | <.001* |
| Duration of IMV (day), median (IQR) | 11.5 (16) | 1 (9) | <.001* |
| Duration of Non-IMV (day), median (IQR) | 1 (5) | 4 (6) | .004* |
| ARDS severity, n (%) | | | |
| Mild | 5 (11.4) | 7 (10.9) | |
| Moderate | 8 (18.2) | 30 (46.9) | .007** |
| Severe | 31 (70.5) | 27 (42.2) | |
| Therapies, n (%) | | | |
| Vasopressor | 39 (88.6) | 22 (34.4) | <.001** |
| Tocilizumab | 11 (25) | 30 (46.9) | .02** |
| Prone positioning | 29 (65.9) | 27 (42.2) | .01** |
| ICU length of stay (day), median (IQR) | 15.5 (20) | 10 (12) | .27* |
| Total hospital length of stay (day), median (IQR) | 20 (21) | 21 (11) | .41* |

*Mann-Whitney *U* test.

**Chi-square test.

IQR, interquartile range; BMI, body mass index; DM, diabetes mellitus; CRD, chronic renal disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IMV, invasive mechanical ventilation; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

The presence of cancer increased the risk 7 times, and the time between diagnosis and intubation increased the risk by approximately 1.5 times. Multivariate analyses of mortality are shown in Table 5.

DISCUSSION

The difference between this present study from others evaluating the role of obesity on mortality is that it focused on

critically ill patients with ARDS. Our study found that most of our patients admitted to the ICU had moderate to severe ARDS. The frequency of overweight and obesity was 39% and 33%, respectively. However, neither ARDS severity nor mortality was increased in patients with higher BMI compared to the ones with normal BMI. The presence of cancer and the time between diagnosis and intubation were independent predictors of hospital mortality.

Table 5. Multivariate LR Analysis of Prediction of Mortality

| | Multivariate LR OR (95% CI) P |
|---------------------------------------|----------------------------------|
| Age | 1.044 (0.998-1.092).06 |
| Gender | 0.753 (0.255-2.219) .60 |
| BMI | 1.036 (0.937-1.146) .49 |
| Hypertension | 0.881 (0.274-2.834) .83 |
| DM | 0.846 (0.279-2.568) .76 |
| CRD | 0.885 (0.024-32.00) .94 |
| CAD | 1.303 (0.346-4.915) .69 |
| Cancer | 7.338 (1.636-32.914) .009 |
| COPD | 1.069 (0.237-4.818) .93 |
| Hyperlipidemia | 1.167 (0.107-12.683) .89 |
| Time between diagnosis and intubation | 1.318 (1.150-1.509) <.001 |
| Tocilizumab | 2.028 (0.675-6.090) .20 |

OR, odds ratio; BMI, body mass index; DM, diabetes mellitus; CRD, chronic renal disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease.

Obesity was associated with an increased risk for death or critical illness from COVID-19 infection.¹³ Coronavirus disease 2019 patients with obesity had a significantly higher risk for ICU admission.^{14,15} A study found that BMI was significantly higher in patients with COVID-19 related ARDS compared with other ARDS patients.¹⁶ In the other study of 280 patients in China showed that patients with severe COVID-19 disease had significantly higher mean BMI (25.8 kg/m²) than those with mild disease (23.6 kg/m²).⁸ The suggested mechanisms for COVID-19 infection being more severe in people with obesity are multiple; alteration of the mechanics of the lungs and chest wall,¹⁷ presence of comorbid diseases,^{3,8} and impaired immunological responses.¹⁸ Abdominal obesity is also associated with impaired ventilation of the lungs. The altered dynamics of pulmonary ventilation with decreased diaphragmatic excursion and a relative increase in anatomical dead space may be associated with the increased incidence of severe COVID-19 disease in patients with obesity.¹⁹ The frequency of overweight and obese patients was higher compared to under-weight and normal-weight patients in this present study. Furthermore, more than half of our patients admitted to the ICU had severe ARDS. Our results were similar to the aforementioned studies.

The mortality rates among patients with COVID-19 disease requiring ICU admission were reported to be 16%²⁰ and 78%³ in Wuhan, 26% in the Italian cohort,²¹ and 52.4% in Washington State.²² Among ARDS patients, mortality was 35-46%.²³ The hospital mortality was found 40.7% in this present study. These different mortality rates may be associated with a different organization of healthcare systems worldwide, as well as the heterogeneity in the study populations might explain these differences.

Some studies have previously reported that obesity was associated with lower mortality in patients with ARDS,²⁴ or

others showed no association^{25,26} between excess weight and outcomes in lung injury due to different reasons. Although obesity is a risk factor for several chronic diseases, recent studies have suggested that in some obese adults, survival is paradoxically better compared to individuals of normal weight.^{27,28} This phenomenon has been termed as "obesity paradox." Recently, a meta-analysis reported that COVID-19 patients with obesity had a higher risk for hospitalization, ICU admission, and need for IMV. However, obesity was not associated with an increased risk for death, which was probably due to the obesity survival paradox.²⁹ There are several reasons for the reduction of mortality in obese or overweight patients. First, increased adipose tissue is associated with increased renin-angiotensin system activity. This increased activity leads to hypertension, which could have protective hemodynamic effects in septic patients and reduced fluid or vasopressor requirement.³⁰ Second, excess adipose reserves may provide increased beneficial energy stores during the catabolic septic state.³¹ Third, higher concentration of several pro-inflammatory cytokines such as TNF-alpha and IL-6, mainly produced by visceral and subcutaneous adipose tissue, characterize a chronic low-grade inflammation which leads to a defect in the innate immunity. When an antigen is presented in such an environment, reduced antigen response, reduced function of macrophages, natural killer cells, dendritic cells, and blunted pro-inflammatory cytokine production occur.^{18,32} Thus, the presence of chronic pro-inflammatory status in obesity may prevent the detrimental effects of a more aggressive second hit.³³ Lastly, obese individuals receive better medical treatment (statin and heparin prophylaxis) which could have a favorable impact on outcomes.^{4,34} Although very few patients used statins, all our study population was received low molecular weight heparin prophylaxis.

In our study, we did not find a significant relationship between BMI and mortality, at least mortality was not increased in patients with obesity. Moreover, it seemed to be lower in the overweight group compared to the obese and normal-weight groups. Thus, we might think that this result is due to a possible obesity paradox in these COVID patients as well. Additionally, higher use of tocilizumab therapy may also be another reason for the low mortality rate in overweight patients. Larger studies are needed to evaluate the obesity-ARDS paradox in critically ill patients with ARDS due to COVID-19.

On the other hand, it has also been shown that the type of obesity may also have different effects; central obesity was demonstrated to be a risk factor for mortality even among individuals with a normal BMI.³⁵ Thus, if we had determined the waist circumference, it might have provided a different association for mortality. Smoking depresses pulmonary immune function and is a risk factor for the progression of COVID-19 infection.³⁶ However, the majority of our patients were not smoking, which could be associated with better outcomes.

It is well known that obesity increases the risk of chronic disease. Obesity-associated comorbidities such as DM, hypertension, CAD, pro-inflammatory respiratory diseases,³ different

types of cancer,³ and CRD^{3,37} were risk factors for severe COVID-19 disease. Previous studies reported that obesity was associated with an increased risk of CRD^{23,24} and hypertension.^{38,39} Our results were found to be consistent with the literature.

In the present study, the presence of 3 or more comorbidities was significantly higher in non-survivor patients. Additionally, it was observed that patients with cancer and CRD had a worse prognosis. Similar to our study, a multicenter nationwide study showed that COVID-19 patients with CRDs had significantly higher mortality than patients without kidney disease.⁴⁰ Liang et al found that patients with cancer were at increased risk of SARS-CoV-2 infection and poorer outcomes like our study.⁴¹

The other risk factors for mortality in patients with COVID-19 related ARDS, such as increasing age,⁴² and male sex⁴³ were reported in studies. Although nearly 70% of our study cohort was men, there was no relationship between mortality and the male gender. However, age seemed to be a factor affecting increased mortality.

On the other hand, we found that time-to-intubation was associated with increased hospital mortality in patients with ARDS by SARS-CoV-2 infection. Invasive mechanical ventilation support was delayed in the early phase of the pandemic to high demand for ICU beds. Additionally, some authors claimed to use a more conservative approach. They tried noninvasive methods to prevent worse outcomes.⁴⁴ Vera et al.⁴⁵ found that COVID-19 patients intubated late (after 48 h from hospital admission) had increased mortality. However, the other study including 231 ICU patients found no difference between the timing of intubation and mortality.⁴⁶ During the admission of the patient to this present study, IMV was postponed in our ICU due to bed shortage and the prevention of worse outcomes. However, based on the results of our study, late intubation timing was associated with increased hospital mortality. Further studies are needed to decide the best time for intubation.

Obesity has recently been reported as a risk factor for disease severity and mortality from COVID-19 infection in studies from numerous different countries, such as the United States,^{9,13} China^{7,8,15} Italy,¹⁶ France,²⁴ and United Kingdom.⁴⁷ We think that our study will contribute to the literature from Turkey on this subject.

Our study has several limitations. First, this is a single-center study with a small number of patients with a retrospective design. Second, we could not compare to demographic parameters and outcomes of COVID-19 versus non-COVID-19 ARDS. Third, we could not take into account waist circumference measurement as well as BMI in the definition of obesity. Patients with a high percentage of abdominal fat distribution might be in the normal-weight group.

CONCLUSION

Our study found that most of our patients admitted to the ICU had moderate to severe ARDS. Furthermore, compared with normal-weight patients, overweight and obese patients were found to be more common among ARDS patients, but neither

the severity of ARDS nor the mortality was higher compared to the normal-weight population. Studies with larger populations should be planned to clarify the ARDS obesity paradox for COVID-19 infection.

Ethics Committee Approval: This study was approved by Ethics committee of Koç University (Approval Number: 2020.371.IRB1.148).

Informed Consent: The study was conducted with an Institutional Review Board-approved waiver of informed consent.

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