ARTICLE

Clinical Research

Obesity and mortality in critically ill COVID-19 patients with respiratory failure

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Abstract

Background Patients with obesity are at increased risk of severe COVID-19, requiring mechanical ventilation due to acute respiratory failure. However, conflicting data are obtained for intensive care unit (ICU) mortality.
Objective To analyze the relationship between obesity and in-hospital mortality of ICU patients with COVID-19.
Subjects/methods Patients admitted to the ICU for COVID-19 acute respiratory distress syndrome (ARDS) were included retrospectively. The following data were collected: comorbidities, body mass index (BMI), the severity of ARDS assessed with PaO_2/FiO_2 (P/F) ratios, disease severity measured by the Simplified Acute Physiology Score II (SAPS II), management and outcomes.
Results For a total of 222 patients, there were 34 patients (15.3%) with normal BMI, 92 patients (41.4%) who were overweight, 80 patients (36%) with moderate obesity (BMI:30–39.9 kg/m^2), and 16 patients (7.2%) with severe obesity (BMI ≥ 40 kg/m^2). Overall in-hospital mortality was 20.3%. Patients with moderate obesity had a lower mortality rate (13.8%) than patients with normal weight, overweight or severe obesity (17.6%, 21.7%, and 50%, respectively; $P = 0.011$. Logistic regression showed that patients with a BMI ≤ 29 kg/m^2 (odds ratio [OR] 3.64, 95% CI 1.38–9.60) and those with a BMI > 39 kg/m^2 (OR 10.04, 95% CI 2.45–41.09) had a higher risk of mortality than those with a BMI from 29 to 39 kg/m^2. The number of comorbidities (≥2), SAPS II score, and P/F < 100 mmHg were also independent predictors for in-hospital mortality.
Conclusions COVID-19 patients admitted to the ICU with moderate obesity had a lower risk of death than the other patients, suggesting a possible obesity paradox.

Introduction

The disproportionate impact of COVID-19 on patients with obesity is now well established [1–5]. Several observational studies have clearly demonstrated that obesity leads to the severe form of COVID-19, and is associated with a greater risk of advanced levels of treatment such as admission to intensive or critical care, invasive mechanical ventilation, and death [3, 5–19]. The association between BMI and in-hospital mortality has been explored in hospitalized patients with COVID-19. Overall, the results are conflicting. Some studies reported that obesity has no effect on in-hospital mortality [12, 20, 21], whereas recent cohort studies found a significant association between obesity and in-hospital

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mortality, after adjustment for confounding factors. Williamson et al. [22] reported a dose-response independent relationship between BMI and mortality with an increase in the fully adjusted hazard ratio from 1.05 for patients with a BMI between 30 and 34.9 kg/m^2 to 1.92 for patients with a BMI ≥ 40 kg/m^2. Anderson et al. [6]. found that a BMI ≥ 35 kg/m^2 was associated with an increased risk of death or intubation, although there was an interaction between BMI and age of admission with a significant impact only for patients aged under 65 years. A French cohort study including 5795 patients reported that obesity doubles mortality independently of known chronic comorbidities in patients hospitalized with Covid-19 [9]. Consequently, the hypothesis of a survival obesity paradox with COVID-19 is controversial [2, 6, 23, 24].

In critically ill adult COVID-19 patients, the relationship between obesity and mortality is less clear. Results assessing if obesity is an independent risk factor for intensive care unit (ICU) mortality are contradictory. No definitive conclusion on excess weight and the COVID-19 mortality rate adjusted for key confounding factors has been published by the long-running ICNARC case-mix registry [25]. In the large New York cohort study of Cummings et al. [26], obesity was not identified as an independent risk factor for mortality. Lower BMI was associated with mortality in the study of Auld et al. [27]. On the contrary, severe obesity was independently associated with death in a recently published US multicenter cohort study [28]. The role of obesity was not analyzed in the first systematic review and meta-analysis of the outcome of patients admitted to ICU with COVID-19, probably due to a lack of data [29]. Moreover, the relative importance of different underlying health conditions and patient status on admission for prognosis in the ICU is unclear.

The aim of our study was to evaluate the relationship between BMI and in-hospital mortality in critically ill patients with Acute Respiratory Distress Syndrome (ARDS) due to COVID-19. We attempted to determine a BMI threshold for increased mortality.

Methods

Study design and participants

Our cohort study enrolled all consecutive adult patients with severe SARS-CoV-2 pneumonia, admitted to 4 ICUs at Nancy University Hospital during the early epidemic phase from February 27th to April 18th, 2020. The diagnosis of SARS-Cov-2 infection was defined according to World Health Organization guidance either by real-time reverse transcription-polymerase chain reaction (RT-PCR) for nasal or pharyngeal samples or the presence of hallmark COVID-19 lesions on CT scans. Patients in the ICU with a positive COVID-PCR without pneumonia and hospitalized for another reason were excluded.

Clinical data were collected by manual review of electronic medical records, using a standardized case report form. The recorded data included both administrative data (age, sex, and length of ICU and hospital stay) and clinical data (height, weight, comorbidities). Variables were derived from these collected data. In order to measure the burden of any underlying conditions, we prespecified the following 7 variables for the assessment of the number of comorbidities, based on published studies and completeness of data: diabetes, hypertension, dyslipidemia, coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), immunodeficiency (diseases causing immunosuppression or use of immunosuppressant medications) and chronic kidney disease (CKD). We also collected data on management including mode of ventilator support, mechanical ventilation, the fraction of inspired oxygen (FiO$_2$), arterial partial pressure in oxygen (PaO$_2$), PaO$_2$/FiO$_2$ ratio, specific treatment (corticosteroids, hydroxychloroquine, antiviral agents). Severity was assessed using Sequential Organ Failure Assessment (SOFA) score [30] and Simplified Acute Physiology Score II (SAPS II) [31] at admission. ARDS severity was defined as a PaO$_2$/FiO$_2$ ratio of 300 to 201, 200 to 101, and ≤100 mm Hg for mild, moderate, and severe ARDS, respectively. The BMI was calculated using weight and height measurements at admission and patients were classed into five groups: underweight (BMI < 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), mild to moderate obesity (30–39.9 kg/m^2) and severe obesity (≥40 kg/m^2), respectively.

According to French regulations, this study was declared to the French National Data Protection Authority (CNIL: Commission nationale de l'informatique et des libertés) and registered on ClinicalTrials.gov (No: 2020PI082). It was also approved by the Nancy University Hospital ethics committee.

The primary outcome was in-hospital death. Secondary outcomes included 30-day mortality, clinical characteristics, duration of mechanical ventilation, and length of ICU and hospital stays, according to BMI categories.

Statistical analysis

The descriptive analysis of characteristics was carried out using frequency distribution for categorical variables, the mean and standard deviation for normally distributed continuous variables, or median and interquartile range (IQR) for continuous variables with skewed distribution. Characteristics were compared by groups using the two-tailed t-test or Chi² test, as appropriate. Assumptions for tests were tested and checked.

Logistic regression models were built to analyze the associations between BMI and all-cause in-hospital/30-day

mortality, using the group with the lowest mortality rate as a reference. Potential confounders were selected by clinical relevance and/or a P-value <0.10 in the univariate analysis. Results are given with their odds ratio (OR) and 95% confidence interval (CI 95%). Statistical analysis was performed with R 3.6.3 statistical software.

Results

From February 28th to April 18th, 2020, for 226 eligible patients, we included 222 critically ill patients with acute respiratory failure admitted to ICUs with laboratory-confirmed ($n = 212$) or highly probable ($n = 10$) COVID-19 infection, during the first pandemic wave at Nancy University Hospital. Two patients withdrew their consent and two patients had missing BMI data.

Patients had a mean age of 62.4 ± 12 years, median BMI of $29.1 \, kg/m^2$ (IQR, 25.8–32.8), and 72% were male (Table 1). Obesity (BMI $\geq 30 \, kg/m^2$) was present in 96 patients (43.24%) and severe obesity (BMI $\geq 40 \, kg/m^2$) in 16 patients (7.2%). Diabetes (26.6%), hypertension (48.6%), dyslipidemia (35.6%), cardiovascular disease (24.3%) including CHD (14%), pre-existent respiratory diseases (18.9%), including COPD (6.3%), CKD (6.8%) and immunosuppression (10.8%) were the most frequent comorbid conditions. Thirty-two percent of patients had no identified comorbidities, 25.2% had one, 21.2% two, and 21.6% three or more comorbidities. The median number of comorbid conditions was 1 (IQR, 0–2).

Mortality

Forty-one patients (18.5%) died in the ICU, while 4 others died after ICU discharge to a medical ward. The overall in-hospital mortality was 20.3%. The characteristics of patients at ICU admission according to survival or death ($n = 45$) are shown in Table 1.

Older patients were more likely to die. There were no statistically significant differences in sex distribution. Patients with moderate obesity (BMI 30–39.9 kg/m^2) had a lower in-hospital death rate (13.8%) compared to normal weight (17.6%) and overweight (21.7%) patients, while patients with severe obesity had the highest mortality rate (50%, $P = 0.011$) (Table 1 and Fig. 1). Univariate analysis showed that hypertension, dyslipidemia, COPD, CHD, and CKD were also significantly associated with increased hospital mortality. A preexisting disease could not be identified in 37.3% of survivors compared to 11.1% for non-survivors ($P < 0.001$). About 31% of non-survivors had 2 co-morbidities compared to 18.6% for survivors and the same was true for 3 comorbidities or more (37.8 vs. 17.5%; $P < 0001$).

Patients who died were more likely to have presented with more severe illness and organ dysfunction. In non-survivors, the incidence of severe ARDS was higher than in survivors 77.7% vs. 36.7%, $P < 0.001$. Death was associated with lower worst PaO_2/FiO_2 values (PaO_2/FiO_2 85 mm Hg [IQR, 70.7–97.7] in non-survivors vs. 118.5 mm Hg [IQR, 82.0–153], in survivors, $P < 0.001$). The SAPS II and day 1 SOFA scores were significantly associated with overall in-hospital mortality (both $P < 0.001$).

One hundred and eighty-three (82.4%) of all patients required invasive mechanical ventilation, 93.3% in non-survivors vs. 79.7% in survivors ($P = 0.053$). The median duration of ventilation was about 13 days for both survivors and non-survivors. Compared with survivors, non-survivors were more likely to receive corticosteroids ($P = 0.008$).

Role of obesity

The distribution of age and sex was relatively homogenous across BMI categories (Table 2). Patients with severe (BMI $\geq 40 \, kg/m^2$) and moderate obesity (BMI 30 to <40 kg/m^2) had higher rates of diabetes (62.5% and 38.8%, respectively) compared to patients with normal weight or overweight (23.5% and 10.9%, respectively; $P < 0.001$). The prevalence of hypertension ($P < 0.004$) and obstructive sleep apnea ($P < 0.001$) progressively increased with the BMI category from normal weight to severe obesity. The proportion of patients with no comorbidities was highest in the normal weight group (44.1%). The proportion of patients with 3 or more comorbidities ranged from 12% in overweight patients to 43.8% for those with BMI $\geq 40 \, kg/m^2$.

There was a trend, albeit not significant, for patients with moderate or severe obesity (50.0% and 68.7%, respectively) to have a higher risk of severe ARDS compared to patients with normal BMI (32.3%) or were overweight (41.3%) ($P = 0.106$) (Table 2 and Fig.1). Conversely, PaO_2/FiO_2 and the prevalence of minor ARDS progressively decreased with BMI category from the normal BMI group to those with severe obesity, despite the fact that the proportion of patients receiving invasive mechanical ventilation was the same in all groups. SAPS II and SOFA scores were comparable in patients with or without obesity. In-hospital mortality was significantly lower for patients with moderate obesity (BMI 30–39.9 kg/m^2) (13.8%) compared to patients with normal weight, overweight or severe obesity (17.6%, 21.7%, and 50%, respectively; $P = 0.011$). The results for 30-day mortality were similar.

Multivariable logistic regression

In order to discriminate the role of BMI categories, we performed an exploratory analysis with 4 categories (Supplementary Table 1). This model showed a similar risk for

**Table 1** Characteristics of patients according to their vital status.

	Overall (n = 222)	Survivors (n = 177)	Non-survivors (n = 45)	p-value
Age at admission	64.0 (55.3–72.0)	62.0 (54.0–70.0)	72 (62.0–75.0)	**<0.001**
18–45 years	19 (8.6)	19 (10.8)	0 (0.0)	**0.007**
45–54 years	34 (15.5)	28 (15.9)	6 (13.6)	
5–64 years	63 (28.6)	53 (30.1)	10 (22.7)	
65–74 years	72 (32.7)	57 (32.4)	15 (34.1)	
75 years and more	32 (14.5)	19 (10.8)	13 (29.5)	
Male sex	160 (72.1)	128 (72.3)	32 (71.1)	1.000
BMI (kg/m^2)	29.1 (25.8–32.8)	29.3 (25.9–32.8)	28.7 (25.7–32.3)	0.251
BMI categories				**0.024**
Normal weight	34 (15.3)	28 (15.8)	6 (13.3)	
Overweight	92 (41.4)	72 (40.7)	20 (44.4)	
Moderate obesity	80 (36.1)	69 (39.0)	11 (24.4)	
Severe obesity	16 (7.2)	8 (4.5)	8 (17.9)	
Diabetes mellitus	59 (26.6)	44 (24.9)	15 (33.3)	0.337
Hypertension	108 (48.6)	78 (44.1)	30 (66.7)	**0.011**
Dyslipidemia	79 (35.6)	56 (31.6)	23 (51.1)	**0.024**
Chronic pulmonary disease	42 (18.9)	29 (16.4)	13 (28.9)	0.089
Including COPD	14 (6.3)	5 (2.8)	9 (20.0)	**<0.001**
Including OSAS	22 (9.9)	16 (9.0)	6 (13.3)	0.561
Cardiovascular disease	54 (24.3)	39 (22.0)	15 (33.3)	0.167
Including CHD	31 (14.0)	20 (11.3)	11 (24.4)	0.042
including chronic heart failure	5 (2.3)	3 (1.7)	2 (4.5)	0.568
Immunodeficiency	24 (10.8)	17 (9.6)	7 (15.6)	0.379
Including immunosuppressant medication	9 (4.1)	7 (4.0)	2 (4.4)	1.000
Including active cancer	9 (4.1)	5 (2.8)	4 (8.9)	0.156
Chronic kidney disease	15 (6.8)	8 (4.5)	7 (15.6)	**0.021**
Neurological disorder	10 (4.5)	7 (4.0)	3 (6.7)	0.703
Number of comorbidities				**<0.001**
0	71 (32.0)	66 (37.3)	5 (11.1)	
1	56 (25.2)	47 (26.6)	9 (20.0)	
2	47 (21.2)	33 (18.6)	14 (31.1)	
3 and more	48 (21.6)	31 (17.5)	17 (37.8)	
ARDS severity[a]				**<0.001**
Mild	13 (5.9)	13 (7.3)	0 (0)	
Moderate	109 (49.1)	98 (55.4)	11 (24.4)	
Severe	100 (45)	66 (37.3)	34 (75.6)	
PaO$_2$/FiO$_2$ (mmHg)	109 (79.0–142.0)	118.5 (84.0–153.0)	85 (70.0–97.0)	**<0.001**
Mechanical ventilation	183 (82.4)	141 (79.7)	42 (93.3)	0.053
Mechanical ventilation duration (days)	12.5 (8.0-18.0)	12.0 (7.0-18.0)	13.0 (8.0-19.0)	0.518
Hydroxychloroquine	31 (14.3)	25 (14.5)	6 (13.3)	1.000
Antiviral therapy	42 (19.0)	32 (18.2)	10 (22.2)	0.686
Corticosteroids	53 (23.9)	35 (19.8)	18 (40.0)	**0.008**
SAPS II	44.5 (32.3–62.0)	42.0 (28.0–59.0)	62.0 (44.0–75.0)	**<0.001**
SOFA score	7.0 (4.0–8.0)	7.0 (4.0–8.0)	8.0(7.0–11.0)	**<0.001**
ICU length of stay (days)	13.0 (5.0–22.0)	13.0 (5.0–22.0)	12.0 (6.0–19.0)	0.360
Length of hospital stay (days)	18.0 (10.0–28.0)	20.0 (12.0–29.0)	13.0 (7.0–22.0)	**0.001**

Data are expressed as median (IQR), n (%).

Boldface p-value is statistically significant (p < 0.05).

ARDS acute respiratory distress syndrome, *CHD* coronary heart disease, *COPD* chronic obstructive pulmonary disease, *ICU* intensive care unit, *OSAS* obstructive sleep apnea syndrome, *PaO$_2$/FiO$_2$* arterial partial pressure in oxygen/ fraction of inspired oxygen, SAPS II simplified acute physiology score II, SOFA sequential organ failure assessment.2 2 arterial partial pressure in oxygen/ fraction of inspired oxygen, *SAPS II* simplified acute physiology score II, *SOFA* sequential organ failure assessment.

[a]ARDS severity was defined as a PaO$_2$/FiO$_2$ ratio of 300 to 201, 200 to 101, and ≤100 mm Hg for mild, moderate, and severe ARDS, respectively.
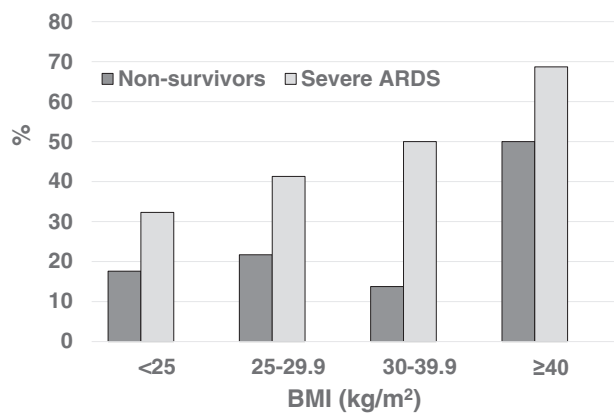
Fig. 1 Mortality rate (%) and prevalence of severe ARDS (%) according to BMI (kg/m²) categories. Severe ARDS was defined based on a PaO2/FiO2 ≤ 100 mmHg.

overweight and normal BMI patients but both were non-significant. These results supported pooling the normal and overweight BMI categories.

Multivariable analysis was performed for models A and B using these 3 BMI categories (normal weight or over-weight, moderate obesity (BMI 30 to <40 kg/m²), and severe obesity (BMI ≥ 40 kg/m²). In model A, logistic regression analysis showed that age (OR 1.03, 95%CI 1.01–1.12), COPD chronic obstructive pulmonary disease (OR 13.01, 95%CI 3.24–52.28), the presence of severe hypoxemia (PaO$_2$/FiO$_2$ ≤ 100 vs. >100 mm Hg: OR 3.73, 95%CI 1.55–8.95), and SAPS II score (OR 1.03, 95%CI 1.01–1.06) were variables independently associated with in-hospital mortality. Due to the small number of patients with some co-morbidities, the number of co-morbidities was introduced in model B. Logistic regression analysis identified BMI ≥ 40 kg/m², number of co-morbidities (≥2), lowest PaO$_2$/FiO$_{2,}$ and SAPS II score, as independent predictors of in-hospital mortality (Table 3). As BMI categories were related to in-hospital mortality in a J-shaped manner with a nadir at BMI > 29 to 39 kg/m², these cut-off points for the definition of moderate obesity were used in model C. The mortality rate decreased to 13% for patients with BMI > 29 to 39 kg/m², whereas it was 21.8% for patients with BMI ≤ 29 and 45% for those with BMI > 39 kg/m² (P = 0.002). This specific BMI classification was added to model C as a covariate with age, the number of comorbidity categories, SAPS II, and PaO$_2$/FiO$_2$. The logistic regression model revealed a paradoxical association between BMI categories and mortality, with a significantly higher risk among those with a BMI ≤ 29 (OR 3.64, 95% CI 1.38–9.60) and those with a BMI > 39 kg/m² (OR 10.45, 95% CI 2.45–41.09), compared to those with BMI > 29 to 39 kg/m². The 2 or more comorbidities categories, SAPS II score, and PaO$_2$/FiO$_2$ < 100 mm Hg remained significant predictors for in-hospital mortality.

The same paradoxical association remained for 30-day mortality, but the effect was significant only for BMI > 39 Category (Supplementary Table 2).

Discussion

To our knowledge, this is the first study reporting the absence of an increase in mortality in COVID-19 patients with moderate obesity admitted to the ICU and even a significant survival benefit in the optimal BMI range (BMI 29–39 kg/m²) for this population, after full adjustment for confounding factors. Patients with severe obesity (BMI ≥ 40 kg/m²) and patients with normal BMI or who were overweight, had a higher mortality rate, suggesting that the BMI-associated mortality curve is J-shaped. This unexpected finding has been termed the Obesity–ARDS paradox [32]. Older age, the high number of comorbidities, in particular COPD, the severity of ARDS, and SAPS II severity score were other independent predictors of in-hospital mortality.

Patients with obesity and a severe form of COVID 19 were over-represented in the ICU [5, 33]. We noted a high prevalence of obesity (BMI ≥ 30 kg/m²) of 43.3%, and severe obesity (7.3%), whereas patients with obesity usually account for 20% of intensive care inpatients [34, 35]. In another French study, the prevalence of obesity in critically ill COVID-19 patients was almost 3 times higher than in critical patients without COVID-19, after standardization for age and sex [8]. According to the ICNARC report, 31.3% and 7.9% of patients admitted to ICUs with con-firmed COVID-19 had a BMI ≥ 30 kg/m² or a BMI ≥ 40 kg/m² compared with 28.9% and 2.9% of the general popula-tion, respectively, after adjusting for age and sex [3, 25].

Obesity may impact COVID-19 severity according to several different mechanisms including abnormal ventila-tion, low-grade chronic inflammation with adipose-lung cell crosstalk, impaired immune response to viral infection, endothelial dysfunction, local biological effects of ectopic fat deposition (in visceral, mediastinal, and epicardial tis-sues and even in the alveolar space) and extensive coagu-lopathy [2, 4, 18, 32, 36, 37]. Moreover, obesity increases the risk of numerous comorbidities considered to be risk factors for severe complications of COVID-19, in parti-cular, hypertension, cardiovascular disease, type 2 diabetes, non-alcoholic fatty liver disease, and obstructive sleep apnea, [3, 4]. Some were overrepresented in our critically ill patients and were included in the regression analysis. Dia-betes has been identified as a risk factor for worse outcomes in COVID-19 patients [38]. However, this was not the case in our ICU study, probably because of regular blood glu-cose monitoring and the use of insulin. In our hands, only one pre-existing disease, COPD was an independent pre-dictor of in-hospital mortality after adjustment for

Table 2 Characteristics of patients according to their BMI status.

	Normal weight (n = 34)	Overweight (n = 92)	Moderate obesity (n = 80)	Severe obesity (n = 16)	p-value
Age at admission	62.0 (54–73.5)	66.0(58.8–72.0)	62.0 (54.0–71.0)	60.5 (50.0–66.8)	0.255
18-45 years	3 (9.1)	7 (7.6)	7 (8.9)	2 (12.5)	0.296
45-54 years	8 (24.2)	9 (9.8)	14 (17.7)	3 (18.8)	
55-64 years	10 (30.3)	21 (22.8)	28 (35.4)	4 (25.0)	
65-74 years	6 (18.2)	39 (42.4)	22 (27.8)	5 (31.2)	
75 years and more	6 (18.2)	16 (17.4)	8 (10.1)	2 (12.5)	
Male sex	25 (73.5)	67 (72.8)	58 (72.5)	10 (62.5)	0.850
Diabetes mellitus	8 (23.5)	10 (10.9)	31 (38.8)	10 (62.5)	**<0.001**
Hypertension	8 (23.5)	43 (46.7)	47 (58.8)	10 (62.5)	**0.004**
Dyslipidemia	9 (26.5)	28 (30.4)	34 (42.5)	8 (50.0)	0.144
Chronic pulmonary disease	4 (11.8)	10 (10.9)	21 (26.2)	7 (43.8)	**0.003**
including COPD	0 (0.0)	5 (5.4)	8 (10.0)	1 (6.2)	0.235
including OSAS	1 (2.9)	4 (4.3)	12 (15.0)	5 (31.2)	**0.001**
Coronary heart disease	5 (14.7)	10 (10.9)	14 (17.5)	2 (12.5)	0.657
Chronic kidney disease	2 (5.9)	6 (6.5)	4 (5.0)	3 (18.8)	0.251
Number of comorbidities					**0.011**
0	15 (44.1)	30 (32.6)	22 (27.5)	4 (25.0)	
1	11 (32.4)	28 (30.4)	15 (18.8)	2 (12.5)	
2	2 (5.9)	23 (25.0)	19 (23.8)	3 (18.8)	
3 and more	6 (17.6)	11 (12.0)	24 (30.0)	7 (43.8)	
ARDS severity[a]					0.106
Mild	4 (11.8)	3 (3.3)	5 (6.2)	1 (6.2)	
Moderate	19 (55.9)	51 (55.4)	35 (43.8)	4 (25.0)	
Severe	11 (32.3)	38 (41.3)	40 (50.0)	11 (68.8)	
PaO$_2$/FiO$_2$ (mmHg)	116.0 (86.0–170.0)	111.0 (82.0–142.8)	101.5 (74.8–141.0)	87.0 (69.8–108.0)	**0.032**
Mechanical ventilation	25 (73.5)	77 (83.7)	66 (82.5)	15 (93.8)	0.337
Mechanical ventilation duration (days)	13.0 (8.0–22.0)	11.5 (6.0–17.0)	13.0 (9.0–18.0)	11.0 (8.0–21.0)	0.289
Mechanical ventilation duration for survivor only (days)[b]	9.0 (7.5–20.0)	11.0 (6.0–16.0)	14.0 (9.0–19.2)	21.0 (10.5–24.0)	0.233
Hydroxychloroquine	2 (5.9)	14 (15.6)	15 (18.8)	0 (0.0)	0.136
Antiviral therapy	9 (26.5)	14 (15.4)	13 (16.2)	6 (37.5)	0.114
Corticosteroids	6 (17.6)	23 (25.0)	19 (23.8)	5 (31.2)	0.736
SAPS II	50.0 (25.5–62.0)	45.0 (31.0–61.3)	43.0 (33.5–62.0)	46.5 (40.3–62.0)	0.989
SOFA score	6.5 (3.3–9.8)	7.0 (4.0–8.0)	7.0 (4.0–8.03.91)	7.0 (5.8–12.0)	0.139
ICU length of stay (days)	14.5 (8.3–21.8)	12.0 (4.0–20.3)	13.5 (6.8–23.0)	13.0 (7.0–22.5)	0.394
ICU length of stay for survivors only (days)[c]	11.0 (7.5–18.0)	12.0 (4.0–20.3)	15.0 (7.0–23.0)	22.50 (13.0–27.8)	0.196
30-day death[d]	4 (11.8)	20 (21.7)	12 (15.6)	8 (50.0)	**0.009**
In-hospital death	6 (17.6)	20 (21.7)	11 (13.8)	8 (50.0)	**0.011**
Length of hospital stay (days)	22.0 (14.5–34.8)	16.0 (8.0–26.0)	18.0 (12.5–27.0)	16.5 (7.0–27.8)	0.085
Length of hospital stay (days) for survivors[c]	21.0 (12.8–35.0)	18.0 (9.0–27.3)	23.0 (13.0–29.0)	29.5 (19.3–43.0)	0.070

Data are expressed as median (IQR) or n (%).

Boldface p-value is statistically significant (p < 0.05).

ARDS acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease, *ICU* intensive care unit, *OSAS*: obstructive sleep apnea syndrome, *PaO$_2$/FiO$_2$* arterial partial pressure in oxygen/ fraction of inspired oxygen, *SAPS II* simplified acute physiology score II, *SOFA* sequential organ failure assessment.

[a]ARDS severity was defined as a PaO$_2$/FiO$_2$ ratio of 300 to 201, 200 to 101, and ≤100 mm Hg for mild, moderate, and severe ARDS, respectively.

[b]Survivors, n = 141.

[c]Survivors n = 177.

[d]Data available n = 219.

Table 3 Factors associated with in-hospital mortality.

Model A	OR	95%CI	Model B	OR	95%CI	Model C	OR	95%CI
BMI categories			*BMI categories*			*BMI categories*		
Normal/overweight	2.37	(0.84–6.73)	Normal/overweight	2.38	(0.94–6.06)	29 kg/m² and less	3.03	(1.19–7.72)
Moderate obesity	1		Moderate obesity	1		29.1–39 kg/m²	1	
Severe obesity	12.25	(2.53–59.45)	Severe obesity	7.67	(1.78–33.03)	More than 39 kg/m²	6.74	(1.75–25.82)
Age at admission	1.06	(1.01–1.12)	Age at admission	1.05	(0.97–1.10)	Age at admission	1.05	(0.99–1.10)
Diabetes mellitus	0.56	(0.18–1.72)	*Number of comorbidities*			*Number of comorbidities*		
Hypertension	1.16	(0.45–3.01)	0	1		0	1	
Dyslipidemia	1.84	(0.70–4.84)	1	2.17	(0.61–7.78)	1	2.33	(0.65–8.37)
Coronary heart disease	0.92	(0.26–3.28)	2	3.71	(1.05–13.04)	2	4.24	(1.18–15.28)
COPD	12.94	(3.22–51.97)	3 or more	4.45	(1.22–16.17)	3 or more	4.89	(1.33–18.05)
Chronic kidney disease	3.14	(0.61–16.08)						
PaO$_2$/FiO$_2$ ≤100 mmHg	3.75	(1.56–8.99)	PaO$_2$/FiO$_2$ ≤100 mmHg	3.99	(1.74–9.18)	PaO$_2$/FiO$_2$ ≤100 mmHg	4.26	(1.81–9.96)
SAPS II	1.03	(1.01–1.06)	SAPS II	1.04	(1.01–1.06)	SAPS II	1.04	(1.01–1.06)

OR odds ratio, *95%CI* 95% confidence interval, *COPD* chronic obstructive pulmonary disease, *PaO$_2$/FiO$_2$* arterial partial pressure in oxygen/ fraction of inspired oxygen, *SAPS II* simplified acute physiology score II.

confounding factors. The role of COPD [26, 39], coronary artery disease [28], active cancer [28], hypercholesterolemia, and diabetes [39] has been demonstrated in previous ICU studies.

Most of our patients admitted to the ICU had moderate (49.1%) to severe ARDS (45%). The proportion of severe ARDS reached 68.7% for patients with severe obesity and 50% for those with moderate obesity. As in previous COVID-19 ICU studies, a low PaO$_2$/FiO$_2$ was associated with a higher death rate [27, 28, 39]. We reported a high rate of mechanical ventilation (82.4%) compared to others studies [Simmonet 68.6% [16], Gupta 67.4% [28], Auld 76% [27], Cummings 79% [26] because of the severity of our patient's illness: the median PaO$_2$/FiO$_2$ of 109 mm Hg (IQR, 79–142) was lower than in other Covid-19 studies: 124 mm Hg (IQR, 86–166) in the Gupta study [28], 129 mm Hg (IQR, 80-203) in the Cummings study [26] and 132 mm Hg (IQR, 100–178) in the Auld study [27]. Despite these figures, the in-hospital and 30-day mortality rates in this study (20.3% and 20.1%, respectively) were lower than that reported in a US cohort (35.4% for 28-day mortality) [28] and close to that for critically ill patients with COVID-19 in Lombardy (26%) [39]. An in-ICU mortality rate of 41.6% was found in a systematic review and meta-analysis of ICU outcomes in patients with COVID-19 across 24 international studies [29]. The authors underlined that reported mortality rates fell from above 50% in March 2020 to close to 40% at the end of May 2020. This change is probably due to differences in the case-mix or treatment and care protocol [28, 29, 39].

In this study, severe obesity was associated with a higher risk of death, supporting a recently published US

multicenter cohort study [28]. Patients with BMI ≥ 40 kg/m^2 had a higher ICU mortality rate than their normal-weight counterparts, after adjusting for confounding factors, in particular the PaO$_2$/FiO$_2$ and liver or renal component of the SOFA score [28]. On the contrary, in a cohort of 257 ICU patients admitted for SARS-CoV-2, severe obesity was found to be associated with mortality by univariate analysis, but this relation disappeared after multivariate analysis [26]. A meta-analysis found that patients with HI1N1 influenza A (H1N1) infection affected by severe obesity were twice as likely to be admitted to the ICU or die, then H1N1 patients with BMI < 40 kg/m^2 [40].

Although our patients with mild to moderate obesity tend to develop more frequently severe ARDS, they were also more likely to recover once the acute lung insult resolved. These findings support the "obesity paradox" theory mentioned above, by which obesity increases the risk of obesity-related diseases and long-term mortality but is paradoxically associated with a survival benefit during some types of acute illness [23, 34, 41–43]. This was the case in our study in which the number of comorbidities was increased in patients with obesity. Validation of the obesity paradox requires that the inverse correlation between BMI and mortality persists, even when the analysis is corrected for confounding variables [23, 34]. The PaO$_2$/FiO$_2$ was the main confounding variable in our study, whereas severity scores and the number of comorbidities were less important. Using slightly different cut-offs for BMI reference category (>29 to 39 kg/m^2) the multivariable analysis demonstrated that BMI ≥ 39 kg/m^2 and BMI < 29 kg/m^2 were independently associated with higher in-hospital mortality after adjusting for other key factors (high number of co-morbidities (≥2), higher SAPS II score,

lower PaO_2/FiO_2). This suggests that mild to moderate obesity may have a protective effect in critical illness and in particular ARDS.

Many experts consider that COVID-19 challenges the obesity paradox [2, 6, 23, 24] because observational cohort study studies demonstrated a strong association between obesity and COVID-19 in-hospital morbidity and mortality. However, most clinical studies or meta-analyses published to date have analyzed data for hospitalized COVID-19 patients [6, 10, 12–14, 22]. To our knowledge, this is the first study to address the role of obesity specifically in critically ill patients with ARDS due to COVID-19. Our findings are consistent both with the study of Goyal et al. [12] and with previous studies in patients with ARDS outside COVID-19 [44]. Goyal et al. [12]. reported a J-shaped pattern for in-hospital mortality among 1687 hospitalized patients in 2 New York City hospitals, although the statistically significant difference in death rate according to BMI classes disappeared in those with respiratory failure; the fully adjusted hazard ratio (HR) for death (normal BMI as reference) was lowest in patients with a BMI of 25–40 kg/m^2: overweight HR 0.76, 95% CI 0.52–1.12; mild to moderate obesity HR 0.82, 95% CI 0.53–1.27; vs. severe obesity HR 1.29, 95% CI 0.58–2.86. A J-shaped distribution in mortality risk according to BMI has previously been observed in patients with ARDS [44]. A large meta-analysis evaluated the effect of obesity on ICU morbidity and mortality and demonstrated that there was no change in mortality for patients with obesity, despite their increased morbidity [41, 42]. A meta-analysis of 6 studies ($n = 7165$) found that patients with overweight or obesity admitted to the ICU with septic shock, excluding patients with BMI ≥ 40 kg/m^2, had a reduced risk of mortality compared to patients with normal BMI [43]. This reduced mortality for patients with obesity was also reported in the subgroup of ARDS patients [45, 46].

This survival paradox's actual existence and mechanisms in critical patients with obesity are controversial [23, 32, 34, 43]. The J or U-shaped relationship between BMI and outcome during acute disease may simply be due to increased mortality at the extremes (i.e., underweight or severe obesity). Moderate obesity may therefore reflect relatively good health. Moreover, the paradoxical association may be mediated by other confounding factors such as deprivation, malnutrition, smoking status, and by unmeasured variables such as the effect of fluid retention on BMI classification that are responsible for a poorer or a better outcome in some BMI groups. Surprisingly, there were no underweight patients in this study. Patients with obesity might be admitted to the ICU at a different level of severity or because of different admission criteria to those for patients without obesity. This could be due to a perceived difference in risk for the subjects with obesity or due to real difficulties in providing adequate care in the ward setting [44]. Disparities in care processes may lead to triage of patients with obesity to higher levels and standards of care due to their higher physical care requirements, which could have a favorable impact on outcomes [41]. There may also be a "selective survivor" effect, in which highest-risk patients with obesity and many comorbidities die before hospital admission.

Despite multiple chronic morbidities, this unexpected survival of critically ill patients with obesity may be explained by several reasons [23, 32, 34]. Excess adipose tissue and increased fat-free mass provide additional metabolic reserves during the catabolic state. Obesity is associated with increased activity of the renin-angiotensin system contributing to hypertension, but it may also have protective hemodynamic effects in the ICU due to a decreased need for fluid or vasopressor support which in excess can adversely impact outcomes [43]. Finally, obesity may constitute a preconditioned chronic pro-inflammatory status, creating a protective environment that limits the detrimental effects of a more aggressive second hit during critical illness [32].

Our study has both methodological strengths and limitations. By focusing on critically ill COVID-19 patients with ARDS, we reduced selection bias by restricting the study population. All medical data were reviewed twice to guarantee their quality. Only 2 patients were excluded for missing data. The admission weight ignored any recent weight change, in particular unintentional weight loss before ICU admission. Height measurements are often inaccurate in the ICU and this can result in misclassifications in the BMI. As this bias is the same for survivors and non-survivors, it should not affect the interpretation of our results. Our small sample size limited the significance of the association between in-hospital and 30-day mortality and standard BMI categories, therefore our results need to be confirmed in a larger study. However, the same J-shaped curve was observed for both in-hospital and 30-day mortality. Smoking status, a healthy or unhealthy metabolic profile [21], and the potential role of excess visceral adipose tissue [47] could not be taken into account due to the lack of data.

Conclusions

Our data showed that patients treated at the ICU with moderate obesity survived more often than patients with normal BMI, overweight or severe obesity and suggest that the ARDS obesity paradox is not broken by COVID-19. Moderate obesity, although potentially associated with many chronic morbidities, may have a protective effect during critical illness and in particular ARDS. This unexpected increase in survival indicates that the management of

severe COVID-19 is not compromised by challenges in diagnosis and treatment caused by the physical effects of obesity, at least for a BMI below 40 kg/m^2. ICU admission and aggressive treatment should therefore be encouraged because of their good potential outcome.

Obesity must still be considered as a potential risk factor for severe adverse outcomes, including mortality. Our findings should not be interpreted to suggest that obesity per se has a protective effect on COVID-19 as this could give a false safety message to people with moderate obesity, especially during the reopening phase. The association between obesity and COVID-19 disease severity underlines the need for sustained long-term actions to address obesity [1, 3, 5].

Compliance with ethical standards

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