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Association of obesity on short- and long-term survival in patients with moderate to severe pneumonia-related ARDS: a retrospective cohort study

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Abstract

Background The incidence of obesity among patients admitted to the intensive care unit (ICU) is increasing, and pneumonia remains the leading cause of acute respiratory distress syndrome (ARDS). The association of obesity on both short- and long-term outcomes in patients with pneumonia-induced ARDS has been the subject of only limited research.

Methods We conducted a retrospective analysis of a prospective cohort consisting of ARDS patients who had microbiologically confirmed pneumonia and a PaO_2/FiO_2 ratio ≤ 150 mmHg. Patients were assessed for mortality at 28 days, 90 days, and at 1 year from the diagnosis of ARDS and compared between obese defined by a body mass index (BMI) ≥ 30 kg.m^2 and non-obese patients. Models were adjusted for age, sex, COPD, coronary artery disease, immunodepression, severity score and acute kidney injury on admission to the ICU, severity of ARDS (PaO_2/FiO_2 ratio ≤ 100 mmHg), severe hypercapnia ($PaCO_2$ ≥ 50 mmHg), ventilatory ratio and plateau pressure the first day of ARDS, influenza, COVID-19, pneumocystosis, and bacteria involved in pneumonia. We also investigated the continuous spectrum of BMI on the risk of mortality.

Results Of 603 patients, 227 patients (37.6%) were obese. Obesity was associated with female gender ($p = 0.009$), hypertension ($p < 0.001$), diabetes mellitus ($p < 0.001$), COVID-19 pneumonia ($p = 0.008$), and PaO2/FiO2 ratio ≤ 100 mmHg ($p = 0.006$). Obesity was independently associated with lower mortality at 28 days (adjusted Odds Ratio (OR) 0.55, 95% confident interval (CI) 0.33–0.90, $p = 0.02$) but not at 90 days (adjusted OR 0.70, 95% CI 0.45–1.09, $p = 0.11$) nor at 1 year from the diagnosis of ARDS (adjusted OR 0.73, 95% CI 0.47–1.13, $p = 0.16$). Mortality at 28 days was significantly lower in obese patients than in non-obese patients when propensity score matching was used (15.2% versus 22%, p = 0.04). BMI was also independently associated with lower mortality at 28 days ($p = 0.038$) but not with mortality at 90 days ($p = 0.12$) and 1 year ($p = 0.12$).

Conclusion Our results suggest that in patients with pneumonia-related ARDS, obesity is independently associated with better survival at 28 days but not at 90 days and 1 year from the diagnosis of ARDS.

Keywords ARDS, Pneumonia, Obesity, Cohort study, Mortality

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Introduction

Individuals affected by obesity face an escalated vulnerability to pneumonia, including infection caused by influenza virus [1–3], severe respiratory syndrome coronavirus 2 (SARS-CoV-2) [4, 5] or bacteria [6]. Moreover, obesity is associated with an increased risk for developing acute respiratory distress syndrome (ARDS), necessitating intensive care units (ICUs) admission and ventilator support [7]. Beyond the ICU setting, obesity within the broader population is linked to a reduced disease-free lifespan and a heightened risk of premature mortality when compared with those maintaining a healthy weight [8–10]. Contrary to expectations, an inverse relationship between obesity and mortality has been described not only in patients with cardiovascular disease or diabetes [11, 12] but also in patients with pneumonia [13]. Within the intensive care setting, a paradoxical trend regarding mortality in critically ill patients [14], and especially those with ARDS [15, 16] has also been reported. Termed the "obesity paradox", this phenomenon raises questions, particularly as most studies define obesity based on the body mass index (BMI) of patients, a measure that provides limited insight into the amount and distribution of body fat [17]. Furthermore, the potential protective effect of obesity, whether in the short-term or long-term, or both, on ARDS patients remains unclear and may depend on the etiology of ARDS.

While pneumonia remains the predominant trigger for ARDS [18], limited research has assessed the impact of obesity on both short- and long-term outcomes specifically in patients with pneumonia-induced ARDS. To contribute to the knowledge on this topic, we investigated the association between obesity and the 28-day, 90-day and 1-year mortality in a cohort of patients with moderate to severe ARDS due to pneumonia.

Patients

This is a retrospective study on data collected prospectively in ARDS patients with microbiologically documented community-acquired or hospital acquired-pneumonia and PaO_2/FiO_2 ratio ≤ 150 mmHg with a $FiO_2 \geq 50\%$ and a positive end-expiratory pressure (PEEP) level ≥ 5 cmH_2O. The ethics committee of the Centre Hospitalier Universitaire de Rennes approved the study (n°16–117). Due to its observational nature, patient signed consent was waived by the ethical committee in compliance with French law on observational studies on anonymized data. Patients with pneumonia associated to mechanical ventilation were excluded from the study. In addition to the presence of abnormal findings on chest X-ray and/or CT scans, the diagnosis of pneumonia was made in patients presenting with acute respiratory symptoms, fever or hypothermia, and an abnormal leukocyte count. ARDS was diagnosed based on Berlin criteria [19], and worst PaO_2/FiO_2 ratio was considered at the time of ARDS diagnosis after optimization of mechanical ventilation. Patients were admitted from January 2006 to January 2022 and all received lung protective ventilation (LPV) aiming to limit plateau pressure under 30 cmH_2O with initial tidal volume of 6 mL per kilogram of predicted body weight (PBW). We tolerated plateau pressure up to 30 cmH_2O in some obese patients, but not above 30 cmH_2O in non-obese patients. Patients received neuromuscular blocking agents for at least 48 h, with the exception of a small number of control patients who were included in the ACURASYS trial. Neuromuscular blockade was used throughout the study period despite evolving recommendations. The constitution of our database started with the ACURASYS study [20]. Prone positioning [21] and neuromuscular blockades [20] have been proven to be effective along with protective mechanical ventilation in patients with a PaO_2/FiO_2 ratio below 150 mmHg. Consequently, the threshold of 150 mmHg PaO_2/FiO_2 is important to assess ARDS patients in studies [22]. The diagnosis of pneumonia was made at the time of admission in the ICU, consequently most of the patients had community-acquired pneumonia and very few patients had hospital-acquired infection. All patients had at least one year of follow-up and there was no missing data regarding the analyzed variables.

Microbiological diagnosis

COVID-19 and influenza were diagnosed based on a positive result on a real-time reverse transcriptase polymerase chain reaction (RT-PCR) on a respiratory specimen. Bacteriological cause of pneumonia was retained in patients with positive culture on tracheal aspirates or bronchoalveolar lavage (BAL), and/or positive blood samples, and/or positive results for urinary antigens for *Streptococcus pneumonia* and *Legionella pneumophila* [23]. *Pneumocystis jirovecii* pneumonia was diagnosed by microscopic examination including immunofluorescent staining and PCR based on the European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC-MSG) revised criteria [24]. Patients with suspected but non-documented pneumonia were excluded from the study.

Data collection

Collected data included demographic information: gender, age, body mass index (BMI), and the following comorbidities: liver cirrhosis Child B or C, diabetes mellitus, immunodepression (defined as patients with aplasia and/or recent chemotherapy for a solid tumor or haematologic disease), previous coronary artery disease, arterial hypertension atrial fibrillation. In addition, we recorded

the results of the following laboratory tests: worst results for PaO2, and PaCO2 recorded between 12 and 24 h of mechanical ventilation from the diagnosis of ARDS and after optimization of mechanical ventilation, and kidney function (urea and creatinine). We considered acute kidney injury (AKI) stage 2 and 3 on admission according to KDIGO criteria [25]. Severity scores including Simplified Acute Physiology Score (SAPS) II on admission [26] and sequential organ failure assessment (SOFA) [27] were recorded. The following worst ventilator parameters recorded the first day of ARDS after optimization of mechanical ventilation were noted: tidal volume, plateau pressure, level of positive end-expiratory pressure (PEEP) applied. In patients who died while on mechanical ventilation, we considered zero free days for ventilator-free days at 28 days. In addition, treatments used in the ICU including steroids treatment within the first 7 days of admission, inotropic support, renal replacement therapy, prone positioning, and extracorporeal membrane oxygenation (ECMO) were recorded. Outcomes were all-cause mortality at 28 days, 90 days, and 1 year from the diagnosis of ARDS.

Definitions

BMI was calculated as weight (kg)/height^2 (m^2). Weight and height measurements were taken at the time of admission to the ICU for all patents. Obesity was defined as a BMI ≥ 30 kg.m^2 [8, 11]. Ventilatory ratio (VR) a surrogate of dead space was calculated as [minute ventilation (mL/mn) x $PaCO_2$ (mmHg)] / (PBW $\times 100 \times 37.5$)] [28]. Stage 2 AKI was defined by an increase in the serum creatinine level to 2.0–2.9 times baseline and stage 3 AKI by an increase in the serum creatinine level to 3 times baseline [25].

End-points

The primary endpoint was to compare mortality at 28 days, 90 days, and 1 year from the diagnosis of ARDS between obese and non-obese patients. The secondary end-point was to investigate the continuous spectrum of BMI in relation to the risk of mortality at 28 days, 90 days, and 1-year from the diagnosis of ARDS.

Statistical analysis

We followed the Strengthening the Reporting of Observational Studies in Epidemiology recommendations for reporting this study. Continuous variables were described as median (25th-75th percentiles) and compared using Mann–Whitney test. Categorical variables were described as number (%) and compared using Chi square test or Fisher's exact test when required. We assessed mortality at 28 days, 90 days and at one year from the diagnosis of ARDS and analyses were conducted first with BMI dichotomized for obesity (i.e., BMI ≥ 30 kg.m^{-2} or < 30 kg.m^{-2}) and second used as a continuous variable. Survival curves were constructed by using the Kaplan–Meier method and compared by the log-rank test. We first used a logistic regression analysis to determine whether obesity was independently associated with prognosis at day-28, day-90, and at 1 year in an adjusted and adjusted analysis. Models were adjusted a priori for potential confounders and included age, sex, SAPS II score, acute kidney injury on admission to the ICU, immunodepression, COPD, coronary artery disease, severity of ARDS (PaO_2/FiO_2 ratio ≤ 100 mmHg), severe hypercapnia ($PaCO_2 \geq 50$ mmHg) [29], ventilatory ratio and plateau pressure the first day of ARDS, influenza, COVID-19, pneumocystosis, and bacteria involved in pneumonia. Because of the collinearity between the SAPS II and SOFA scores, only the SAPS II was considered in the adjusted analysis. Furthermore, because patients were admitted over a long period, during which the prognosis of ARDS may have changed, the year of admission was entered in the model as a continuous covariate. Logistic regression analysis was also performed on two distinct populations of patients: the first population comprised patients with viral pneumonia, and the second population comprised patients with bacterial pneumonia. The covariates were used also to determine the propensity score of obesity for each patient. One patient with obesity was matched with one patient without obesity according to the propensity score using a nearest neighbor matching. The maximum distance allowed between two matched patients was set at 0.25 (ie, caliper restriction), resulting in a relatively narrow difference between matched variables. We used the E-value methodology to assess the robustness of the 28-day results to unmeasured confounding [30]. Calculation of the E-value aims to estimate how strong would the unmeasured confounding have to be to negate the observed results [31]. Secondly, given the nonlinear association between BMI and mortality, to evaluate for potential nonlinear associations between BMI and risk of mortality at day-28, day-90, and at 1-year, we used generalized additive models (GAMs) and smooth curves were produced. Tests were two-sided, and we considered a $p < 0.05$ to be significant. All analyses were performed using R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

During the study period, 1011 patients with ARDS and PaO_2/FiO_2 ratio ≤ 150 mmHg were admitted to our ICU and pneumonia was microbiologically documented in 603 patients (59.7%), among them 227 patients (37.6%) with BMI ≥ 30 kg.m^{-2} (Fig. 1). Obesity was diagnosed

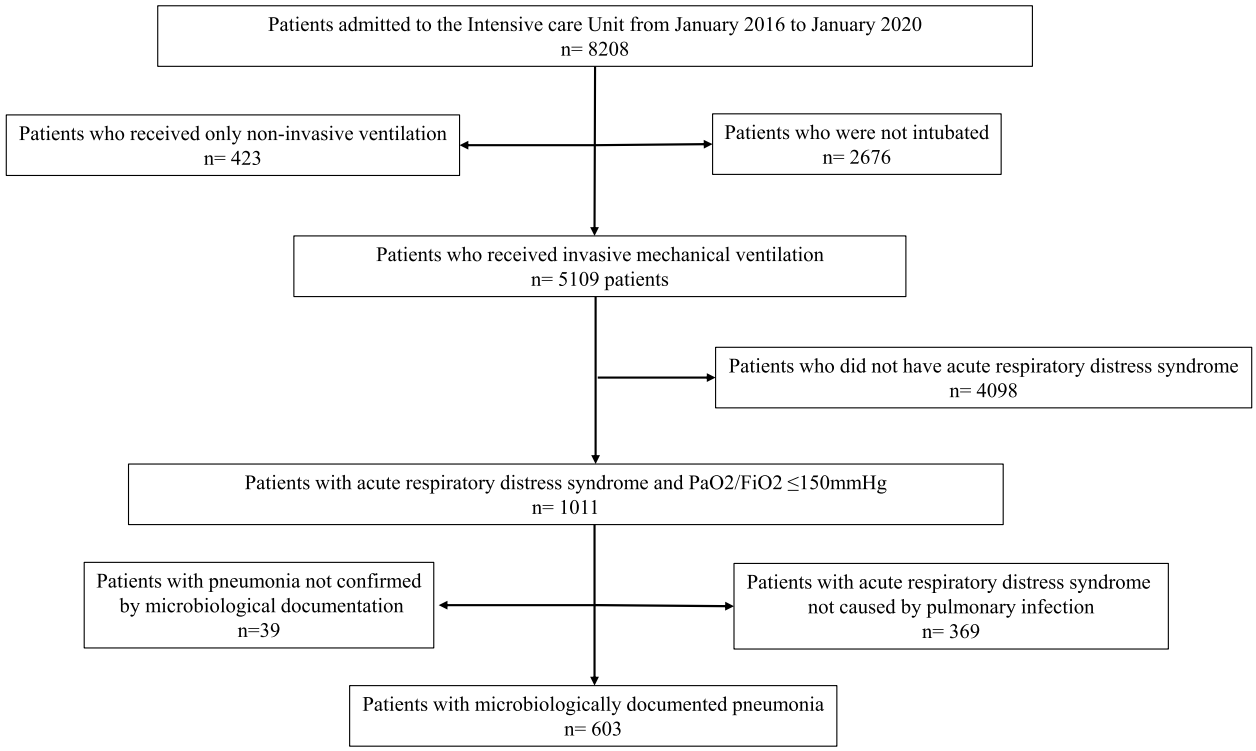

Fig. 1 Flowchart

in 35.3% of the patients with ARDS not due to pneumonia ($p=0.31$ after comparison with patients with pneumonia-related ARDS).Thirty-seven patients (6.1%) had hospital-acquired pneumonia while they did not receive mechanical ventilation. Demographics and clinical characteristics for the overall cohort and stratified by obesity are presented in Table 1. Three patients were HIV positive but the main cause for immiunodepression was lymphoma in two of them and bronchial carcinoma in one. There was no significant difference for age nor severity scores between patients with and without obesity. The majority of obese patients were women. Diabetes mellitus and arterial hypertension were more frequent in patients with obesity than in patients without obesity while patients without obesity were more frequently immunosuppressed than patients with obesity. Pathogens involved in pneumonia differed between the two groups of patients. Proportion of patients with bacterial pneumonia was higher in patients with obesity than in patients without obesity (see Supplemental Table 1 for bacteria involved in pneumonia). Conversely, proportion of patients with COVID-19 was higher in obese patients than in non-obese patients. Proportions of patients with influenza and pneumonia due to *Pneumocystis jirovecii* did not differ between obese and non-obese patients. The first day of ARDS, severe ARDS was more frequent in patients with obesity while severe hypercapnia was more frequent in patients without obesity. Plateau pressure did not differ significantly between patients with and without obesity. Prone positioning was more frequently used in obese patients. Patients without obesity had fewer ventilator-free days at 28 days than patients with obesity but the difference did not reach significance. Further classification of patients by BMI is depicted in Supplemental Table 2.

Obesity and mortality at day-28, day-90, and at 1-year from diagnosis of ARDS

Mortality stratified by BMI categories as defined by the World Health Organization BMI classification is reported in Supplemental Fig. 1. Mortality Kaplan–Meier survival curves showed that survival differed significantly at 28 days, 90 days, 1-year from the diagnosis of ARDS between obese and non-obese patients. Obese patients had the highest survival rate at 28 days, 90 days, and 1-year ($p=0.0074$, $p=0.01$ and $p=0.0056$ respectively as determined by the log-rank test, (Supplemental Fig. 2A, 2B, and 2C). Extensive results for adjusted analysis are shown in Supplemental Figs. 3A, 3B and 3C. While diabetes and hypertension were more frequent in obese patients, mortality at 28 days was significantly lower in obese patients than in non-obese

Table 1 Demographic, clinical, mechanical ventilation characteristics the first day of ARDS, support used in the ICU, and mortality stratified by obesity

	All patients ($n=603$)	Patients without obesity ($n=376$)	Patients with obesity ($n=227$)	*P* Value
Age, years	62 (52,71)	63 (52, 72)	61 (50,69)	0.054
Male gender, n (%)	404 (67)	267 (71)	137 (60)	0.009
SAPS II score, points	43 (32,58)	43 (33, 59)	41 (32,56.25)	0.24
SOFA score, points	7 (5,10)	8 (5, 10)	7 (5,10)	0.09
BMI, $kg.m^{-2}$	27.4 (23.9, 28.8)	24.79 (22.4, 27.1)	33.98 (31.9,38.1)	< 0.001
Hypertension, n (%)	227 (37)	116 (31)	111 (49)	< 0.001
Diabetes mellitus, n (%)	91 (15)	30 (8)	61 (27)	< 0.001
Atrial fibrillation, n (%)	51 (9)	28 (7)	23 (10)	0.32
Coronary artery disease, n (%)	58 (10)	35 (9)	23 (10)	0.85
COPD, n (%)	133 (22)	93 (25)	40 (18)	0.05
Immunosupression, n (%)	113 (19)	82 (22)	31 (14)	0.02
Influenza*, n (%)	91 (15)	58 (15)	33 (14)	0.86
Covid-19*, n (%)	259 (43)	149 (40)	110 (48)	0.04
Bacteria involved in pneumonia*, n (%)	212 (35)	135 (36)	57 (25)	0.008
Pneumocystosis, n (%)	41 (7)	29 (8)	12 (5)	0.32
Acute kidney injury, n (%)	141 (23)	83 (22)	58 (26)	0.38
$PaO_2/FiO_2 \leq 100$ mmHg, n (%)	339 (60)	194 (52)	145 (64)	0.006
$PaCO_2 \geq 50$ mmHg, n (%)	324 (54)	213 (57)	111 (49)	0.08
Vt/PBW, ml/kg	6.24 (5.98,6.59)	6.21 (5.96,6.50)	6.34 (6.04,6.75)	< 0.001
Plateau pressure, cmH_2O	25 (22,25)	25 (22,28)	23 (23,28)	0.24
PEEP, cmH_2O	12 (10,12)	10 (8,12)	12 (10,14)	0.007
Ventilatory ratio	2.31 (1.89,2.86)	2.32 (1.85,2.88)	2.31 (1.94,2.81)	0.68
Prone positioning, n (%)	383 (63)	213 (56)	170 (75)	< 0.001
Renal replacement, n (%)	131 (22)	80 (21)	51 (22)	0.81
ECMO, n (%)	46 (8)	26 (7)	19 (8)	0.73
Treatment with steroids the first week of ARDS, n (%)	442 (73)	274 (73)	168 (74)	0.72
Vasopressors, n (%)	513 (85)	328 (87)	185 (82)	0.07
Ventilator-free days at 28 days	7 (0,17)	6 (0,17)	9 (0,17)	0.39
Mortality at 28 days, n (%)	109 (19)	87 (23)	32 (14)	0.009
Mortality at 90 days, n (%)	177 (29)	124 (33)	53 (23)	0.015
Mortality at 1 year, n (%)	197 (33)	138 (36)	59 (26)	0.009

Data are presented as median (interquartile range) for continuous measures

ARDS Acute Respiratory Distress Syndrome, *COPD* Chronic Obstructive Pulmonary Disease, *ECMO* Extracorporeal Membrane Oxygenation, *PEEP* Positive End-Expiratory Pressure, *PBW* Predict Body Weight, *SAPS* Simplified Acute Physiology Score, *SOFA* Sequential Organ Failure Assessment, *Vt* tidal volume

* Involved in pneumonia, including mixed infections

Table 2 Unadjusted and adjusted odds ratios (ORs) for obesity and mortality at 28 days, 90 days, and 1-year mortality from the day of acute respiratory distress (ARDS) diagnosis

	Unadjusted OR	(95% CI)	*P* Value	Adjusted OR	(95% CI)	*P* value
Obesity, yes						
28-day mortality	0.54	(0.34–0.83)	0.007	0.55	(0.33–0.90)	0.02
90-day mortality	0.61	(0.42–0.90)	0.01	0.70	(0.45–1.09)	0.11
1-year mortality	0.60	(0.42–0.89)	0.006	0.73	(0.47–1.13)	0.16

Variables used for adjustment: Age, Sex, Simplified Acute Physiology Score 2, COPD, coronary artery disease, immunodepression, acute kidney injury, influenza, COVID-19, bacterial involved in pneumonia, *Pneumocystis jirovecii* pneumonia, severe ARDS defined by PaO2/FiO2 ratio ≤ 150 mmHg, severe hypercapnia defined by PaCO2 ≥ 50 mmHg, plateau pressure and ventilator ratio the first day of ARDS, and year of admission to the ICU

CI confidence interval

patients (15.2% versus 22% respectively; $p=0.04$). On the other hand, mortality rates at 90 days and 1-year did not differ significantly between obese and non-obese patients (28.1% versus 34.4% respectively, $p=0.12$). Results for unadjusted and adjusted analysis are shown in Table 2. Obesity was associated with lower mortality at the three date of points in the unadjusted analysis but remained independently associated with lower mortality only at 28 days. The result for the E-value was 2.06.

After classifying cases as viral or bacterial pneumonia, the adjusted ORs were 0.59 (0.28–1.11), $p=0.09$, in patients with viral pneumonia, and 0.61 (0.23–1.33), $p=0.11$, in patients with non-viral pneumonia.

The characteristics of the 217 obese patients matched with non-obese patients are listed in Table 3. At day-28, mortality was lower in obese patients than in non-obese patients (14% versus 23% respectively, $p=0.02$) but not at 90 days and 1 year (see Supplemental Fig. 4 and Supplemental Table 3 for quality of the matching process).

Secondary end-point: BMI and mortality

In generalized additive models, greater BMI was significantly associated with mortality at 28 days in the unadjusted (p for association = 0.017) and adjusted analysis (p for association = 0.038, Fig. 2). BMI was not associated with mortality at 90 days nor at 1 year in the unadjusted analyses (p for association = 0.23 and 0.12, respectively) (Supplemental Fig. 5A, and 5B).

Discussion

In a cohort of patients with moderate to severe ARDS due to pulmonary infection, we found that patients with obesity had better survival at 28 days from the diagnosis of ARDS compared to patients without obesity. This finding persisted after adjustment for known risk factors for mortality in ARDS patients, and in sensitivity analysis using propensity score matching. BMI used as a continuous variable, was also associated with mortality at 28 days using GAM for analysis. Conversely, obesity did not remain independently associated with survival at 90 days and 1 year from the diagnosis of ARDS. Our data showed a U-shaped relationship between BMI and mortality.

The exclusion of patients with non-documented pneumonia limits the generalizability of the study. However, our primary concern was to ensure that the inclusion of ARDS was restricted to patients with pulmonary infection. It was hypothesized that the probability of documenting infection would be high in patients with ARDS, primarily due to community-acquired pneumonia. Therefore, we assumed that there was a high risk of including patients with non-pulmonary ARDS in cases where infection had not been documented. Pulmonary infection is the most common cause of ARDS [18, 32], and obesity promotes viral and bacterial pneumonia [33, 34]. To our knowledge, obesity is not a risk factor for *Pneumocystis jirovecii* pneumonia [35]. The influenza A

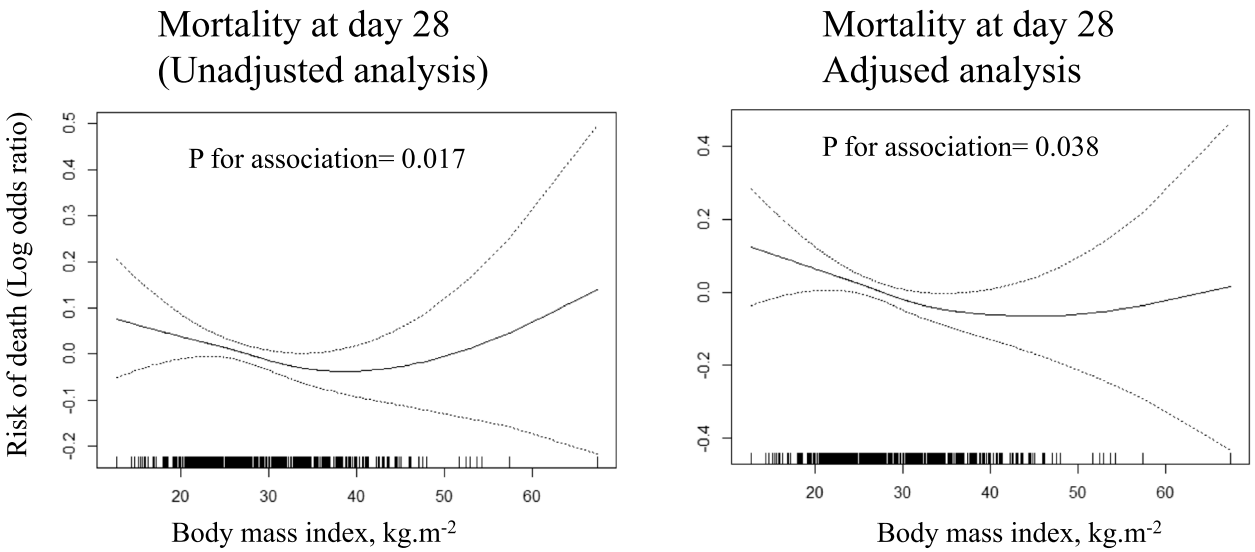

Fig. 2 Odds ratio of mortality at 28 days for BMI adjusted for age, sex, SAPSII score, acute kidney injury on admission to the ICU,COPD, coronary artery disease, immunodepression, severity of ARDS (PaO2/FiO2 ratio ≤ 100 mmHg), severe hypercapnia (PaCO2 ≥ 50 mmHg), ventilatory ratio and plateau pressure the first day of ARDS, influenza, COVID-19, pneumonia to *Pneumocystis jirovecii*, and bacteria involved in pneumonia. The solid lines represent estimated odds ratio and the dashed lines represent 95% confidence bands

Table 3 Demographic, clinical, mechanical ventilation characteristics first day of ARDS, life support, and mortality after propensity score matching

	Patients without obesity ($n=217$)	Patients with obesity ($n=217$)	*P* Value
Age, years	62 (52,72)	61 (52,69)	0.24
Male gender, n (%)	136 (63)	133 (61)	1
SAPS II score, points	42 (32,56)	42 (32,56)	0.90
SOFA score, points	7 (5,10)	7 (5.10)	0.66
BMI, $kg.m^{-2}$	25.3 (22.9,27.8)	33.8 (31.8,38.1)	< 0.001
Hypertension, n (%)	63 (29)	109 (50)	< 0.001
Diabetes mellitus, n (%)	19 (9)	58 (27)	< 0.001
Atrial fibrillation, n (%)	16 (7)	23 (1)	0.41
Coronary artery disease, n (%)	20 (9)	22 (10)	0.31
COPD, n (%)	41 (19)	40 (18)	1
Liver cirrhosis, n (%)	9 (4)	5 (2)	0.41
Immunosupression, n (%)	31 (14)	30 (14)	1
Influenza*, n (%)	31 (14)	30 (14)	1
Covid-19*, n (%)	111 (51)	113 (52)	0.92
Bacterial CAP*, n (%)	63 (29)	56 (2)	0.52
Pneumocystosis, n (%)	15 (7)	12 (6)	0.69
Acute kidney injury, n (%)	51 (23)	54 (25)	0.82
$PaO_2/FiO_2 \leq 100$ mmHg, n (%)	129 (59)	136 (63)	0.55
$PaCO_2 \geq 50$ mmHg, n (%)	110 (51)	109 (50)	1
Vt/PBW, $ml.kg^{-1}$	6.22 (6.00,6.49)	6.33 (6.04,6.74)	0.06
Plateau pressure, cmH2O	26 (23,28)	26 (22,28)	0.51
PEEP, cmH_2O	12 (10,13)	12 (12,14)	0.47
Ventilatory ratio	2.28 (1.82,2.89)	2.34 (1.94,2.8)	0.42
Prone positioning	137 (63)	161 (74)	0.02
Renal replacement	41 (19)	51 (23)	0.29
ECMO	14 (7)	18 (8)	0.58
Treatment with steroids the first week of ARDS	166 (76)	160 (74)	0.56
Vasopressors	188 (87)	175 (81)	0.12
Ventilator-free days at 28 days	10 (0,18)	9 (0,17)	0.99
Mortality at 28 days, n (%)	50 (23)	30 (14)	0.02
Mortality at 90 days, n (%)	67 (31)	51 (24)	0.11
Mortality at 1 year, n (%)	75 (35)	57 (26)	0.09

Data are presented as median (interquartile range) for continuous measures

ARDS Acute Respiratory Distress Syndrome, *CAP* Community Acquired Pneumonia, *COPD* Chronic Obstructive Pulmonary Disease, *ECMO* Extracorporeal Membrane Oxygenation, *PEEP* Positive End-Expiratory Pressure, *PBW* Predict Body Weight, *SAPS* Simplified Acute Physiology Score, *SOFA* Sequential Organ Failure Assessment, *Vt* tidal volume

* Involved in pneumonia, including mixte infections

(H1N1) pdm2009 and the COVID-19 pandemics marked the past decades. Previous studies demonstrated that obese patients are at higher risk for developing pneumonia and severe forms of pneumonia due to influenza [2, 36] and SARS-CoV-2 infection [5, 37]. In some studies, mortality was not found to be higher in obese patients than in non-obese patients with influenza A (H1N1) infection in critical illness [38] or in ARDS patients [39]. However, these results may be explained in part by the low number of patients studied and consequently by a lack of power to detect statistical differences. Contrasting effects of obesity on outcomes are reported in large series of critically ill COVID-19 patients. For example, a protective effect of obesity on mortality at day-90 was noted in the prospective cohort of 4,244 critically ill adults with COVID-19 admitted in France, Belgium, and Switzerland, including 1,607 patients (41%) with obesity [40]. In contrast, obesity was not associated with outcomes in a cohort of 1,909 invasively ventilated patients conducted in Argentina including 44.4% of patients with obesity [41] or was even associated with higher mortality in a retrospective cohort study of 504 patients, with 215 obese patients (43%) [42]. Large studies were also conducted in cohorts of patients with influenza- or COVID-19-related ARDS who received ECMO. Obesity was not associated with a lower mortality rate in influenza patients [43] nor in a large multicenter prospective observational study including 1215 patients with COVID-19 supported by ECMO among whom 44% were obese [44]. However, other authors reported recently a lower ICU mortality among 790 patients receiving ECMO for ARDS of various origins with bacterial and viral pneumonia representing 33.3% and 26.4% of etiologies [45].

We found a protective effect of obesity at 28 days, which did not persist beyond 90 days and 1 year. The vast majority of our patients presented with ARDS following community-acquired pneumonia. Results of a meta-analysis suggest better survival in obese patients with pneumonia than in non-obese patients [13] and other authors [46] recently reported a protective effect of obesity at 30 days, 6 months, and 1 year in these patients. However, authors also report contrary findings. In a secondary analysis of a multicenter trial including 773 patients with community-acquired pneumonia, 30-day survival was not better in the 169 patients (21.8%) with obesity compared to non-obese patients [47]. Zhi G et al. [16] performed a meta-analysis on 24 observational studies including patients with ARDS or acute lung injury of various origins. In contrast to our findings, they found that obesity was associated with lower mortality at 60 and 90 days compared to normal weight, but not at 28 days. Obesity was also associated with lower mortality in another meta-analysis [15]. Adjustments for

confounders were not possible in these two meta-analyses. The protective effect of obesity at 28 days persisted in the matched population. We believe that this result diminishes the possibility that the short-term protective effect noted in our study was explained by a performance bias due to a more aggressive care in obese patients than in non-obese patients or by a collider stratification bias due to a higher proportion of ARDS of moderate severity in obese patients than in non-obese patients. There was a trend, but not a significant association, between obesity and mortality at 28 days post-admission. This was observed in both the subgroup of patients with viral pneumonia and the one with bacterial pneumonia. This result may be attributable to insufficient power, given the limited number of patients in each of subgroup.

In pneumonia-related ARDS patients, several explanations can be proposed for the obesity paradox: 1) a selection bias due to restrictive admission criteria in obese patients, 2) an overestimation of the severity of ARDS, explained in a part by an increased risk of atelectasis in obese patients, 3) reduced trans-pulmonary pressure mediated lung damage, 4) a greater capacity to tolerate extensive weight loss, and increased metabolic reserve, 5) an increased amount of lean muscle mass in addition to increased adiposity, 5) and various, sometimes contradictory hypotheses on the relationship between obesity and the inflammatory response to infection including the immunomodulatory effects of adipose tissue and a chronic low-grade inflammation enhancing immune response [33, 34, 48]. The controversial results on the protective effect of obesity in ARDS patients are probably explained in a large part by the use of BMI for the diagnosis of obesity. BMI can be affected by fluid balance before admission to the ICU [49]. In addition, BMI is not informative on the amount and distribution of body fat or the muscle mass. However, BMI is simple, by far the more frequently used anthropometric tool to assess obesity in ICU patients, including in large clinical trials focusing on nutrition [50]. The waist-to-height ratio is an index that reflects central obesity well but not skeletal mass, and although simple to calculate, it is, to our knowledge little used and not validated in the ICU setting. Having an accurate estimator of body fat for critically ill patients would be desirable. However most estimators of body fat, such as dual-energy X-ray absorptiometry, are not available in the ICU. In addition, surrogate measures of body fat that account for sex and age use similarly to BMI height and weight in the equations [51]. Consequently, today, BMI remains the most commonly used tool to assess obesity in the ICU and to compare findings between studies. As described previously by authors [33, 52], we found a U-shaped relationship between BMI and mortality. Both extremes of the BMI were associated with an increased risk of death, especially in underweight patients. When BMI was considered as a continuous variable rather than a categorical measure (obese versus non-obese), the results of GAMs analyses showed that BMI was significantly associated with survival at 28 days but not at 90 days and 1-year. The U-shaped relationship between BMI and mortality at 28 days indicates that both low and high BMI values are associated with an increased mortality risk. This U-shaped pattern underscores the importance of considering BMI as a dynamic and multidimensional risk factor rather than as a linear predictor of health outcomes. In addition, we believe that it is imperative to exercise caution when interpreting these results, given the non-linear relationship between BMI and mortality. However, the association at 28 days did not remain independently associated after adjustment for other prognostic variables. A non-linear relationship between BMI and the prevention of progression to severe respiratory failure in patients with early respiratory failure was also recently demonstrated in a trial evaluating the efficacy of non-invasive ventilation [53]. Early non-invasive ventilation prevented progression to severe respiratory failure in patients with a BMI between 20 and 29 kg/m^2, but not in those with a lower or higher BMI. Often, BMI does not differ significantly between critically ill survivors and non-survivors in studies. On one hand, BMI as a continuous variable may provide a nuanced view of the relationship between obesity and outcomes in critically ill patients. In the other hand, the significance of BMI as a continuous variable might not reflect consistently this relationship.

Our study has several strengths. We studied a large number of homogeneous patients, all of whom had ARDS related to microbiologically documented pneumonia and who all received protective lung ventilation in the first days of MV after the diagnosis of ARDS. The protective effect of obesity on short-term outcomes has been reported in patients with pneumonia and in patients with ARDS of various etiologies, suggesting that our results are consistent. The proportion of patients with obesity in the studied population (37.6%) is within the range of the percentages reported in studies conducted in Europe or the United States of America. In addition to the SAPS II score and severity of pulmonary and kidney dysfunctions, factors associated with mortality in ARDS patients (increased plateau pressure and ventilatory ratio) were used for adjustments. We were able to determine the survival of patients up to 1 year after the diagnosis of ARDS.

In addition to its retrospective nature, our study has several limitations. It is evident that the initial limitation is that obesity was diagnosed based on the BMI values. We did not assess lean body mass, body fat, nor the distribution of adiposity because they were not available.

The study was conducted at a single site; thus, our results may not be applicable to other hospitals. The data were collected exclusively from patients diagnosed with ARDS who exhibited a PaO2/FiO2 ratio of less than 150 mmHg. This restriction precludes the generalizability of the findings to patients with higher ratios. Even though we compared patients using propensity score matching, we cannot exclude uncontrolled confounders. Nevertheless, the result for the E-value suggests that an unmeasured or unknown confounder would have a substantially greater effect on mortality at 28 days, with a relative risk exceeding 2.06 (95% CI: 0.63–3.49). The OR for mortality at 28 days for immunodepression, one of the most powerful risk factors for mortality in ARDS patients was 2.5 in the present study. Consequently, it is not likely that an unmeasured confounder would have a substantially greater effect on mortality at 28 days than the factors used here for adjustments [31].

Conclusions

Among patients with moderate to severe ARDS caused by pulmonary infection, those with obesity had lower mortality at 28 days from the diagnosis of ARDS, even after propensity score matching. Our results suggest that the protective effect of obesity is short-lived in these patients since the effect no longer existed at 90 days, a result confirmed at 1 year. These findings have implications for the understanding of the "obesity paradox" reported in critically ill patients.

Abbreviations

AKI	Acute Kidney Injury
ARDS	Acute Respiratory Distress Syndrome
BMI	Body Mass Index
ECMO	Extracorporeal Membrane Oxygenation
GAM	Generalized Additive Model
ICU	Intensive Care Unit
LPV	Lung Protective Ventilation
OR	Odds Ratio
PBW	Predicted Body Weight
SAPS	Simplified Acute Physiology Score
SOFA	Sequential Organ Failure Assessment
VR	Ventilatory ratio

Supplementary Information

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Supplementary Material 1.

Authors' contributions

Arnaud Gacouin and Adel Maamar were involved in the conception and design of the study. Arnaud Gacouin was responsible for the data collection. Arnaud Gacouin and Adel Maamar were in charge of the analysis. Nicolas Terzi and Jean-Marc Tadié accessed and verified the data. All the authors were involved in the interpretation and critically reviewed the first draft. All the authors read and approved the final manuscript.

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Data availability

The data supporting our findings are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent from study subjects was waived because of the retrospective design. The cohort study was approved by the institutional review board of the Centre Hospitalier Universitaire de Rennes. All the methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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