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### ► To cite this version:

Sébastien Bailly, Louis-Marie Galerneau, Stéphane Ruckly, Alexandre Seiller, Nicolas Terzi, et al.. Impact of obstructive sleep apnea on the obesity paradox in critically ill patients. *Journal of Critical Care*, 2020, 56, pp.120-124. 10.1016/j.jcrc.2019.12.016 . hal-03011300

**HAL Id: hal-03011300**

**<https://hal.science/hal-03011300>**

Submitted on 7 Mar 2022

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**Title: Impact of obstructive sleep apnea on the obesity paradox in critically ill patients.**

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**Keywords:** intensive care units; Obstructive Sleep Apnea; Obesity Paradox; nested exposed-unexposed design; patient prognosis

**Funding:** This study was funded by an unrestricted grant from the “Fondation Agir pour les maladies chroniques”. RT, JLP and SB are supported by a research grant from the French National Research Agency (ANR-12-TECS-0010) in the framework of the “Investissements

d'avenir" program (ANR-15-IDEX-02) and the "e-health and integrated care" Chair of excellence of the University Grenoble Alpes Foundation.

**Role of the sponsors:** The sponsors had no role in the design of the study, the collection, analysis or interpretation of the data, and the preparation of the manuscript.

**Financial/nonfinancial disclosures:** None associated with this manuscript.

**Abstract:**

**Objective:** Patients admitted to an intensive care unit (ICU) frequently suffer from multiple chronic diseases, including obstructive sleep apnea (OSA). Until recently OSA was not considered as a key determinant in an ICU patient's prognosis. The objective of this study was to document the impact of OSA on the prognosis of ICU patients.

**Methods:** Data were retrospectively collected concerning adult patients admitted to ICU at two university hospitals. In a nested study OSA status was checked using the hospital electronic medical records to identify exposed and unexposed cases. The following outcomes were considered: length of stay in the ICU, ICU mortality, in-hospital mortality, ventilator-associated pneumonia (VAP).

**Results:** Out of 5,146 patients included in the study, 289 had OSA at ICU admission (5.6%). After matching, the overall impact of OSA on length of ICU stay was not significant ( $p=0.24$ ). In a predefined subgroup analysis, there was a significant impact of OSA on the length of ICU stay for patients with BMI over 40 kg/m<sup>2</sup> (IRR: 1.56 [1.05; 2.32],  $p=0.03$ ). OSA status had no impact on ICU or hospital mortality and VAP.

**Conclusion:** In general, known OSA did not increase the ICU stay except for patients with both OSA and morbid obesity.

## Introduction

Obstructive sleep apnea (OSA) is nowadays considered as one of the most frequent chronic diseases, with multi-organ consequences and a high societal burden. OSA is associated with a relatively high risk of cardiovascular and metabolic comorbidities, along with an increased risk of mortality.[1-3] OSA patients often present multiple comorbidities [4] such as obesity, diabetes, hypertension, ischemic heart disease, heart failure and/or stroke, which are also frequently the underlying causes for intensive care unit (ICU) admission.[5]

OSA is frequently associated with obesity, which has reached epidemic levels in some countries.[6, 7] The prevalence of obese patients in critical care units reaches nearly 25%, with a progressive increase in the proportion of patients with morbid obesity.[8-10] Obese patients admitted to an ICU require more complex management and those with OSA often need continuous positive airway pressure (CPAP) treatment.[11] For patients admitted and surviving acute hypercapnic respiratory failure the prevalence of OSA increases to 65%.[12, 13] In addition, extensive data have demonstrated that undiagnosed OSA syndrome is associated with an increased risk of poor outcomes and higher mortality in the postoperative period.[14, 15] During an ICU stay obese patients are more prone to infectious complications such as ventilator acquired pneumonia or catheter related infections.[10] There is also at greater risk of adverse events such as decubitus complications, eschars or phlebitis.[16, 17] Finally, while obesity in ICU patients is not systematically associated with an increase in mortality,[13] obese patients have longer lengths of ICU stay than non-obese patients.[9, 18-20]

The prevalence of OSA in the ICU population has been reported as being between 7.8% and 10.3% according to two retrospective American surveys.[5, 21] These studies suggested a significant impact of OSA on ICU prognosis (length of stay, ICU or hospital mortality) but

were partially flawed by a poor assessment of confounding factors. Indeed, while they reported that OSA was associated with reduced mortality, the impact of potential confounders (obesity, comorbidities) was not assessed. Another small study showed an apnea-hypopnea index (AHI)  $\geq 15$  in 61% (22/36) of patients 10 days after ICU discharge.[22] The obesity paradox was evoked by the authors to explain improved survival without adjustment on body mass index. In the literature the obesity paradox is defined as improved survival in some specific obese subpopulations.[23] In general, obesity is associated with lower ICU mortality, [24, 25] and this is particularly true for obese patients presenting with ARDS or acute lung injury [26]. The suggested explanations for this survival advantage are an increased metabolic reserve and more intense monitoring as interventions in this population are considered to have higher risk. [23] As the majority of OSA patients are obese, this obesity paradox may contribute to ICU outcomes and should be considered as an important confounding factor.

Our main hypothesis was that obesity is causally linked to both OSA and survival; (i.e. it acts as a confounder in the relationship between OSA and prognosis).

The objective of this retrospective observational study was to investigate the impact of OSA on ICU patients' outcomes (length of stay in ICU, ICU mortality, in-hospital mortality, and ventilator-associated pneumonia (VAP)).

## **Material and Methods**

### **Data source**

Patients with OSA were identified in the prospectively recorded data from two ICUs participating in the French “OutcomeRea” network. The two centers were selected because of the availability of hospital medical records containing OSA status. Methods for data collection and quality control of the database have been described in detail elsewhere.[27] In accordance with French law, the OutcomeRea database was registered with the French data protection agency, “La Commission Nationale de l’Informatique et des Libertés (#999262)”. The objectives of this data collection were approved by the institutional review board (#5891) of Clermont-Ferrand University Hospital (Clermont-Ferrand, France).

### **Study population and OSA identification**

The hospital records of patients aged 18 years and older and included in the OutcomeRea database between January 2006 and May 2017 were screened. Patients with therapeutic limitations or discharged alive within one day of ICU admission were not included in this study. Patients with physician reported OSA assessment at ICU admission were classified into two groups according to their OSA status (diagnosed OSA at ICU admission or no-OSA). OSA status was based on patient self-reporting or reports by their primary care or respiratory physician following OSA assessment by respiratory polygraphy or polysomnography prior to ICU admission. We did not have access to detailed data from sleep studies allowing us to grade OSA severity; and adherence to CPAP (if implemented) was not available.

### **Primary and secondary objectives**

The primary objective was the length of ICU stay. Sensitivity analyses were performed for patients who were alive at ICU discharge and according to morbid obesity (BMI > 40 kg/m<sup>2</sup>)

or not ( $\text{BMI} \leq 40 \text{ kg/m}^2$ ). The secondary objectives were: 1) ICU mortality, 2) in-hospital mortality and 3) ventilatory acquired pneumonia (VAP).

### **Statistical analyses**

A nested “exposed-unexposed” design was chosen owing to the large size of the initial cohort (5,146 eligible patients). It was technically impossible to run a quality control on more than five thousand hospitalization reports, so a case-control design was preferred to a standard cohort study. The data quality was then verified for each individual case and control. We used 1:n matching to improve the study power [28, 29] with OSAS patients matched (1:n, where  $n \leq 2$ ) with non-exposed patients using an exact matching method with replacement based on the following characteristics: gender, body mass index (BMI) and age (more details on matching criteria are given in the supplementary material). As the number of unexposed patients was higher than the number exposed to OSA, a minimal sample size of 576 patients (one exposed for two unexposed) was calculated as being sufficient to reach a power greater than 90 % to show a one-day increase in ICU stay ( $\pm 4$  days). [5, 18] The quality of matching was assessed using the standardized mean differences. A sensitivity analysis was performed by including the SAPS II score as a matching factor. The results were not different and are presented in Supplementary Material Tables S4 and S5.

A description of the patients’ characteristics was performed using number and percentage for qualitative variables, and median and interquartile range for quantitative variables. A chi square test for qualitative variables, or a Mann-Whitney test for quantitative variables, was performed to compare OSA and non-OSA patients.

The primary outcome was assessed by using a negative binomial regression stratified on the matched pairs. A univariate analysis was first performed to select variables for which

significant differences remained after matching (p-value <0.05). The following variables were selected for their clinical relevance and were included in the final model: alcohol consumption, chronic cardiovascular disease (New York Heart Association NYHA class IV), chronic hepatic disease (biopsy proven cirrhosis and documented portal hypertension; episodes of past upper gastro-intestinal bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma), chronic respiratory disease (chronic restrictive, obstructive, or vascular lung disease resulting in severe exercise restriction; documented hypoxemia or hypercapnia; secondary polycythemia; severe pulmonary hypertension (>40 mmHg); ventilator dependence), chronic obstructive pulmonary disease (COPD), the SAPS II score, BMI and OSA status. Multicollinearity analysis was conducted by using the V-Cramer test to avoid the inclusion of dependent variables in the multivariable analysis. To account for a possible relation between OSA and BMI, an interaction term was added to the model.

The impact of OSA syndrome on the secondary objectives (in-ICU and in-hospital mortality and VAP) was assessed using conditional logistic regression.

Statistical analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA). A p value less than 0.05 was considered significant.

## **Results**

### **Population and patient characteristics**

From 22,388 patients registered in the OutcomeRea® database, data from 5,146 patients from two representative centers were considered, for whom 289 (5.6%) had a physician-validated diagnosis of OSA (Figure 1). Overall, patients had a median age of 61 years (interquartile range IQR: [48.1; 72.7]), were mainly males (N=3112, 60.5%), had a median BMI of 22.5 [21.2; 26.1] and a SAPS II score at ICU admission of 42 [29; 56]. The reasons for ICU admission was mainly medical (N=4,273, 83.1%) (Table 1).

OSA patients were older with a median age of 65.3 [58.5; 73.5], had a higher BMI (29.4 [23.5; 35.3] kg/m<sup>2</sup>) and a higher prevalence of chronic disease than non-OSA patients (Table 1).

### **Matched populations**

OSA patients were matched to non-OSA ones by age, sex and BMI. The final dataset included 867 patients, 289 OSA and 589 non-OSA patients. A comparison of the two matched groups showed no significant difference except for the following types of comorbidity: respiratory, cardiovascular, kidney, hypertension and COPD (Supplemental Tables S1 and S2). There were no differences between the groups in the primary outcome, the length of ICU stay: 5 days [3; 11] for OSA patients versus 5 days [3; 12] for the non-OSA group (p=0.59) (Table 2). There were no differences between the groups in the secondary outcomes: in-ICU death (p=0.39), in-hospital death (p=0.19), 28-day death (p=0.69), 90-day death (p=0.28), 1-year death (p=0.40), number of VAP (p=0.62) and duration of invasive mechanical ventilation (p=0.30).

### **Primary outcome**

After adjustment for comorbidities (respiratory, cardiovascular, kidney, hypertension and COPD) and the SAPS II score, the impact of OSA on length of ICU stay was not significant ( $p=0.24$ ). However, in subgroup analysis, the combination of OSA and a BMI above 40 kg/m<sup>2</sup> was associated with a significant increase in the length of ICU stay: IRR: 1.56 [1.05; 2.32],  $p=0.03$ . In patients remaining alive in the ICU, the results remained unchanged (Figure 2). A sensitivity analysis (Table S3) including three BMI bands (less or equal to 30, 30 to 40 and more than 40 kg/m<sup>2</sup>) confirmed that the link between obesity and poor OSA outcomes was restricted to BMI > 40 kg/m<sup>2</sup>.

### **Secondary outcomes**

There was no significant impact of OSA on in-ICU mortality (OR: 0.85 (0.54; 1.35),  $p=0.49$ ), in-hospital death (OR: 0.83 (0.56; 1.22),  $p=0.34$ ) or VAP: OR: 0.81 (0.51; 1.28),  $p=0.37$ ). When 28-day, 90-day or 1-year mortality were considered, there was no significant impact of OSA on the patient outcomes (Figure 2).

## Discussion

Patients presenting with OSA at ICU admission were generally older, with a higher BMI and a larger number of comorbidities than non-OSA patients; consistent with the current literature, and reflecting the quality of the database. Nevertheless, using an appropriate exposed/unexposed matched design we demonstrated no negative impact of OSA on the length of ICU stay or mortality in the whole studied population. However, after adjustment for confounders, OSA significantly increased the length of ICU stay in the morbidly obese, i.e. with a BMI above 40kg/m<sup>2</sup>.

The global prevalence of OSA in the middle-aged population is above 20%. [30, 31] This prevalence has substantially increased over the last few decades owing to the parallel epidemics of obesity and type 2 diabetes. OSA prevalence is even higher in patients suffering from cardiovascular diseases, reaching 50% in hypertension, arrhythmia or stroke patients. [2] The physician-reported prevalence of OSA of only 5.6% found in our study reflects a massive under-diagnosis of OSA in ICU patients. The small number of studies implementing polysomnographic assessment of ICU survivors reported a much higher OSA prevalence. [12, 13, 22] OSA prevalence certainly appears to differ from one ICU to another depending on the predominant ICU activity (i.e. surgical versus medical, pediatric neurological or trauma oriented ICU).

There is little data regarding the specific impact of OSA on the outcomes of ICU patients. Available studies are flawed by small sample sizes, retrospective design and poor adjustment for confounders. One study even suggested a protective effect of OSA with a reduction in both ICU and hospital mortality: the obesity paradox. [5] The link between obesity and ICU prognosis has been extensively studied. [10] For an unselected obese population admitted to an ICU, obesity was not associated with an increase in ICU mortality, although it did lengthen the duration of ICU stay and increased the use of hospital resources.

When examining the different sub-groups, length of ICU stay seemed to be longer in extremely obese subjects.[10] Our data from a well-managed prospective cohort shows that associated OSA is one of the factors contributing to this increase in length of ICU stay in patients with a BMI  $\geq 40$  kg/m<sup>2</sup>. This combination of OSA and morbid obesity might be associated with some specific frailties. OSA is known to be associated with renal decline[32, 33] and it has been reported that OSA is linked with a higher risk of acute kidney damage in critically ill patients.[34] Also, sleep apnea and deterioration in sleep quality might impair immune responses and protection against infections;[35] e.g. for influenza patients with exacerbation OSA was a significant contributor to the reasons for ICU admission.[36] Moreover, OSA patients are more sensitive to opioids developing central apneas after extubation.[37] Intravenous fluid loading also influences OSA severity [38, 39]. Taken together, these reports advocate that, as for obese individuals, the detection of underlying OSA should impact ICU management.

Our study has several limitations. As discussed above, OSA prevalence was probably underestimated. This might have masked or reduced the impact of OSA on poor ICU outcomes. Moreover, all OSA diagnoses were self-reported by physicians; patients had been assessed by polysomnography or respiratory polygraphy, but detailed data were not available. This prevented us from performing a dose-response type analysis between OSA severity and outcomes. Our ICU population was characteristic of “medical” ICUs with only a small proportion of perioperative patients referred to the unit. While, there is considerable evidence that OSA patients are at high risk of perioperative complications, [40] this was beyond the scope of our data. We did not have access to the detailed data from sleep studies that would have enabled us to grade OSA severity. In addition, data on adherence to CPAP treatment and CPAP usage during the ICU stay were not available. Finally, some heterogeneity in ICU admission criteria and patient management between the two study centers might have

introduced a selection bias; although we attempted to mitigate this by using a nested case-control study design.

### **Conclusion and perspectives**

OSA prevalence is largely underestimated in ICU populations. According to our results, known OSA is not demonstrated to be an independent risk factor for adverse outcomes in ICU patients. For morbidly obese ICU patients, it is necessary to implement appropriate screening techniques and management to minimize OSA associated risk of prolongation of their ICU stay.

### **Acknowledgement**

We thank Alison Foote (Grenoble Alpes University Hospital, France) for critically editing the manuscript.

**Author contributions:** JFT is the guarantor of the study. SB, JLP and JFT conceived the study; LMG, NT, CS, CD, RT, BM, JLP and JFT acquired the data. SB, SR, AS and JFT performed the statistical analysis. All authors contributed to the interpretation of the findings. SB, LMG, JLP and JFT prepared the first draft of the manuscript, and all authors critically revised the manuscript for intellectually important content. All authors gave final approval for the publication of the work, and accept responsibility for the integrity of the work.

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## **Figure title and legends**

**Figure 1 Title: Study flow chart**

**Figure 2: Multivariable stratified negative binomial or logistic regressions assessing OSA impact on outcomes.** Interaction between OSA and BMI was significant ( $p < 0.01$ ). The type III p value for the primary outcome was not significant ( $p = 0.24$ ). All models were adjusted on comorbidities (respiratory, cardiovascular, kidney, hypertension and COPD) and initial severity which was assessed by the SAPS II score.

**Table 1: Baseline characteristics at ICU admission according to OSA status**

Characteristics	All patients N=5,146	No OSA N=4,855	OSA N=291	P value
Age (years)	61.1 [48.1 ; 72.7]	60.7 [47.6 ; 72.7]	65.3 [58.3 ; 73.5]	<.01
Gender (male)	3112 (60.5)	2904 (59.8)	208 (71.5)	<.01
Body Mass Index (kg/m <sup>2</sup> )	22.5 [21.2 ; 26.1]	22.5 [21.2 ; 25.7]	29.4 [23.5 ; 35.3]	<.01
Obesity	616 (12)	478 (9.8)	138 (47.4)	<.01
SAPS II score	42 [29 ; 56]	42 [29 ; 56]	43 [30 ; 55]	0.30
Charlson score	1 [0 ; 3]	1 [0 ; 2]	2 [1 ; 3]	<.01
Main symptom requiring ICU admission				<.01
Scheduled surgery, trauma or continuous monitoring	1381 (26.9)	1320 (27.2)	61 (21)	
Multiple organ failure or shock	1198 (23.3)	1122 (23.1)	76 (26.1)	.
Coma	1061 (20.6)	1022 (21.1)	39 (13.4)	.
Renal failure	208 (4)	195 (4)	13 (4.5)	.
Respiratory distress	1294 (25.2)	1192 (24.6)	102 (35.1)	.
Type of ICU admission				0.59
Scheduled surgery	242 (4.7)	225 (4.6)	17 (5.9)	.
Emergency surgery	628 (12.2)	595 (12.3)	33 (11.4)	.
Medicine	4273 (83.1)	4033 (83.1)	240 (82.8)	.
Chronic diseases				
Immunosuppression	953 (18.5)	916 (18.9)	37 (12.7)	<.01
Liver	254 (4.9)	230 (4.7)	24 (8.2)	<.01
Respiratory	406 (7.9)	335 (6.9)	71 (24.4)	<.01
Cardiovascular	455 (8.8)	400 (8.2)	55 (18.9)	<.01
Kidney	418 (8.1)	401 (8.3)	17 (5.8)	0.14
Hypertension	543 (10.6)	470 (9.7)	73 (25.1)	<.01
COPD	455 (8.8)	397 (8.2)	58 (19.9)	<.01
Diabetes	1015 (19.7)	914 (18.8)	101 (34.7)	<.01

**Table 2. Patient outcomes according to OSA status**

Outcomes	No OSA N=578	OSA N=289	Pvalue*
In ICU death (%)	103 (17.8)	45 (15.6)	0.39
In hospital death	136 (23.5)	57 (19.7)	0.19
Death at 28d	110 (19)	52 (18)	0.69
Death at 90d	142 (24.6)	62 (21.5)	0.28
Death at 1y	161 (27.9)	73 (25.3)	0.40
Length of ICU stay (alive)	5 [3 ; 12]	5 [3 ; 11]	0.59
Number of VAP			0.62
0	504 (87.2)	257 (88.9)	
1	50 (8.7)	18 (6.2)	
2	19 (3.3)	11 (3.8)	
>2	5 (0.9)	3 (1)	
Duration of IMV	2 [0 ; 9]	1 [0 ; 6]	0.30

\*p value: conditional logistic regression on matched dataset, ICU: intensive care unit, VAP: ventilator

associated pneumonia, IMV: invasive mechanical ventilation

5,146 eligible patients  
from two ICU centers

291 patients  
diagnosed with OSA  
(5.6%)

4,855 patients  
without a diagnosis  
of OSA (94.4%)

Exact matching

289 cases

578 controls

### Primary outcome: Number of days in ICU

No OSA and BMI  $\leq$  40

No OSA and BMI >40

OSA and BMI  $\leq$  40

OSA and BMI >40

IRR [95% CI], pvalue

Ref.

0.95 [0.70; 1.30], p=0.77

0.90 [0.71; 1.14], p=0.40

1.56 [1.05; 2.32], p=0.03

### Sensitivity analyses

Alive patients only

0.89 [0.70; 1.14], p=0.36

### Secondary outcomes

In- ICU mortality

0.85 [0.54; 1.35], p=0.49

In-hospital mortality

0.83 [0.56; 1.22], p=0.34

28-day mortality

0.96 [0.63; 1.46], p=0.85

90-day mortality

0.86 [0.60; 1.25], p=0.44

1-year mortality

0.94 [0.66; 1.34], p=0.72

Ventilatory acquired pneumonia

0.81 [0.51; 1.28], p=0.37

