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ABSTRACT

Background

Patients with obesity are at higher risk for community-acquired and nosocomial infections. However, no study has specifically evaluated the relationship between obesity and ventilator-associated pneumonia (VAP).

Research question

Is obesity associated with increased incidence of VAP?

Study design and methods

Post-hoc analysis of the NUTRIREA-2 open-label RCT, performed in 44 French ICUs. Adults receiving invasive mechanical ventilation and vasopressor support for shock, and parenteral nutrition or enteral nutrition were included. Obesity was defined as body mass index (BMI) ≥ 30 kg/m2 at ICU admission. VAP diagnosis was adjudicated by an independent blinded committee, based on all available clinical, radiological, and microbiological data. Only first VAP episodes were taken into account. Incidence of VAP was analyzed using Fine and Gray model, with extubation, and death as competing risks.

Results

699 (30%) of the 2325 included patients had obesity. 224 first VAP episodes were diagnosed (60, and 164 in obese, and non-obese groups; respectively). The incidence of VAP at day 28 was 8.6% vs 10.1% in the two groups (HR: 0.85, (95% CI 0.63-1.14), p=0.26). After adjustment on gender, McCabe score, age, anti-ulcer treatment, and SOFA at randomization, the incidence of VAP remained non-significant between obese and non-obese patients (HR 0.893 (95% CI 0.66-1.2), p=0.46). Although no significant difference was found in duration of mechanical ventilation, and ICU length of stay; 90-day mortality was significantly lower in

obese than in non-obese patients (272 of 692 (39.3%) patients vs 718 of 1605 (44.7%), p=0.02). In a sub-group of patients (n=123) with available pepsin, and alpha-amylase measurements, no significant difference was found in rate of abundant microaspiration of gastric contents, or oropharyngeal secretions between obese and non-obese patients.

Interpretation

Our results suggest that obesity has no significant impact on the incidence of VAP.

Clinical trial registration: Not applicable

Key words:

Obesity, intubation, mechanical ventilation, microaspiration, pneumonia

Abbreviations:

BMI, body mass index; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; SAPS, simplified acute physiology score; VAP, ventilator-associated pneumonia

INTRODUCTION

The prevalence of obesity is high in the ICU, ranging from 19% up to 66% of critically ill patients [1,2]. Obesity appears to be associated with lower mortality in the critically ill patients, but increases the risk of complications in several organ systems [3]. Previous studies have suggested a high incidence of community-acquired and healthcare-associated infections in obese patients [4–7]. Several explanations were suggested for the high incidence of infection in obese patients, including comorbidities, frequent hospitalization, changes in gut microbiota, chronic inflammation, and altered immunity [3,6,8,9]. The interaction between adipocytes and immune cells could be responsible for dysregulation of both innate and adaptive immunity [10]. In addition, adipose tissue produces inflammatory mediators resulting in chronic inflammation and elevated baseline CRP levels in obese patients [10,11].

Previous studies reported higher rates of hospital-acquired and surgical site infections [4,5,12,13]. Similarly, in a post-hoc analysis of a large international database, obesity was found to be associated with higher incidence of ICU-acquired infections. However, no information on ventilator-associated pneumonia (VAP) incidence was given in that study [7].

VAP is the most common ICU-acquired infection [14]. Although mortality attributable to VAP is a matter for debate [15], this infection is associated with increased duration of mechanical ventilation, length of ICU stay and cost [16]. Better understanding of pathophysiology and risk factors for VAP could be helpful to improve its prevention and treatment [17].

To our knowledge, no study has specifically evaluated the relationship between obesity and VAP. However, as discussed above, obesity could be associated with increased

risk for infection. In addition, other specific factors might favor VAP occurrence in obese patients, such as atelectasis, and difficult airway management [3].

Therefore, we perform this post-hoc analysis of the NUTRIREA 2 study to evaluate the relationship between obesity and VAP. The primary aim was to determine the impact of obesity on VAP incidence. Secondary objectives were to evaluate the relationship between obesity, and early-onset VAP, duration of mechanical ventilation, ICU length of stay, and 90-day mortality. The impact of obesity on microaspiration of gastric and oropharyngeal secretions was also evaluated in a subgroup of study patients.

STUDY DESIGN AND METHODS

This was a post-hoc analysis of the randomized controlled multicenter open-label NUTRIREA2 study (ClinicalTrials.gov, identifier NCT01802099), performed in 44 French ICUs. Adults (18 years or older) receiving invasive mechanical ventilation, vasopressor support for shock, and parenteral or enteral normocaloric (20-25 kcal/kg per day) nutrition, within 24 h after intubation were included [18,19].

The study protocol was approved by the ethics committee of the French Intensive Care Society and appropriate French authorities (Comité de Protection des Personnes de Poitiers). According to French law, because the treatments and strategies used in the study were classified as standard care, there was no requirement for signed consent, but the patients or next of kin were informed about the study before enrolment and confirmed this fact in writing.

All patients included in the NUTRIREA2 study were eligible for this study. Patients with no information on body mass index (BMI) were excluded from the current study.

Definitions

The primary outcome was the incidence of VAP. Secondary outcomes were the incidence of early-onset VAP, duration of mechanical ventilation, ICU length of stay, 90-day mortality rate, and the incidence of abundant microaspiration of gastric contents or oropharyngeal secretions.

Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2 at ICU admission. VAP diagnosis was adjudicated by an independent blinded committee, based on all available clinical, radiological, and microbiological data. Early-onset VAP was defined as VAP occurring before day 5 after starting invasive mechanical ventilation [18]. Abundant microaspiration of gastric contents was defined by the presence of pepsin at significant concentration (> 200 ng

/ ml) in >30% of tracheal aspirates [20,21]. Abundant microaspiration of oropharyngeal secretions was defined by the presence of amylase at significant concentration (> 1685 IU / ml) in >30% of tracheal aspirates [20,21]. Methods used for pepsin, and alpha-amylase measurements, collection of tracheal aspirates, and VAP prevention were described elsewhere [21].

Primary and secondary outcomes, except abundant microaspiration, were evaluated in all study patients. The impact of obesity on abundant microaspiration was evaluated in a subgroup of patients with available measurement of pepsin or alpha-amylase (n=123) in tracheal aspirates collected during the 48h after randomization. These patients were included in a planned ancillary study, which evaluated the impact of enteral nutrition on microaspiration [21].

Statistical analysis

Baseline characteristics were compared according to obesity status using student t-tests or Wilcoxon non-parametric tests for continuous variables and $\chi 2$ or Fisher's exact tests for categorical variables.

Incidence of VAP was analyzed using Fine and Gray competing risk model [22], with extubation and death as competing risks. An adjusted analysis was performed including variables collected at ICU admission with $p < 0.2$ in the univariate analysis. The choice of adjustment variables was also based on scientific knowledge and considered potential collinearity.

Incidence of early VAP was analyzed using Fine and Gray competing risk model with extubation and death as competing risks. The rate of patients with abundant microaspiration of gastric contents, or abundant microaspiration of oropharyngeal secretions was compared

between study groups using Chi-square. The related quantitative parameters were studied using Wilcoxon non-parametric tests. Death at day 90 was analyzed using Chi-square. Incidence of ICU discharge alive and extubation were analyzed using a Fine and Gray competing risk model with death as a competing risk.

SAS (version 9.4), and R (version 3.6.3) were used for statistical analyses.

RESULTS

A total of 2410 patients were randomized in the NUTRIREA2 trial, 85 (4%) patients were excluded because BMI was not available. Among the 2325 patients included in this post-hoc analysis, 699 (30.1%) had obesity (Figure 1). Pepsin and alpha-amylase were quantitatively measured in 852 tracheal aspirates, collected from 123 patients.

Patient characteristics

At ICU admission, female gender, age, McCabe score, Knaus score, acute illness at ICU admission and pre-existing illness at ICU admission significantly differed between obese and non-obese patients (Table 1).

At randomization, positive end expiratory pressure (PEEP), FiO_2, renal replacement therapy, insulin use, antiulcer medication, glucose, creatinine, albumin levels, and SOFA score significantly differed between obese and non-obese patients (Table 2).

During the 7 days following randomization, daily calorie intake (median (IQR) 19 (15, 21) vs 19.2 (15.8, 22.2), p=0.01) was significantly lower, and incidence of patients with at least one vomiting (24% vs 19.3%, HR 1.29 (95% CI 1.07-1.54), p=0.008) was significantly higher in obese than in non-obese patients; respectively.

Outcomes

A total of 224 first VAP episodes were diagnosed in study patients (60, and 164 episodes in obese and non-obese patients; respectively). No significant difference was found in the incidence of VAP between obese and non-obese patients at day 28 (8.6% vs 10.1%; HR 0.85 (95% CI 0.63-1.140), p=0.26) (Figure 2). After adjustment on gender, McCabe score, age, anti-ulcer treatment, and SOFA at randomization, the incidence of VAP remained non-significant between obese and non-obese patients (HR 0.89 (95% CI 0.66-1.20), p=0.46).

A sensitivity analysis was performed for center effect. Similar results were found on the primary outcome (HR: 0.85, CI95%: [0.60; 1.19], p=0.33).

A total of 46 first early-onset episodes were diagnosed (12, and 34 in obese and non-obese patients). No significant difference was found in the incidence of early-onset VAP at day 28 between the two groups (1.7% vs 2.1%, HR 0.82 (95% CI 0.43-1.58), p=0.55).

Although the incidence of extubation at day 28 (66.1% vs 65.2% (HR 0.99 (95% CI 0.89-1.08), p=0.71) (Figure 3), and ICU discharge alive at day 28 (58.4% vs 57.9% (HR 0.99 (95% CI 0.89-1.09), p=0.79) (Figure 4) were not significantly different between obese and non-obese patients; 90-day mortality was significantly lower in obese than in non-obese patients (Table 3).

The distribution of study patients and patients with VAP, based on BMI, is presented in table 4.

No significant difference was found between obese in non-obese patients in the percentage of patients with abundant microaspiration of gastric secretions (15 of 49 (30.6%) patients vs 14 of 74 (18.9%), p=0.13) or oropharyngeal secretions (31 of 49 (63.3%) patients vs 48 of 74 (64.9%), p=0.86).

DISCUSSION

The main results of our study are the following: the incidence of VAP was not significantly different between obese and non-obese patients. Similarly, no significant difference was found in the incidence of early-onset VAP between obese and non-obese patients. Obesity had no significant impact on duration of mechanical ventilation, length of ICU stay, or microaspiration of gastric contents, or oropharyngeal secretions. 90-day mortality was significantly lower in obese than in non-obese patients.

To our knowledge, our study is the first to evaluate the relationship between obesity and VAP. The strengths of our study are multicenter design, large number of included patients, and stringent criteria used for VAP definition. However, several limitations should also be outlined. First, our results only apply to patients with shock. Whether obesity is associated with VAP in critically ill patients without shock is still to be investigated. Second, some risk factors for VAP such as antimicrobial use, head-of-bed elevation, and tracheal cuff pressure were not assessed. Third, microaspiration was only evaluated in a small subgroup of patients. However, the impact of obesity on microaspiration was a secondary objective of our study. Fourth, center effect was not taken into account in the analyses. However, we performed a sensitivity analysis for center effect, and similar results were found regarding primary outcome (online supplementary material). In addition, the diagnosis of VAP was adjudicated by an independent blinded committee, which might have also allowed adjustment for center effect. Finally, our study was a post-hoc analysis of the NUTRIREA2 database.

At least two explanations could be provided for the absence of significant impact of obesity on VAP incidence. First, several significant differences were identified between

obese and non-obese patients and could have influenced our results, including gender, comorbidities, and acute illness at ICU admission; PEEP level, FiO_2, renal replacement therapy, insulin use, antiulcer treatment, glucose, creatinine, and albumin level at randomization; daily-calorie intake, and vomiting during the 7 days following randomization. However, after adjustment for several confounders, no significant relationship was found between obesity and VAP. Second, in spite of the strong rationale suggesting that obesity could be associated with high incidence of VAP, obese patients could be at similar risk for developing VAP as non-obese patients. One could argue that the incidence of important risk factors for VAP, such as long duration of mechanical ventilation, tracheobronchial colonization, and microaspiration of contaminated secretions is probably similar in obese and non-obese patients. Our findings on the absence of significant impact of obesity on microaspiration of gastric contents, or orpharyngeal secretions are in line with this possibility. In a case-control matched study, Frat et al. [23] aimed to determine the impact of severe obesity (BMI ≥ 35 kg/m^2) on mortality and morbidity. A lower, but not statistically significant, incidence rate of ventilator-associated pneumonia (VAP) was found (7.8 vs 12.4 VAP episodes per 1000 mechanical ventilation days in obese and non-obese patients; respectively). Our group performed a case-control matched study to determine the accuracy of leptin in predicting VAP occurrence [24]. No significant difference in BMI, or in obesity rate, was found between patients with VAP and their controls.

Our results also suggest that obesity is associated with reduced risk for 90-day mortality rate. This result is in line with recent studies, and confirms the “obesity paradox”. Several mechanisms were suggested to explain this phenomenon. Adipose tissue may provide energy and lipid soluble nutrients during highly metabolic states, and immunomodulatory effects of substances secreted by fat cells might attenuate the

inflammatory response during acute illness and improve survival [9,11,25]. Additionally, better exposure to adequate healthcare was also reported in obese patients [3]. However, 90-mortality was a secondary outcome in our study, and no adjustment was performed for potential confounders.

CONCLUSIONS

Our results suggest that obesity is not associated with increased risk for VAP. Although obesity was associated with reduced 90-day mortality rate, no significant association was found between obesity and duration of mechanical ventilation, length of ICU stay, or microaspiration of gastric and oropharyngeal secretions.

Take-Home Points

Study question: Is obesity associated with increased risk for ventilator-associated pneumonia?

Results: In critically ill patients, receiving invasive mechanical ventilation for >48h, obesity is not associated with increased incidence of ventilator-associated pneumonia.

Interpretation: Obese patients are not at increased risk for ventilator-associated pneumonia.

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Guarantor
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Authors' contribution:
SN, AL, OP, and JR designed the study. AL performed the statistical analyses. All authors collected study data. The first draft was written by SN, AL, and OP. All authors participated in writing, and revising the manuscript.

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Declaration of interests
SN received personal fees from MSD, Bio Rad, BioMérieux, Gilead, and Pfizer. All other authors declare no competing interests.

Data Sharing
All data needed to evaluate the conclusions in this Article are present and tabulated in the main text. For individual de-identified raw data that underlie the results reported in this article, please contact the corresponding author.

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Figure legends

Figure 1

Flowchart

Figure 2

Relationship between obesity and VAP incidence at day 28.

Incidence of VAP at day 28: 8.6% *vs* 10.1%; HR: 0.845, 95% CI: [0.629; 1.140], p=0.26.

Incidence of ICU death without VAP prior at day 28: 26.0% *vs* 26.8%; HR: 0.982, 95% CI: [0.831; 1.160], p=0.83. Incidence of extubation without VAP prior at day 28: 59.8% *vs* 58.2%; HR: 1.00, 95% CI: [0.899; 1.110], p=1

Figure 3

Relationship between obesity and duration of mechanical ventilation.

The incidence of extubation at day 28 was 66.1% and 65.2% in obese and non-obese patients, respectively (HR=0.99; CI95%: [0.89; 1.08], p=0.71).

Figure 4

Relationship between obesity and length of ICU stay.

The incidence of ICU-discharge alive at day 28 was 58.4%, and 57.9% in the obese and non-obese patients; respectively (HR=0.99; 95% CI: [0.89; 1.09], p=0.79).

Table 1. Patient characteristics at ICU admission

	Obese (n=699)	Non-obese (n=1626)	p
Gender			0.02
Female	254 (36.3)	512 (31.5)	
Male	445 (63.7)	1114 (68.5)	
Age, years	67.8 [60.4, 75.3]	66.9 [55.9, 77.1]	0.0009
Weight, kg	97.3 [88.0, 110.0]	70.0 [61.0, 79.0]	-
BMI, kg/m^2	34.6 [31.8, 38.6]	24.6 [21.9, 27.0]	-
SAPS II[a]	58.0 [47.0, 74.0]	59.0 [45.0, 73.0]	0.93
McCabe score			0.01
Death expected within 5 years	237 (33.9)	527 (32.4)	
Death expected within 1 year	20 (2.9)	93 (5.7)	
No fatal underlying disease	442 (63.2)	1006 (61.9)	
Knaus score			<0.0001
Normal health status	97 (13.9)	399 (24.5)	
Moderate activity limitation	400 (57.2)	761 (46.8)	
Severe activity limitation due to chronic disease	190 (27.2)	430 (26.4)	
Bedridden patient	12 (1.7)	36 (2.2)	
Type of patients			0.95
Scheduled surgery	10 (1.4)	26 (1.6)	
Urgent surgery	39 (5.6)	93 (5.7)	
Medical	650 (93.0)	1507 (92.7)	
Acute illness at ICU admission			<0.0001
Cardiac arrest	68 (9.7)	184 (11.3)	
Acute heart failure	152 (21.7)	310 (19.1)	
Acute neurologic failure	43 (6.2)	138 (8.5)	
Acute respiratory failure	334 (47.8)	840 (51.7)	
Trauma	10 (1.4)	35 (2.2)	

Miscellaneous	92 (13.2)	119 (7.3)	
Cause of shock			0.97
Cardiac	133 (19.0)	307 (18.9)	
Sepsis	440 (62.9)	1016 (62.5)	
SIRS with noninfectious causes	45 (6.4)	114 (7.0)	
Other	81 (11.6)	189 (11.6)	
Pre-existing illness at ICU admission	530 (75.9)	1162 (71.6)	0.03
Chronic renal failure	111 (15.9)	201 (12.4)	
Liver disease	59 (8.4)	137 (8.4)	
Cardiovascular disease	166 (23.7)	363 (22.3)	
Chronic respiratory failure	128 (18.3)	215 (13.2)	
Neurological disease	88 (12.6)	222 (13.6)	
Diabetes	288 (41.2)	321 (19.7)	
Cancer or immune deficiency	165 (23.6)	515 (31.7)	
Esophageal, gastric, or duodenal ulcer	43 (6.2)	105 (6.5)	

Results are Median [Q1, Q3] or n (%)

BMI, body mass index; SAPS, simplified acute physiology score; ICU, intensive care unit.

[a]Missing data: 6, 9; in obese and non obese patients, respectively.

Table 2. Patient characteristics at randomization.

	Obese (n=699)	Non obese (n=1626)	p
PEEP, cmH_2O[a]	7.0 (5.0, 10.0)	6.0 (5.0, 9.0)	0.0002
FiO_2, %,	50.0 (40.0, 70.0)	50.0 (35.0, 70.0)	0.002
Prone position	29 (4.1)	72 (4.4)	0.76
Sedative drugs	601 (86.0)	1406 (86.5)	0.75
Dialysis	138 (19.7)	213 (13.1)	<0.0001
Insulin use	334 (47.8)	583 (35.9)	<0.0001
Prokinetic drugs	11 (1.6)	29 (1.8)	0.72
Anti-ulcer medication	328 (46.9)	658 (40.5)	0.004
Anti-infectious treatment	588 (84.1)	1357 (83.5)	0.69
Glucose, mmol/l[b]	9.7 (7.3, 12.5)	9.0 (6.8, 12.2)	0.002
Creatinine, µmol/L[c]	169.0 (107, 283)	125.4 (80, 209)	<0.0001
Lactate, mmol/l[d]	2.6 (1.6, 4.5)	2.6 (1.6, 4.7)	0.98
CRP, mg/l[e]	137.8 (54.5, 263.7)	140.0 (51.0, 254.5)	0.48
Albumin, g/l[f]	26.2 (21.6, 31.0)	25.0 (20.0, 30.0)	0.001
SOFA[g]	11.0 (9.0, 13.0)	10.0 (8.0, 13.0)	0.0001
Time from intubation to randomization, hour	15.3 (7.8, 20.8)	14.4 (7.3, 20.2)	0.14
Enteral nutrition (group of randomization)	354 (50.6)	805 (49.5)	0.62

Results are median [Q1, Q3] or n (%).

PEEP, positive end expiratory pressure; FiO2, fraction of inspired oxygen; CRP, reactive C protein; SOFA, sequential organ dysfunction assessment.

Missing data: [a] 1, 4; [b] 70, 181; [c] 5, 16; [d] 20, 68; [e] 299, 626; [f] 235, 679; [g] 1, 0; in obese and non obese patients, respectively.

Table 3. Impact of obesity on secondary outcomes

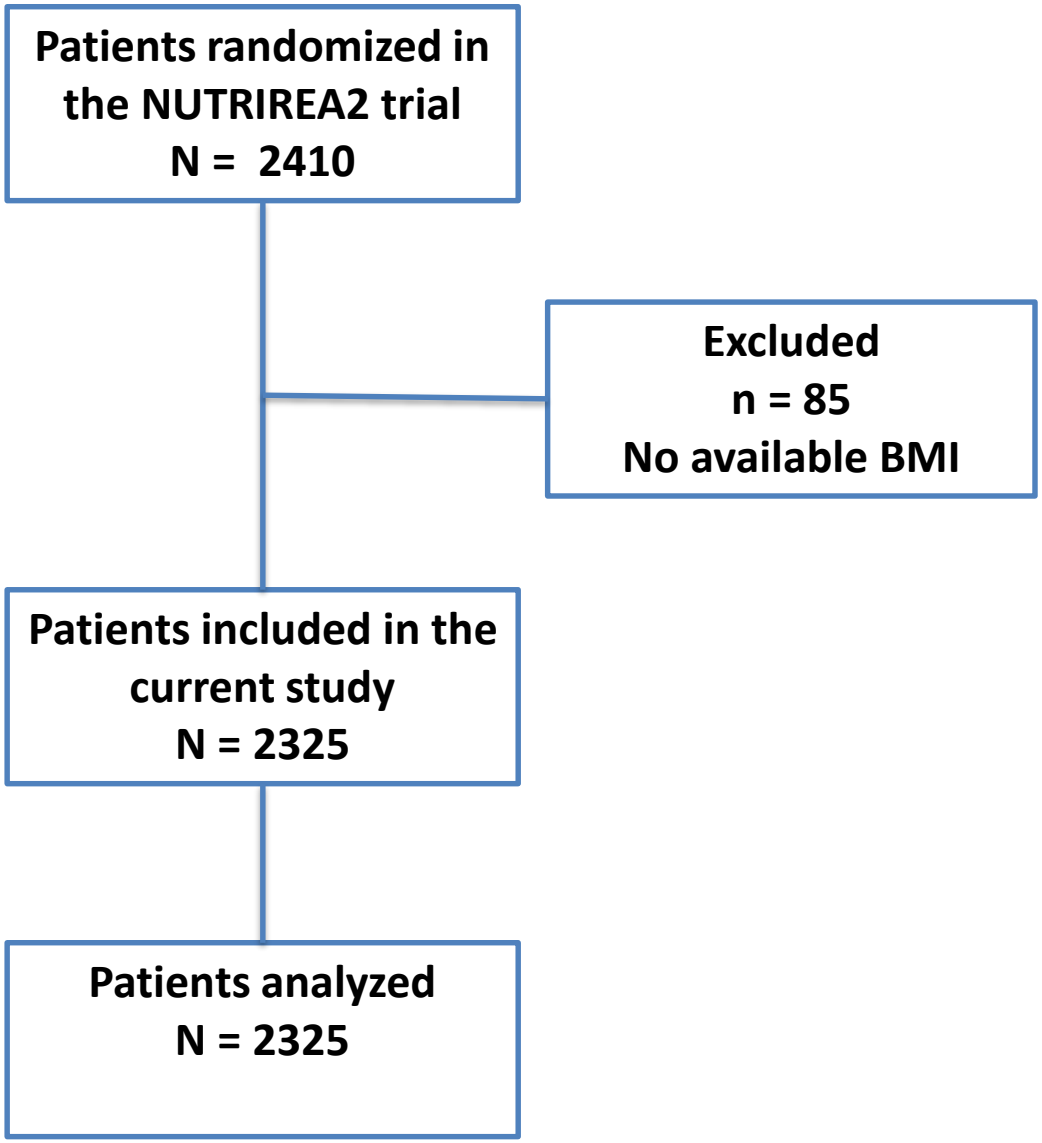
	Obese (n=699)	Non obese (n=1626)	p
Duration of mechanical ventilation			0.71
Patients alive, n1=498, n2=1136	8 (4, 14)	6 (3, 13)	
Patients dead before extubation, n1=201, n2=490	5 (2, 12)	7 (2, 14)	
ICU length of stay			0.79
Patients alive, n1=473, n2=1061	12 (7, 20)	9 (6, 17)	
Patients dead in the ICU, n1=226, n2=565	6 (2, 15)	8 (3, 15)	
90-day mortality	272/692 (39.3)	718/1605 (44.7)	0.02

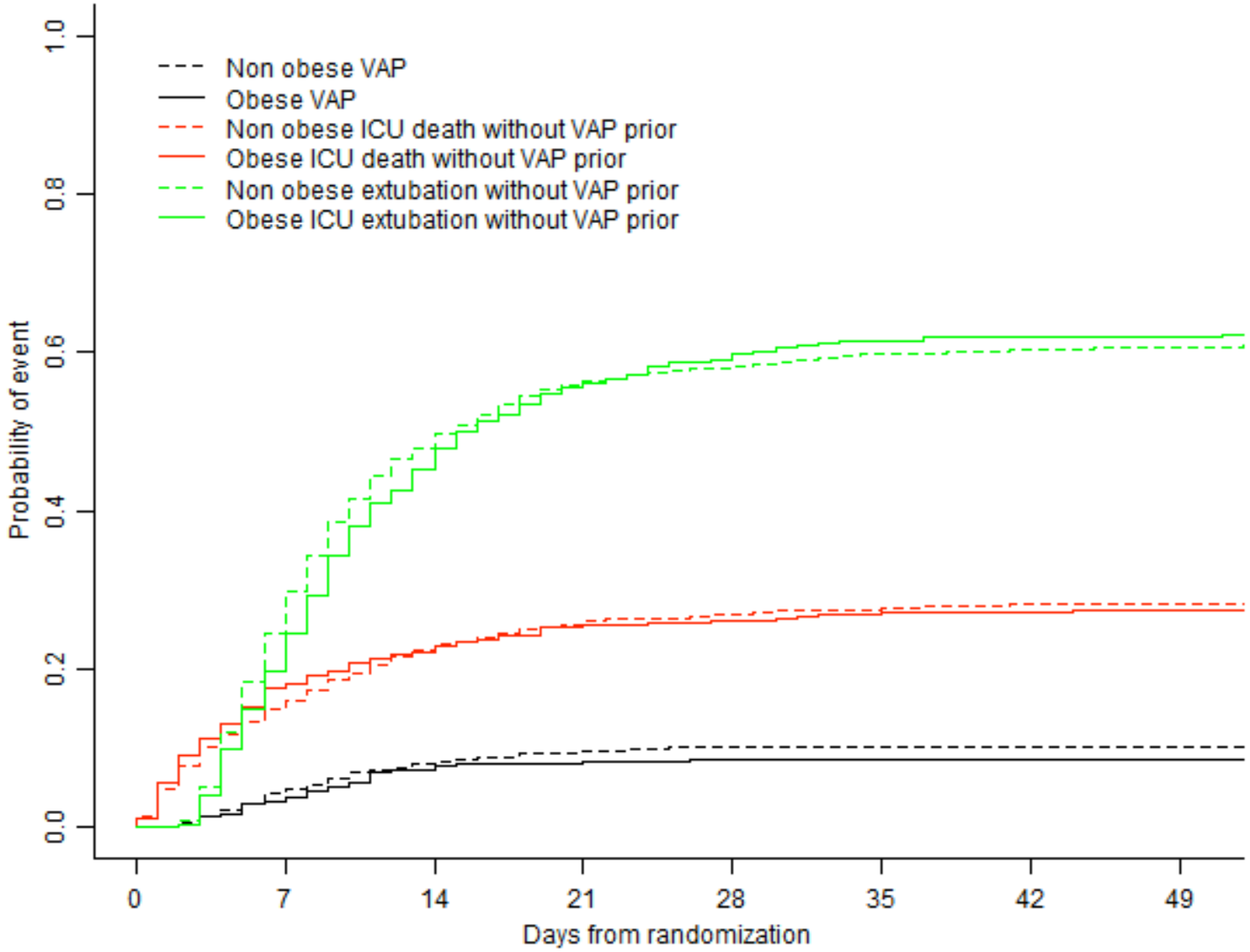
Results are Median [Q1, Q3], or n (%)

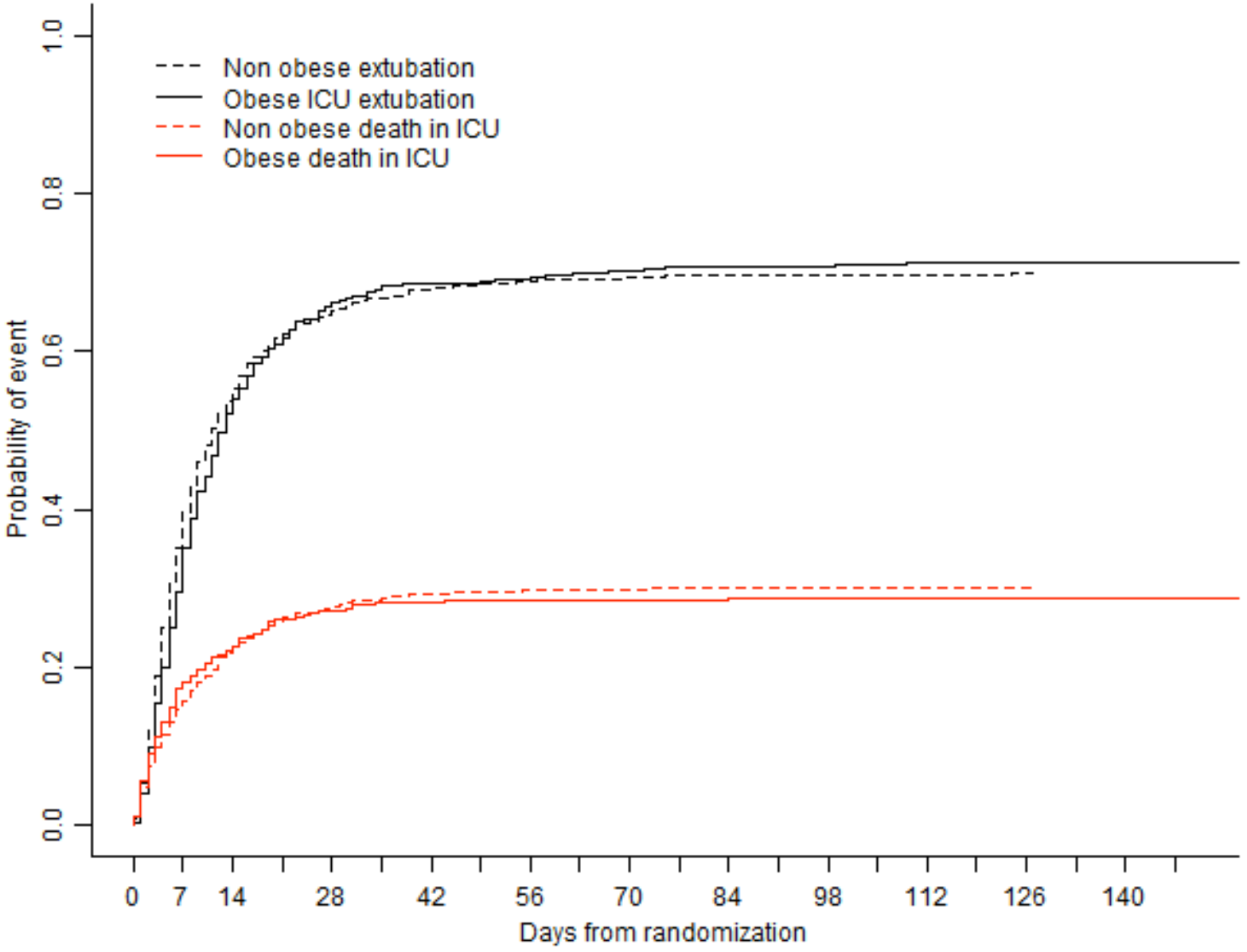
Table 4. distribution of study patients and patients with ventilator-associated pneumonia based on body mass index

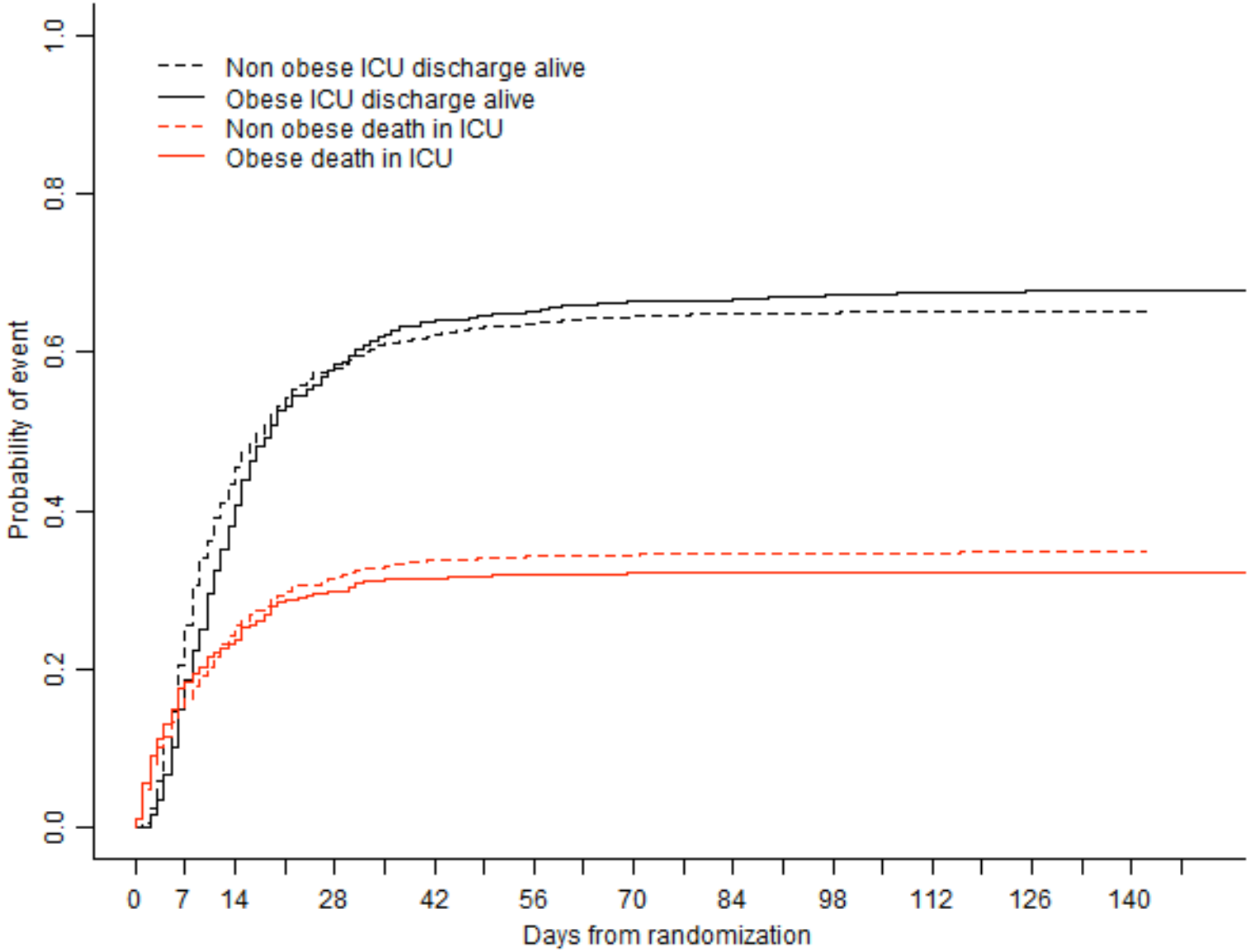
BMI	Number of patients N = 2325	Number of patients with VAP N = 224
<20	203 (8.7)	22/203 (10.8)
20 to <25	690 (29.7)	76/690 (11)
25 to <30	733 (31.5)	66/733 (9)
30 to <35	370 (15.9)	35/370 (9.5)
35 to <40	197 (8.5)	16/197 (8)
≥40	132 (5.7)	9/132 (6.8)

Data are N° (%)


Patients randomized in the NUTRIREA2 trial
N = 2410
Excluded
n = 85
No available BMI
Patients included in the current study
N = 2325
Patients analyzed
N = 2325


Non obese VAP
Obese VAP
Non obese ICU death without VAP prior
Obese ICU death without VAP prior
Non obese extubation without VAP prior
Obese ICU extubation without VAP prior
Probability of event
0.0
0.2
0.4
0.6
0.8
1.0
0
7
14
21
28
35
42
49
Days from randomization


Non obese extubation
Obese ICU extubation
Non obese death in ICU
Obese death in ICU
Probability of event
0.0
0.2
0.4
0.6
0.8
1.0
0
7
14
28
42
56
70
84
98
112
126
140
Days from randomization


Non obese ICU discharge alive
Obese ICU discharge alive
Non obese death in ICU
Obese death in ICU
Probability of event
0.0
0.2
0.4
0.6
0.8
1.0
0
7
14
28
42
56
70
84
98
112
126
140
Days from randomization