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**Risk factors for ventilator-associated pneumonia due to *Staphylococcus aureus* in patients with severe brain injury: A multicentre retrospective cohort study**

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**Authors Contributions:** YL and PS contributed to the study concept and design. PS had access to the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. ELB performed statistical analysis. YL, PS, and BM drafted the manuscript, which was revised for important intellectual content by KA, SL, CD-F and OH.

**Risk factors for ventilator-associated pneumonia due to *Staphylococcus aureus* in patients with severe brain injury: A multicentre retrospective cohort study**

**Background:** The present study aims at identifying the risk factors for ventilator-associated pneumonia (VAP) *Staphylococcus aureus* (*S. aureus*) in patients with severe brain injury (SBI).

**Methods:** In this multicentre, retrospective, observational study, patients  $\geq 18$  year old who had SBI (Glasgow coma scale GCS score  $< 9$ ) who received mechanical ventilation for at least 48 hours were analysed. The main objective was to identify risk factors for *S. aureus* VAP vs VAP due to other pathogens and to identify risk factors for *S. aureus* VAP vs patients who did not experience VAP.

**Results:** 847 patients with SBI were admitted in ICU after severe traumatic brain injury (n = 489, 58%), aneurysmal SAH (n = 156, 18%), stroke (n = 27, 3%), spontaneous intracranial haemorrhage (n = 80, 9%), arteriovenous malformation rupture (n = 25, 3%), and other causes (n = 70, 8%). Three hundred fifty of 847 patients (41%) had VAP with *S. aureus* (n = 161) or other pathogens (n = 189). In patients with VAP, the multivariate analysis shows that age per 10 years of ageing (OR 0.80, 95%CI [0.70; 0.90];  $p < 0.001$ ) and no tobacco use (OR 0.54, 95%CI [0.33;0.88];  $p = 0.014$ ) were protective factors against *S. aureus*. Age per 10 years of ageing remained a protective factor against *S. aureus* VAP vs no VAP (OR 0.80, 95%CI [0.73; 0.89],  $p < 0.001$ ).

**Conclusions:** In this retrospective study involving patients with SBI and who experienced VAP, increased age and no tobacco use were protective factors against VAP due to *S. aureus*. Increased age remained protective against *S. aureus* in VAP vs no VAP analysis.

**Keywords:** Brain injury, ventilator-associated pneumonia, *Staphylococcus aureus*

## 1. Introduction (253 to 226 words)

Patients with brain injuries are particularly at risk of ventilator-associated pneumonia (VAP) [1-4]. Indeed, between 40 and 50% of patients with severe traumatic brain injury (TBI) or severe subarachnoid haemorrhage (SAH) will develop VAP [1-4]. Although the impact on mortality is not well documented, VAP has been associated with longer durations of mechanical ventilation and hospitalisation and with poor neurological outcomes in patients with severe TBI [4,5]. Consequently, the management of VAP is expensive, with an average hospital cost per case of approximately 40,000 \$ [6].

*Staphylococcus aureus* is the most frequent cause of VAP in severe TBI patients and in those with SAH or stroke on mechanical ventilation [1-4,8,9]. Although risk factors for VAP have been well documented in the literature, there is little consideration of risk factors that may specifically explain the prevalence of *S. aureus* severe brain injury (SBI) patients. In patients with TBI, a Glasgow Coma Scale (GCS) score < 9 has been reported as a risk factor for VAP with *S. aureus* [10,11]. Nevertheless, the knowledge of risk factors for VAP from which *S. aureus* is isolated may have an impact on empiric antimicrobial therapy, particularly in countries where the prevalence of methicillin-resistant *S. aureus* (MRSA) is high.

Accordingly, the aim of the present study was to describe the risk factors for VAP with *S. aureus* in pulmonary sample in patients with SBI.

## **2. Patients and Methods**

This retrospective, observational study was conducted from a large multicentre database prospectively implemented by 5 university hospital surgical ICUs from 2013 to 2017 [12]. The database included patients  $\geq 18$  years admitted to surgical ICU for more than 48 hours for severe trauma and/or acute brain injury requiring mechanical ventilation  $> 24$  hours. The non-inclusion criteria were death in the first 24 hours, initial resuscitation for brain death and missing data, except those related to the neutrophil-to-lymphocyte ratio. According to the French legislation, study protocol was approved by the ethics committee of the French Society of Anaesthesia and Intensive Care (Société Française d'Anesthésie Réanimation – Comité d'éthique pour la recherche en Anesthésie-Réanimation) (n°00010254 - 2019- 197) that waived written consent [13].

### **2.1. Objectives**

The primary objective was to identify the risk factors for VAP with *S. aureus* recovered from a pulmonary sample in patients with SBI *versus* VAP due to other pathogens. The secondary objectives were to identify the risk factors for VAP with *S. aureus* recovered *versus* patients who did not experience VAP, to describe the pathogens recovered from pulmonary samples and to report the prevalence of MRSA. The outcomes of both groups were also evaluated.

### **2.2. Patients**

For the purpose of this study, we analysed patients aged more than 18 years with SBI defined by a GCS score  $< 9$  after initial resuscitation, who received mechanical ventilation  $\geq 48$  hours and who experienced VAP during the course of their disease. SBI included severe TBI, aneurysmal SAH, spontaneous intracranial haemorrhage, stroke, arteriovenous malformation (AVM) rupture, and other causes.

### **2.3. Definitions**

VAP was defined by the presence of new or progressive pulmonary infiltrate on chest radiography and two of the following signs: hyperthermia (temperature  $\geq 38$  °C) or hypothermia (temperature  $\leq 36$  °C), leucocytosis  $\geq 12,000/\text{ml}$  or leukopaenia  $\leq 4000/\text{ml}$ , and purulent pulmonary secretions [14]. To confirm pneumonia, bacteriological samples were obtained by endotracheal aspiration, a protected specimen brush or bronchoalveolar lavage. A diagnosis was confirmed if more than  $10^3$ ,

$10^4$  or  $10^6$  colony-forming units/ml were found on the protected specimen brush, in the bronchoalveolar lavage specimens, or in the endotracheal aspiration specimens, respectively. Pneumonia was considered ventilator-associated when it occurred after  $\geq 48$  hours of mechanical ventilation. Early-onset VAP (EO-VAP) was defined as VAP that occurred after  $\geq 48$  hours and  $\leq 5$  days; VAP that occurred after the 5<sup>th</sup> day of mechanical ventilation was considered late-onset VAP (LO-VAP). VAP due to *S. aureus* was diagnosed when this pathogen was found in high amounts in samples from patients suspected of having VAP. Acute respiratory distress syndrome (ARDS) was defined as  $\text{PaO}_2/\text{FIO}_2 < 300$  mm Hg and positive end expiratory pressure  $\geq 5$  cm H<sub>2</sub>O. Obesity was defined as a body mass index  $> 30$  kg/m<sup>2</sup>.

#### **2.4. General care of patients with severe brain injury**

Patients were managed in accordance with current guidelines [15-18]. In brief, for stroke, thrombolysis or neuroradiological endovascular thrombectomy was performed as recommended. Aneurysmal SAH was treated by coils or clips within the first 24 hours of hospitalisation, and ventriculostomy was performed if necessary. TBI and spontaneous intracranial haemorrhage were surgically treated if necessary. AVMs were embolised or surgically treated according to clinical and radiological data. Neurosurgical procedures or other surgeries, such as orthopaedic procedures in the case of multiple-trauma patients, were performed if necessary. Intracranial pressure (ICP) monitoring followed current guidelines [15]. Antibiotic prophylaxis was initiated following French recommendations [19]. No antimicrobial selective oropharyngeal decontamination and/or selective digestive were performed to prevent VAP. Sedative agents and stress ulcer prophylaxis were performed at the discretion of the centres. Early enteral feeding was initiated as soon as possible. Enteral nutrition objectives followed the French recommendations, *i.e.*, 20-25 kcal kg<sup>-1</sup> d<sup>-1</sup> in the acute phase and 25-30 kcal kg<sup>-1</sup> d<sup>-1</sup> thereafter [20]. Weaning from ventilation was at the discretion of the physician. Early tracheostomy was not routinely practised in any of the study centres.

#### **2.5. Data collection**

Age, sex, body mass index (BMI), pre-existing conditions and reasons for ICU admission were recorded. Severity was assessed by the Simplified Acute Physiology Score II (SAPS II), the Sequential Organ Failure Assessment (SOFA), and the initial GCS score.

Onset of intracranial hypertension (defined as an ICP above 20 mmHg in the absence of confounding factors) and use of barbiturates and/or osmotherapy were noted. The incidences of bacteraemia and ARDS, the need for extra renal support, the use and duration of vasopressors, the number of days on mechanical ventilation, the incidence of tracheostomy, and the number of days with arterial and

central venous catheters were assessed. Microorganisms recovered from pulmonary samples were also recorded. The ICU length of stay, in-ICU mortality rate and Glasgow Outcome Score (GOS) at 3 months were reported.

### **2.6. Statistical analysis**

Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC). Quantitative variables are reported as means (standard deviations) or median and interquartile range (IQR) and qualitative variables as numbers (percentages with 95% confident interval [95% CI]). For group comparisons, Student's tests or the Mann-Whitney test, if necessary, were used to compare quantitative variables; Chi<sup>2</sup> tests or Fisher's exact tests, if necessary, were used to compare qualitative variables. The risk factors for VAP due to *S. aureus* were evaluated using univariate logistic regressions, and the results are presented as odds ratios (ORs) and their 95% confidence intervals (CIs). Quantitative variables that did not conform to the hypothesis of log-linearity were transformed into categorical variables. Clinically relevant variables found to be significant, at  $p < 0.20$ , in univariate analysis were included in the multivariate model, and stepwise selection was then performed. Differences were considered statistically significant at a  $p$ -value of  $< 0.05$ .

### 3. Results

During the study period, 847 out of 2,413 patients included in the database met the inclusion criteria (Figure 1). The mean age was  $50 \pm 19$  years, and 555 (66%) were men. The mean SAPS II, SOFA score and GCS score at admission were  $51 \pm 11$ ,  $9 \pm 3$  and  $5 \pm 2$ , respectively. The reasons for ICU admission were severe TBI (n = 489 [58%]), aneurysmal SAH (n = 156 [18%]), spontaneous intracranial haemorrhage (n = 80 [9%]), AVM rupture (n = 25 [3%]), stroke (n = 27 [3%]) and other causes (n = 70 [8%]). A total of 350 patients had VAP (*S. aureus* group, n = 161; other pathogens group, n = 189), 141 (40%) had EO-VAP, and 209 (60%) had LO-VAP.

#### **3.1. Risk factors of *Staphylococcus aureus* VAP versus VAP due to other pathogens**

According to univariate analysis, young age and a low SAPS II score were significantly associated with VAP due to *S. aureus* (Table 1). Age and no tobacco use were found to be protective factors against VAP due to *S. aureus* in multivariate analysis (Table 2).

During hospitalisation, renal replacement therapy was significantly more prevalent in the other pathogens group (Table 4). No statistical difference in patient outcomes was reported (Table 5).

#### **3.2. Microorganisms recovered from pulmonary samples**

A total of 524 microorganisms were recovered from respiratory samples (Table 5). Of the 350 VAP-positive samples screened, 202 (58%) were monomicrobial. Among the 148 (42%) polymicrobial VAP samples, 92 belonged to the *S. aureus* group, and 56 belonged to the other pathogens group. *S. aureus* was the most frequent pathogen (31%) and was mainly methicillin susceptible (97%). One case of VAP due to MRSA occurred in the EO-VAP group, and 3 cases due to MRSA occurred in the LO-VAP group.

#### **3.2. Risk factors of *Staphylococcus aureus* VAP versus no VAP group**

According to univariate analysis, young age, diabetes mellitus, admission for severe TBI and low SAPS II score were significantly associated with VAP due to *S. aureus* (Table 1). Age was found to be a protective factor against VAP due to *S. aureus* in multivariate analysis (Table 3).

During hospitalisation, patients in the no VAP group received less frequent and/or a shorter duration of organ support (catecholamine and mechanical ventilation) and had shorter durations of central arterial and venous catheterisation (Table 4). ICU and Day 90 mortality were higher in the no VAP group (Table 5).

### 3. Discussion

In this retrospective study including 847 SBI patients from 5 French ICUs between 2013 and 2017, VAP occurred in 33%. The most common pathogen involved in VAP was *S. aureus* (31%, 97% being methicillin-susceptible *S. aureus*). An increased age and no tobacco use were the only independent protective factors against VAP with *S. aureus*. Considering the risk factors for VAP due to *S. aureus* versus patients who did not experience VAP, only increased age remained significant.

Patients with SBI had high rates of VAP, with *S. aureus* as the predominant causative pathogen. Brain injuries responsible for coma result in abnormal swallowing and depressed or absent gag reflexes and also alter bronchial clearance. Consequently, micro- and/or macro-aspiration of nasopharyngeal, oropharyngeal and/or gastric flora before initial resuscitation may promote colonisation, resulting in pneumonia [21]. Thereafter, continuous micro-inhalation around the endotracheal tube has been described as being involved in the development of VAP [22]. Immunosuppression observed after trauma may also play a role and favour secondary bacterial pneumonia [23]. As immunosuppression is associated with airway protective reflex impairment, it may have been involved in the pathophysiology and microbiology of VAP in our cohort. To better understand the distribution of VAP pathogens in these coma patients, the *S. aureus* colonisation status would be interesting to analyse. Bronchard et al. demonstrated that nasal carriage of *S. aureus* at admission was a risk factor for EO-VAP [4]. Indeed, among the patients with EO-VAP due to *S. aureus*, 88% were nasal carriers of this pathogen [4]. Nevertheless, our results suggest that EO-VAP is not a risk factor for VAP due to *S. aureus*. The nasal carriage rate of *S. aureus* was not available in our cohort because nasal swabbing was not a standard practice in our ICUs.

The determinants of *S. aureus* carriage in humans have been recently reviewed [24]. Carriage varies with age; a peak was found at ten years old and then decreased over time. One study found young age to be an important risk factor for nasal and throat carriage [25]. Another previous study found that in trauma patients, an age  $\leq 25$  years was significantly associated with *S. aureus* nosocomial pneumonia in univariate analysis [26]. We did not identify a cut-off of 25 years of age as a predisposing or protective factor (OR 0.60, 95%CI [0.34; 1.04];  $p = 0.07$ ), but our results showed that increased age was a protective factor and may be related to a decreased prevalence of nasal carriage. The influence of tobacco has been extensively discussed. Tobacco use appears to be a protective factor for nasal carriage because of bacterial hypoxia due to smoking [24]. Choi et al. observed an increased rate of MRSA nasal carriage in an ex-smokers group, and another study showed that smokers were at risk of developing *S. aureus* nasal carriage [10, 27]. These results were consistent with ours; indeed, no tobacco use was an independent protective factor for VAP due to *S. aureus*. Diabetes and dialysis are classical risk factors for *S. aureus* nasal carriage and infection. In our

cohort, the patient population with brain injury was young; the low incidence of these pathologies may be responsible for the low statistical power for these variables.

Another finding of our study is the low incidence of MRSA. The latest ATS recommendations for the management of nosocomial pneumonia focused on the need to monitor local bacterial resistance and consider this parameter in empiric antibiotic treatments [28]. At least a 10% local isolate resistance threshold is necessary to consider MRSA [28]. Considering its incidence of only 1% in our results, the patients with brain injury reported here were at low risk of MRSA and did not require an empiric antimicrobial regimen active against MRSA. In addition, we observed a low incidence of potentially resistant gram-negative pathogens, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, in this cohort.

Our study was multicentric and included a large cohort of patients with brain injury. We excluded patients with missing data, which reinforced our statistical results. Most studies on VAP risk factors have been conducted in severe TBI populations. We chose to extend our population to all patients with brain injury requiring mechanical ventilation because the level of consciousness seems to be a key factor in the pathogenesis of VAP. Studies on VAP in severe SAH populations and critically ill stroke patients have reported similar findings as studies in severe TBI populations, with all reporting a high prevalence of VAP and that *S. aureus* was the main pathogen involved [2,3,9].

This study had several limitations, the first of which is its retrospective nature. Consequently, we could not obtain some potentially relevant variables, such as nasal carriage of *S. aureus* or antibiotic prophylaxis. Recent results have indicated that antibiotic prophylaxis may be protective against VAP in severe TBI patients, even though the *S. aureus* incidence remained stable [8]. Antibiotic prophylaxis was collected in our database, but as the data were undated, this variable could not be evaluated in our study. Second, a majority of TBIs were included, and other causes of brain injury were underrepresented. Consequently, a lack of power regarding other causes of brain injury could not be excluded. Third, our database did not include preventive strategies for VAP, notably oropharyngeal disinfection. Although they are common in the ICU involved in our network, we cannot guarantee that there was no difference in the implementation of preventive strategies between centres and therefore rule out a potential effect of the centre on the development of *S. aureus* pneumonia. Fourth, this study was performed in France where the prevalence of MRAS is low, and our results must be interpreted within the context of this epidemiologic situation and cannot be extrapolated to countries where ecology differs. Finally, another limitation is the way we diagnosed VAP: we used quantitative traditional criteria for diagnosis, which are considered subjective, and the VAP definition remains under debate. For the most recent definitions, the diagnosis of lung infection

is based on qualitative criteria (infection-related ventilator-associated complications), which are more objective. Consequently, we might have overestimated the rate of pulmonary infection. Although the new definitions are more objective than traditional VAP criteria, no data suggest that they are more accurate for diagnosis [29].

#### **4.1. Conclusion**

We observed a high prevalence of VAP due to *S. aureus*, which was the primary causative pathogen. Increased age and no tobacco use appeared to be protective factors against VAP due to *S. aureus* in patients with severe brain injury within the limitations due to unmeasured confounding factors. Patients with brain injury requiring mechanical ventilation may be considered at low risk of MRSA.

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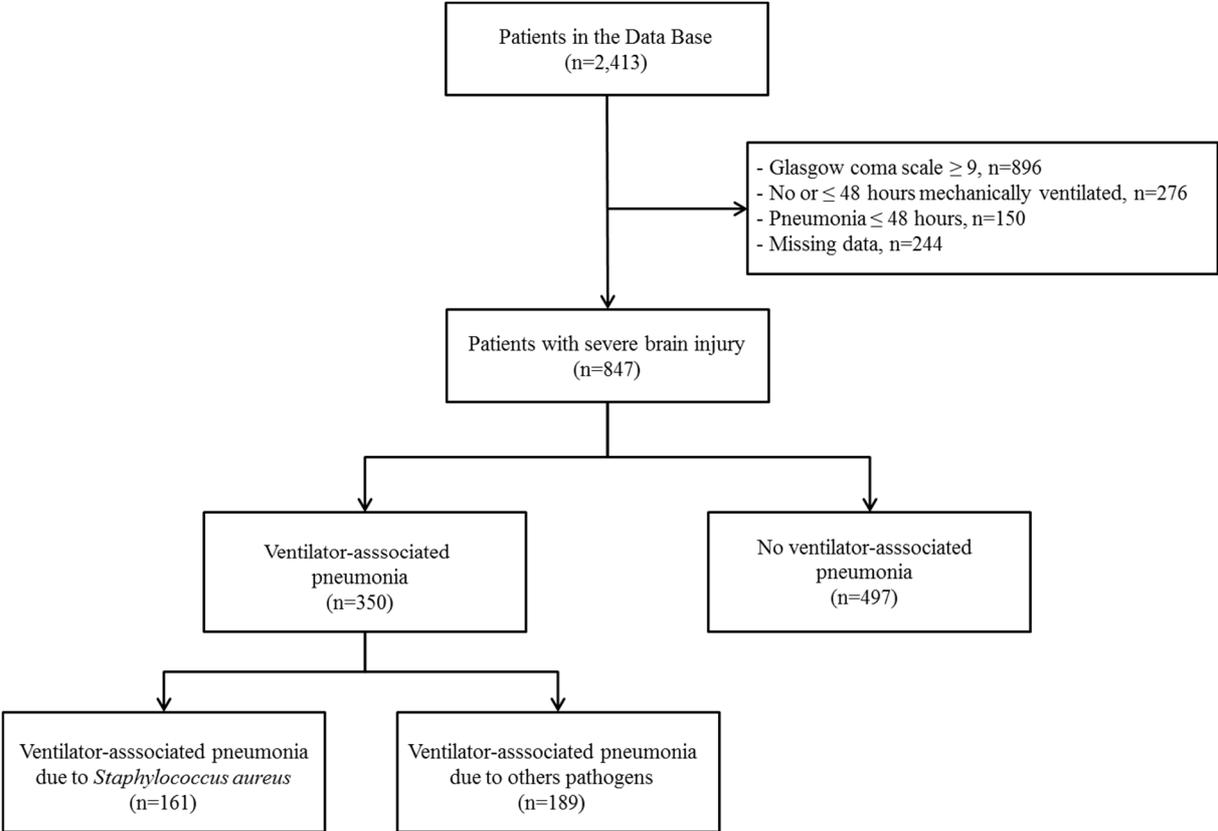
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**Figure legend.**

**Figure 1:** Flow chart.

Figure.



**Table 1. Baseline characteristics in *Staphylococcus aureus* VAP, other microorganism(s) VAP and no VAP groups**

Variables	VAP		OR, 95%CI*	p*	No VAP (n = 497)	OR, 95%CI**	p**
	<i>Staphylococcus aureus</i> (n = 161)	Other pathogens (n = 189)					
Age, years	44 ± 18	51 ± 18	0.98 [0.97; 0.99]	0.001	52 ± 19	0.98 [0.97; 0.99]	<0.001
Sex, male	112 (70)	135 (71)	0.91 [0.58; 1.45]	0.703	308 (62)	1.40 [0.96; 2.05]	0.082
BMI, kg/m <sup>2</sup>							
< 18.5	10 (6)	5 (3)	ref.	0.277	22 (4)	ref.	0.455
≥ 18.5 – < 25	84 (52)	104 (55)	0.40 [0.13; 1.23]		245 (49)	0.75 [0.34; 1.66]	
≥ 25	67 (42)	80 (42)	0.42 [0.14; 1.29]		230 (46)	0.64 [0.29; 1.42]	
Obesity***	17 (11)	34 (18)	0.54 [0.29; 1.01]	0.052	63 (13)	0.81 [0.46; 1.44]	
Pre-existing conditions							
- Respiratory disease	0 (-)	7 (4)	0.00 [0.0; 1.00]	0.984	17 (3)	0.08 [0.00; 1.54]	0.095
- Cardiac insufficiency	1 (1)	5 (3)	0.23 [0.03; 1.99]	0.182	11 (2)	0.28 [0.04; 2.16]	0.212
- Chronic renal disease	0 (-)	1	0.38 [0.0; 36.29]	0.676	12 (	0.12 [0.01; 2.29]	0.159
- Diabetes mellitus	4 (2)	12 (6)	0.38 [0.12; 1.19]	0.096	41 (8)	0.28 [0.10; 0.80]	0.018
- Malignancy	5 (3)	11 (6)	0.52 [0.18; 1.53]	0.233	25 (5)	0.61 [0.23; 1.61]	0.314
-Alcohol addiction	22 (14)	37 (20)	0.65 [0.37; 1.16]	0.143	85 (17)	0.77 [0.46; 1.27]	0.305
-Active smoking	36 (22)	59 (31)	0.63 [0.39; 1.03]	0.064	130 (26)	0.81 [0.53; 1.24]	0.849
Reason for ICU admission							

- Traumatic brain injury	105 (65)	105 (56)	1.50 [0.97; 2.31]	0.067	279 (56)	1.46 [1.01; 2.12]	0.043
- Aneurysmal SAH	28 (17)	41 (22)	0.76 [0.45; 1.30]	0.314	87 (18)	0.99 [0.62; 1.59]	0.974
- SIH	16 (10)	15 (8)	1.28 [0.61; 2.68]	0.512	49 (10)	1.01 [0.56; 1.83]	0.977
- AVM rupture	5 (3)	10 (5)	0.57 [0.19; 1.71]	0.320	10 (2)	1.56 [0.53; 4.64]	0.422
- Stroke	2 (1)	4 (2)	0.58 [0.11; 3.22]	0.535	21 (4)	0.29 [0.07; 1.23]	0.093
- Other	5 (3)	14 (7)	0.40 [0.14; 1.14]	0.086	51 (10)	0.28 [0.11; 0.72]	0.008
Severity assessment							
- SAPS II	49 ± 9	53 ± 12	0.97 [0.95; 0.99]	0.006	52 ± 12	0.98 [0.97; 1.00]	0.040
- SOFA							
< 8	54 (33)	61 (32)	ref.	0.169	209 (42)	ref.	0.096
[8-10]	69 (43)	67 (35)	1.16 [0.71; 1.91]		170 (34)	1.57 [1.04; 2.37]	
> 10	38 (24)	61 (32)	0.70 [0.41; 1.21]		118 (24)	1.25 [0.78; 2.00]	
- GCS at admission	5 ± 2	5 ± 2	1.07 [0.96; 1.21]	0.230	5 ± 2	0.98 [0.89; 1.08]	0.720
Neutrophil-to-lymphocyte ratio	11 [7; 17]†	10 [7; 16]†		0.491		10 [6; 17]†	0.441
EO-VAP							
- No	97 (60)	112 (59)	ref.	0.851	-	-	
- Yes	64 (40)	77 (41)	0.96 [0.63; 1.47]		-	-	

\**Staphylococcus aureus* vs others pathogens. \*\**Staphylococcus aureus* vs no VAP. Data are expressed as means ± standard deviation or median [25<sup>th</sup>;75<sup>th</sup>] and number (percentage). †data available for 124 (77%), 140 (74%) and 296 (60%) patients in the *Staphylococcus aureus*, other pathogens and no VAP groups, respectively. VAP: Ventilator-associated pneumonia. OR: Odds ratio. CI: Confidence interval. BMI: Body mass index. ICU: Intensive care unit. ASH:

Aneurysmal subarachnoid haemorrhage. SIH: Spontaneous intracranial haemorrhage. AVM: Arteriovenous malformation. SAPS II: Simplified acute physiologic score II. SOFA: Sequential organ failure assessment. GCS: Glasgow coma scale. SIH: Spontaneous intracranial haemorrhage. EO-VAP: Early ventilator-associated pneumonia.\*Obesity defined as BMI > 30 kg/m<sup>2</sup>. The neutrophil-to-lymphocyte ratio was analysed in 124 (77%), 130 (69%) and 296 (60%) patients in the *Staphylococcus aureus*, other pathogens and no VAP groups, respectively.

**Table 2.** Multivariate analysis of *Staphylococcus aureus* risk factors for ventilator-associated pneumonia vs other pathogens groups.

Variables	OR, 95%CI	<i>p</i>
Age (per 10 years age)	0.80 [0.70; 0.90]	< 0.001
Tobacco use (ref: no)	0.54 [0.33; 0.88]	0.014

OR: odds ratio. CI: Confidence interval. The following variables were included in the multivariate analysis model: age, obesity, respiratory disease, cardiac insufficiency, diabetes mellitus, alcohol addiction, active smoking, traumatic brain injury, simplified acute physiologic score II and sequential organ failure assessment.

**Table 3.** Multivariate analysis of *Staphylococcus aureus* risk factors for ventilator-associated pneumonia vs no VAP groups.

<b>Variables</b>	<b>OR, 95%CI</b>	<b><i>p</i></b>
Age (per 10 years age)	0.80 [0.73; 0.89]	< 0.001

OR: odds ratio. CI: Confidence interval. The following variables were included in the multivariate analysis model: age, sex, respiratory disease, chronic renal disease, diabetes mellitus, traumatic brain injury, stroke, simplified acute physiologic score II and sequential organ failure assessment.

**Table 4.** Clinical data during intensive care unit stay.

Variables	VAP		<i>p</i> *	No VAP (n = 497)	<i>p</i> **
	<i>Staphylococcus aureus</i>	Other Pathogens			
	(n = 161)	(n = 189)			
Intracranial hypertension	88 (55)	97 (51)	0.533	153 (31)	< 0.001
Osmotherapy	71 (44)	84 (44)	0.948	135 (27)	< 0.001
Barbiturate infusion	46 (29)	55 (29)	0.913	46 (9)	< 0.001
Bacteraemia	14 (9)	22 (12)	0.366	23 (5)	0.052
ARDS	57 (35)	71 (38)	0.676	51 (10)	< 0.001
Renal replacement therapy	0 (-)	6 (3)	0.033	8 (2)	0.210
Catecholamine use	146 (91)	165 (87)	0.316	390 (79)	< 0.001
Catecholamine, days	5 [3; 9]	5 [3; 10]	0.359	4 [2; 5]	< 0.001
Mechanical ventilation, days	21 [13; 29]	20 [13; 27]	0.578	8 [5; 15]	< 0.001
Tracheostomy	42 (26)	48 (25)	0.883	53 (11)	< 0.001
Arterial catheters, days	13 [9; 20]	12 [7; 19]	0.215	6 [4; 10]	< 0.001
Central venous catheters, days	17 [11; 23]	15 [11; 24]	0.746	8 [5; 13]	< 0.001

\**Staphylococcus aureus* vs. other pathogens. \*\**Staphylococcus aureus* vs no VAP. Data are expressed as the means  $\pm$  standard deviation or median [25<sup>th</sup>; 75<sup>th</sup> ] and number (percentage). ARDS: Acute respiratory distress syndrome.

**Table 5.** Length of stay, ICU mortality and Glasgow outcome scale at 3 months

Variables	VAP		<i>p</i> *	No VAP (n = 497)	<i>p</i> **
	<i>Staphylococcus aureus</i>	Other Pathogens			
	(n = 161)	(n = 189)			
ICU length of stay, days	27 [18; 38]	25 [17; 34]	0.237	12 [6; 20]	< 0.001
ICU mortality	28 (17)	36 (19)	0.690	188 (38)	< 0.001
GOS extended at 3 months			0.766		< 0.001
- Death	32 (20)	42 (22)		194 (39)	
-Vegetative state	9 (6)	9 (5)		7 (1)	
-Severe disability	63 (39)	63 (33)		110 (22)	
-Moderate disability	34 (21)	48 (25)		91 (18)	
-Good recovery	23 (14)	27 (14)		95 (19)	

\**Staphylococcus aureus* vs other pathogens. \*\**Staphylococcus aureus* vs no VAP. Data are expressed as the means  $\pm$  standard deviation or median [25<sup>th</sup>; 75<sup>th</sup>] and number (percentage). ICU: intensive care unit. GOS: Glasgow outcome scale.