International Journal of Infectious Diseases 38 (2015) 46–51

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Risk factors for ventilator-associated pneumonia in patients with severe traumatic brain injury in a Serbian trauma centre

Bojan Jovanovic [a,b], Zoka Milan [c,*], Ljiljana Markovic-Denic [d], Olivera Djuric [d], Kristina Radinovic [b], Krstina Doklestic [a,e], Jelena Velickovic [a,b], Nenad Ivancevic [a,e], Pavle Gregoric [a,e], Milena Pandurovic [a,b,f], Djordje Bajec [a,g], Vesna Bumbasirevic [a,b]

[a] *Faculty of Medicine, University of Belgrade, Belgrade, Serbia*
[b] *Centre for Anaesthesiology, Clinical Centre of Serbia, Belgrade, Serbia*
[c] *King's College Hospital, London, SE5 9RS, UK*
[d] *Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia*
[e] *Clinic for Emergency Surgery, Clinical Centre of Serbia, Belgrade, Serbia*
[f] *"Medigroup" Hospital, Belgrade, Serbia*
[g] *Clinic for Digestive Surgery, Clinical Centre of Serbia, Belgrade, Serbia*

ARTICLE INFO

Article history:
Received 27 May 2015
Received in revised form 26 June 2015
Accepted 2 July 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Injury
Neurotrauma
Pneumonia
Predictors

SUMMARY

Introduction: The aims of this study were (1) to assess the incidence of ventilator-associated pneumonia (VAP) in patients with traumatic brain injury (TBI), (2) to identify risk factors for developing VAP, and (3) to assess the prevalence of the pathogens responsible.

Patients and methods: The following data were collected prospectively from patients admitted to a 24-bed intensive care unit (ICU) during 2013/14: the mechanism of injury, trauma distribution by system, the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the Abbreviated Injury Scale (AIS) score, the Injury Severity Score (ISS), underlying diseases, Glasgow Coma Scale (GCS) score, use of vasopressors, need for intubation or cardiopulmonary resuscitation upon admission, and presence of pulmonary contusions. All patients were managed with a standardized protocol if VAP was suspected. The Sequential Organ Failure Assessment (SOFA) score and the Clinical Pulmonary Infection Score (CPIS) were measured on the day of VAP diagnosis.

Results: Of the 144 patients with TBI who underwent mechanical ventilation for >48 h, 49.3% did not develop VAP, 24.3% developed early-onset VAP, and 26.4% developed late-onset VAP. Factors independently associated with early-onset VAP included thoracic injury (odds ratio (OR) 8.56, 95% confidence interval (CI) 2.05–35.70; $p = 0.003$), ISS (OR 1.09, 95% CI 1.03–1.15; $p = 0.002$), and coma upon admission (OR 13.40, 95% CI 3.12–57.66; $p < 0.001$). Age (OR 1.04, 95% CI 1.02–1.07; $p = 0.002$), ISS (OR 1.09, 95% CI 1.04–1.13; $p < 0.001$), and coma upon admission (OR 3.84, 95% CI 1.44–10.28; $p = 0.007$) were independently associated with late-onset VAP (Nagelkerke $r^2 = 0.371$, area under the curve (AUC) 0.815, 95% CI 0.733–0.897; $p < 0.001$). The 28-day survival rate was 69% in the non-VAP group, 45.7% in the early-onset VAP group, and 31.6% in the late-onset VAP group. *Acinetobacter spp* was the most common pathogen in patients with early- and late-onset VAP.

Conclusions: These results suggest that the extent of TBI and trauma of other organs influences the development of early VAP, while the extent of TBI and age influences the development of late VAP. Patients with early- and late-onset VAP harboured the same pathogens.

* Corresponding author. Tel.: +44 203 2999000.
E-mail address: zoka.milan@kcl.ac.uk (Z. Milan).

http://dx.doi.org/10.1016/j.ijid.2015.07.005

1. Introduction

Traumatic brain injury (TBI) is a serious condition associated with a prolonged hospital admission and high mortality.[1] Patients with TBI may also have an airway obstruction, aspiration, or hypoxia.[2,3] Intubation and mechanical ventilation (MV) are indicated for many patients with severe TBI.[3]

Ventilator-associated pneumonia (VAP) is a type of nosocomial pneumonia that occurs in patients who receive >48 h of MV. Early-onset VAP occurs during the first 4 days of MV and is usually caused by antibiotic-sensitive bacteria. The increased systemic inflammatory response in patients with a head trauma may predispose them to develop early-onset VAP.[4,5] Late-onset VAP develops ≥5 days after initiating MV and is caused by multidrug-resistant (MDR) pathogens.[6,7]

Patients with TBI are at high risk of infection, particularly nosocomial infections, during treatment in the intensive care unit (ICU), where the incidence of VAP can be as high as 50%.[8–10]

The duration of MV usually influences the type of organism that causes VAP.[11] Early-onset VAP is caused by antibiotic-sensitive pathogens, whereas late-onset VAP is caused by MDR bacteria, which are more difficult to treat. The microbiological environment can have a marked influence on VAP isolates, particularly during late-onset VAP, but it also influences early-onset VAP.[12]

Patients who acquire VAP have longer ICU stays, higher morbidity and mortality, and a greater number of infectious agents.[13,14]

The risk factors for developing VAP are diverse, and the pathogenesis of intra-hospital infections is complex. Common VAP preventive measures such as early mobility, the daily interruption of sedation, and a readiness-to-extubate assessment may not be applicable because of associated injuries such as severe chest trauma, intra-abdominal bleeding, and other organ damage. Hence, VAP diagnosis can be difficult in a setting of multiple trauma, and significant variations in the diagnosis and management of VAP remain.[11]

The primary objectives of this study were to assess the incidence of VAP in patients with TBI and to identify risk factors for developing VAP in this specific patient population (types of co-injuries in patients with multiple trauma or characteristics on admission). The secondary objective was to assess the prevalence of pathogens responsible for early- and late-onset VAP in patients with TBI.

2. Patients and methods

2.1. Study population and design

A prospective observational cohort study was conducted in a multidisciplinary (medical, surgical, and trauma) ICU at the University Emergency Centre, Clinical Centre of Serbia, Belgrade, Serbia; this ICU has 24 beds. Data recorded prospectively in the database for the surveillance of nosocomial infections were reviewed from January 2013 to December 2014; all consecutive VAP episodes with identified isolates were documented. This study was approved by the Ethics Committee of the Medical Faculty at the University of Belgrade, Serbia (No. 29/IV-14).

2.2. Evaluation on admission

The records of all patients with TBI who were on MV for >48 h after the initial evaluation were reviewed. Patients were transferred either from the emergency room directly to the ICU, or they were transferred to the operating room first and were then admitted to the ICU after surgery. A total of 506 patients with TBI were identified during the study period (Figure 1). Patients with documented gastric aspiration, recent antibiotic therapy, ≥2 days of hospitalization in the preceding 30 days, residence in a nursing home or extended care facility, home therapy, or an underlying malignancy were excluded. In total, 204 patients were transported from another hospital but were excluded due to incomplete data. Patients who were transferred within the hospital if there was an accident or change in the ventilator system, or who had other known risk factors for developing pneumonia, were also excluded. Patients intubated outside the hospital and who had no side effects were not excluded.

Data collected at admission included the mechanism of injury (blunt or penetrating trauma), trauma distribution by system (head, thoracic, abdomen, etc.), the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the Abbreviated Injury Scale (AIS) score, the Injury Severity Score (ISS), and the patient's underlying diseases. Factors such as shock, coma (Glasgow Coma Scale (GCS) score <9), multiple transfusions, use of vasopressors, need for intubation or cardiopulmonary resuscitation on admission, emergency or elective surgery, and the presence of pulmonary contusions on chest X-ray at admission were recorded.

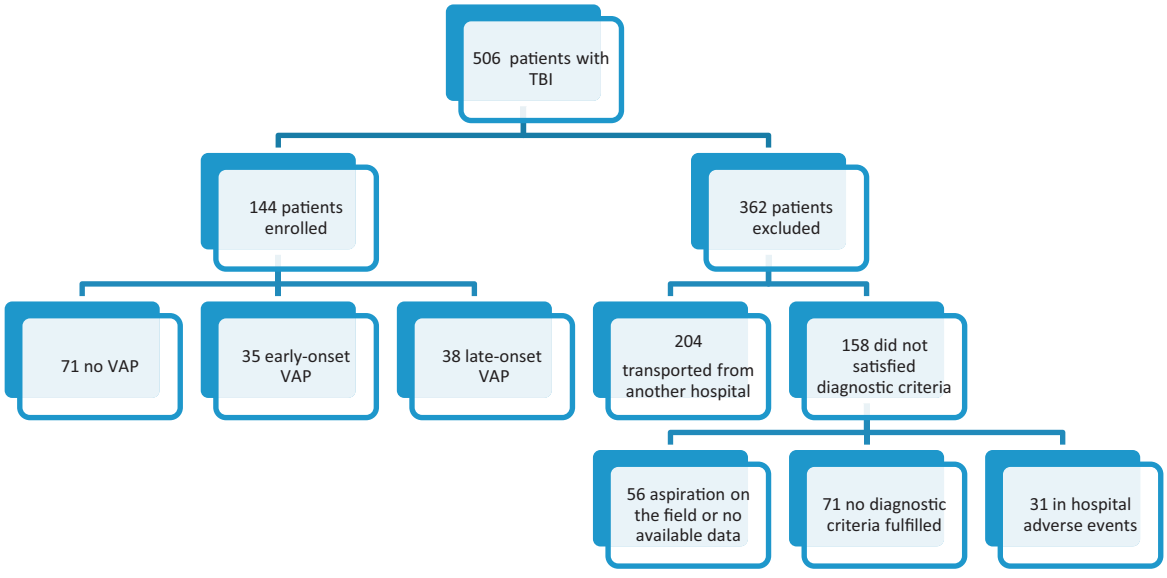

Figure 1. Patient selection diagram.

The patients were divided into three groups, as follows: patients who did not develop VAP, those who developed early-onset VAP, and those who developed late-onset VAP.

2.3. Treatment

The trauma patients were treated by a team that included a neurosurgeon, trauma surgeon, maxillofacial surgeon, orthopaedic surgeon, a radiologist, an intensive care physician, and a physiotherapist. The decision to monitor intracranial pressure (ICP) was made by the neurosurgeon. All patients underwent an emergency brain computed tomography scan. Intracranial hypertension was treated with mannitol with or without a craniotomy. A third-generation cephalosporin (ceftriaxone) and metronidazole were administered as antibiotic prophylaxis for accompanying wound injuries (skin and soft tissue).

VAP preventive strategies performed in the ICU include daily interruption of sedation and a readiness-to-extubate assessment, early facilitation of mobility, elevating the head of the bed to 30–45°, use of endotracheal tubes with subglottic secretion drainage ports and a closed/in-line endotracheal suctioning system, change of the ventilator circuit if visibly soiled or malfunctioning, stress ulcer prophylaxis, residual gastric volume monitoring, early parenteral nutrition, and deep venous thrombosis prophylaxis. An infusion of midazolam and propofol was used for sedation, and remifentanil was infused for analgesia.

2.4. Diagnosis and outcomes

The clinical, radiographic, and laboratory data of all patients were reviewed daily for the development of pneumonia. The chest X-rays were interpreted by a radiologist. The VAP diagnosis was made by the intensive care physician. All patients were managed with a standardized protocol if VAP was suspected.[13,15] The Sequential Organ Failure Assessment (SOFA) score and the Clinical Pulmonary Infection Score (CPIS) were measured on the day of VAP diagnosis.

Respiratory samples for a bacteriological examination were usually collected from tracheobronchial aspirates. Bronchoalveolar lavage (BAL) fluid was used only when BAL would not increase the hypoxia severity to a dangerous level or increase ICP. Protected specimen brushes are not used routinely in this patient population. Respiratory samples were quantitatively cultured according to standard microbiological laboratory procedures. Samples with a neutrophil count <25 and/or >10 squamous epithelial cells in the field were defined as contaminated. Microbiological confirmation of VAP was defined as the presence of at least one potentially pathogenic microorganism in the respiratory sample at predefined thresholds (10^4 colony-forming units (CFU)/ml in BAL fluid, or 10^6 CFU/ml in a tracheobronchial aspirate). Samples with numbers of microorganisms under these thresholds were excluded because of low specificity.

Antibiotics were changed based on the microbiological findings of the BAL fluid or tracheobronchial aspirate.

2.5. Definitions

Trauma was defined as the presence of TBI either as an isolated injury or associated with other injuries and a need for ICU admission and/or surgery. Disease severity was evaluated in all patients using the APACHE II score during the first 24 h of ICU admission. The VAP diagnosis was based on chest radiographic, systemic infection, and pulmonary criteria. The chest radiography criteria included a new pulmonary infiltrate, worsening of X-ray findings in patients with a contusion, pleural effusion, or cavitation. The systemic criteria were fever >38 °C, leukopenia (white blood cell count $<4 \times 10^9$/ml), or leukocytosis (white blood cell count $>12 \times 10^9$/ml). The pulmonary criteria were new-onset purulent sputum (or change in the sputum character, increased respiratory secretions, or increased suctioning requirement), worsening gas exchange (desaturation, increased oxygen requirement, or increased ventilator demand), new onset or worsening cough, dyspnoea or tachypnoea, and rales or bronchial breath sounds.

Pneumonia was considered early onset if it occurred within 2–4 days. Patients with very early onset pneumonia were defined as those who developed the infection within the first 48 h and were not included in the study. Late-onset pneumonia began on day 5 or later after admission.[13]

The CPIS considers clinical and radiographic data to determine a numerical value that predicts the presence or absence of VAP; a score ≥6 has a good correlation with the presence of VAP.[16] Coma was diagnosed when the GCS score was <9 (both sedation and non-sedation) for more than 24 h. Acute respiratory distress syndrome was diagnosed according to the Berlin definition criteria.[17] Shock was defined as systolic blood pressure <90 mmHg mHg despite adequate fluid resuscitation and the need for vasopressor agents. Polytransfusion was defined as the need for >10 units of packed red cells within 24 h. Pulmonary contusion was defined by a radiologist on a chest X-ray. The AIS was used to compare injuries. The AIS is the most widely used anatomic scale for rating injury severity[18,19] and has historically been used in conjunction with the ISS to identify the effects of multiple injuries on trauma victims.[20]

2.6. Statistical analysis

Data are presented as the mean (standard deviation) for continuous variables and as the frequency (%) for categorical variables. The *t*-test was used for the two-group mean comparisons (early-onset VAP vs. without VAP, and late-onset VAP vs. without VAP). Categorical data were compared using Pearson's Chi-square test or Fisher's exact test, where appropriate. Two logistic regression analyses were performed to investigate the associations between demographics, the injury and clinical characteristics of the patients at admission to the ICU, and the probability of VAP onset. Each patient characteristic (age, sex, and pre-existing medical conditions), injury characteristics and severity (type and number of injuries, injured body regions, AIS, and ISS), and clinical characteristics (presence of haemorrhagic shock, coma, or pulmonary contusion on admission and sustaining reanimation, multiple transfusions, surgery, or vasopressor use) were analysed in a univariate logistic regression analysis. Variables that were significantly associated with the onset of VAP in the univariate analysis, with a *p*-value of <0.1, were entered into a multivariate model, and stepwise logistic regression was performed. Odds ratios (OR) with 95% confidence intervals (CI) were computed, and Pearson's goodness-of-fit test was performed to assess overall model fit. Measures of discrimination (Nagelkerke r^2 and area under the receiver operating characteristic curve (AUC)) were calculated for all regression models. All statistical tests were two-sided and were performed at the 5% significance level. The statistical analysis was performed using IBM SPSS Statistics version 20.0 software (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Characteristics of the patients with TBI

Of the 144 patients with TBI (with or without additional injury) who underwent MV for >48 h, 71 (49.3%) did not develop VAP, 35 (24.3%) developed early-onset VAP, and 38 (26.4%) developed

late-onset VAP. No patient was diagnosed with more than one episode of VAP and all had positive microbiological findings.

Table 1 compares the demographic, injury, and clinical characteristics of the patients in the three groups. Patients who developed early-onset VAP were significantly younger (36.5 ± 15 vs. 53.1 ± 20 years; $p < 0.001$), and a lower number presented with a pre-existing condition (11.4 vs. 45.1%; $p < 0.001$) compared to those without VAP; they also had fewer pre-existing conditions (31% vs. 39%; $p < 0.003$) and had less frequent cardiac disease (2.9% vs. 33.8%; $p < 0.001$) than those without VAP. Patients with early-onset VAP had less isolated TBI and a greater number of additional injuries (8.6% vs. 38%; $p < 0.01$), had more frequent thoracic (74.3% vs. 31%; $p < 0.01$), abdominal (37.1% vs. 12.7%; $p = 0.03$), and spinal injuries (34.3% vs. 12.7%; $p < 0.0009$), and had more frequent AIS scores ≥3 for the head (77.1% vs. 52.1%; $p = 0.013$), thorax (57.1% vs. 8.5%; $p < 0.001$), and extremities (40% vs. 18.3%; $p = 0.016$), as well as more frequent mean ISS scores ≥3 (32 ± 13 vs. 17.8 ± 10; $p < 0.001$) compared to those without VAP. More patients with early-onset VAP presented with haemorrhagic shock (25.7% vs. 99.9%; $p = 0.032$), coma (GCS <9 71.4% vs. 42.3%; $p = 0.005$), and pulmonary contusions (60% vs. 12.7%; $p <$ 0.001%) on admission than patients without VAP.

Patients with late-onset VAP were significantly older (64.7 ± 15 vs. 36.5 ± 15 years; $p = 0.001$), had more frequent head AIS ≥3 (76.3% vs. 52.1%; $p = 0.014$), and more patients had higher mean ISS ≥3 (27.1 ± 15 vs. 17.8 ± 10; $p < 0.001$) compared to patients without VAP. Patients with late-onset VAP presented more frequently with coma on admission (GCS <9 71.1% vs. 42.3%; $p = 0.004$) and were subject to reanimation (7.9% vs. 0%; $p = 0.040$) and multiple transfusions (21.1% vs. 5.6%; $p = 0.023$) in greater numbers than patients without VAP. In addition, patients with late-onset VAP had a more severe overall clinical

Table 1
Characteristics of patients with TBI on admission to the ICU

	Without VAP ($n = 71$)	Early-onset VAP[a] ($n = 35$)	p-Value[b]	Late-onset VAP[a] ($n = 38$)	p-Value[c]
General characteristics					
Age, years, mean (SD)	53.1 (20)	36.5 (15)	<0.001	64.7 (15)	0.001
Male, *n* (%)	59 (83.1)	28 (80.0)	0.696	28 (73.7)	0.243
Comorbidities, *n* (%)	32 (45.1)	4 (11.4)	0.001	22 (57.9)	0.202
No. of comorbidities, *n* (%)					
0	39 (54.9)	31 (88.6)	0.003	16 (42.1)	0.258
1	19 (26.8)	2 (5.7)		16 (42.1)	
≥2	13 (18.3)	2 (5.7)		6 (15.8)	
Comorbidity, *n* (%)					
COPD	1 (1.4)	1 (2.9)	1.000	1 (2.6)	1.000
Asthma	2 (2.8)	0 (0.0)	1.000	1 (2.6)	1.000
Chronic renal disease	3 (4.2)	2 (5.7)	1.000	3 (7.9)	0.418
Chronic liver disease	3 (4.2)	1 (2.9)	1.000	0 (0.0)	0.550
Chronic immune suppression	2 (2.8)	1 (2.9)	1.000	0 (0.0)	0.542
Diabetes	9 (12.7)	2 (5.7)	0.332	6 (15.8)	0.653
Cardiac disease	24 (33.8)	1 (2.9)	<0.001	16 (42.1)	0.391
Injury characteristics					
Type of injury, *n* (%)					
Blast	67 (94.4)	34 (97.1)	1.000	36 (94.7)	0.936
Penetrating	4 (5.6)	1 (2.9)		2 (5.3)	
Number of injured systems, *n* (%)					
TBI only	27 (38.0)	3 (8.60)	<0.001	11 (28.0)	0.597
TBI +1	23 (32.4)	7 (20.0)		11 (28.9)	
TBI +2	11 (15.5)	11 (31.4)		9 (23.7)	
TBI +3	10 (14.1)	14 (40.0)		7 (18.4)	
Injury by system, *n* (%)					
Face	25 (32.5)	13 (37.1)	0.845	15 (39.5)	0.660
Thorax	22 (31.0)	26 (74.3)	<0.001	16 (42.1)	0.246
Abdomen	9 (12.7)	13 (37.1)	0.003	5 (13.2)	0.943
Extremities/pelvis	14 (19.7)	11 (31.4)	0.182	10 (26.3)	0.428
Spine	9 (12.7)	12 (34.3)	0.009	6 (15.8)	0.653
AIS ≥3, *n* (%)					
Head	37 (52.1)	27 (77.1)	0.013	29 (76.3)	0.014
Face	21 (29.6)	8 (22.9)	0.465	13 (34.2)	0.619
Thorax	6 (8.5)	20 (57.1)	<0.001	6 (15.8)	0.336
Abdomen	6 (8.5)	4 (11.4)	0.727	3 (7.9)	0.920
Extremities	13 (18.3)	14 (40.0)	0.016	11 (28.9)	0.202
ISS, mean (SD)	17.8 (10)	32.0 (13)	<0.001	27.1 (15)	0.001
Clinical characteristics					
On admission, *n* (%)					
Haemorrhagic shock	7 (9.9)	9 (25.7)	0.032	7 (18.4)	0.236
Vasopressor use	3 (4.2)	4 (11.4)	0.215	5 (13.2)	0.124
Multiple transfusion	4 (5.6)	6 (17.1)	0.078	8 (21.1)	0.023
Coma (GCS <9)	30 (42.3)	25 (71.4)	0.005	27 (71.1)	0.004
Surgery (urgent/elective)	26 (36.6)	13 (37.1)	0.958	12 (31.6)	0.599
Pulmonary contusion on admission	9 (12.7)	21 (60.0)	<0.001	9 (23.7)	0.140
Reanimation	0 (0.0)	0 (0.0)	NA	3 (7.9)	0.040
APACHE II, mean (SD)	14.0 (6)	16.1 (6)	0.091	18.4 (6)	0.001

TBI, traumatic brain injury; ICU, intensive care unit; VAP, ventilator-associated pneumonia; SD, standard deviation; COPD, chronic obstructive pulmonary disease; AIS, Abbreviated Injury Scale score; ISS, Injury Severity Score; GCS, Glasgow Coma Scale score; APACHE, Acute Physiology and Chronic Health Evaluation score.

[a] Clinical Pulmonary Infection Score (CPIS), mean (SD) 7.9 (3.3) vs. 9.7 (4.6); $p > 0.05$. Sequential Organ Failure Assessment (SOFA) score, mean (SD) 6.3 (1.6) vs. 6.6 (1.5); $p > 0.05$.

[b] For comparison between 'without VAP' and 'early-onset VAP'.

[c] For comparison between 'without VAP' and 'late-onset VAP'.

Table 2
Factors associated with early-onset of VAP

	Unadjusted model			Age-adjusted model		
	β (SE)	OR (95% CI)	*p*-Value	β (SE)	OR (95% CI)	*p*-Value
Cardiac disease	−3.56 (1.27)	0.03 (0.01–0.35)	0.005	−2.31 (1.44)	0.10 (0.01–1.66)	0.108
Injury of thorax	2.15 (0.73)	8.56 (2.05–35.70)	0.003	2.31 (0.76)	10.04 (2.26–44.68)	0.002
ISS	0.08 (0.03)	1.09 (1.03–1.15)	0.002	0.08 (0.03)	1.08 (1.03–1.14)	0.004
Coma	2.60 (0.75)	13.40 (3.12–57.66)	<0.001	2.51 (0.75)	12.29 (2.83–53.46)	0.001

VAP, ventilator-associated pneumonia; SE, standard error; OR, odds ratio; CI, confidence interval; ISS, Injury Severity Score.

state on admission, as indicated by a higher mean APACHE II score (18.4 ± 6 vs. 14.0 ± 6; $p = 0.001$). However, the two groups did not differ in the numbers of comorbidities, injured body regions, or the presence of pulmonary contusions at admission.

3.2. Factors associated with early-onset VAP

After including all significant variables from the univariate logistic regression into the multivariate model, four variables were found to be independently associated with early-onset VAP, including absence of cardiac disease (OR 0.03, 95% CI 0.01–0.35; $p = 0.005$), thoracic injury (OR 8.56, 95% CI 2.05–35.70; $p = 0.003$), ISS (OR 1.09, 95% CI 1.03–1.15; $p = 0.002$), and coma on admission (OR 13.40, 95% CI 3.12–57.66; $p < 0.001$). Age was returned to the model to control for the potential confounding effects of age on the association between cardiac disease and early-onset VAP. The crude and age-adjusted models are presented in Table 2. As expected, the absence of cardiac disease was no longer associated with the onset of VAP after adjusting for age, as the risk estimates became insignificant (adjusted OR 1.10, 95% CI 0.01–1.66; $p = 0.108$). The Nagelkerke r^2 for the adjusted model was 0.641, and the AUC was 0.921 (95% CI 0.862–0.980; $p < 0.001$).

3.3. Factors associated with late-onset VAP

Table 3 show the logistic regression results to examine the factors associated with developing late-onset VAP. Age (OR 1.04, 95% CI 1.02–1.07; $p = 0.002$), ISS (OR 1.09, 95% CI 1.04–1.13; $p < 0.001$), and coma on admission (OR 3.84, 95% CI 1.44–1.28; $p = 0.007$) were independently associated with late-onset VAP (Nagelkerke $r^2 = 0.371$; AUC 0.815, 95% CI 0.733–0.897; $p < 0.001$).

The BAL fluid microbiology findings are presented in Table 4. *Acinetobacter spp* was the most common pathogen encountered in both patients with early-onset and late-onset VAP.

4. Discussion

The 49.7% incidence of VAP in patients with severe TBI in this study is very high, but similar to that of a previous study.[15] The results of the present study demonstrated injury severity to be an independent risk factor for developing VAP, particularly in patients with multiple trauma. Patients who developed VAP had very high AIS scores (≥3 points) for head injury (77.1% in the early-onset and 76.3% in late-onset VAP groups). These data demonstrate that the system injured with the TBI, particularly a chest injury, is an independent factor for the development of early-onset VAP. Other important factors associated with the development of early-onset VAP are abdominal trauma and a spinal injury. The results suggest that underlying disease, such as a coronary condition and the trauma severity with an isolated brain or chest injury, should be considered in the therapeutic decision for patients with VAP.

A unique feature of this study is that the subpopulation of patients who developed early-onset VAP were significantly younger (mean age 33 years) compared to those who did not develop VAP (mean age 50 years) and those who developed late-onset VAP (mean age 63.5 years). Although the cause of injury was not recorded, severe car and motorbike accidents, assaults, and falls are known to be specific for the young population in this region. About 75% of the early-onset VAP subpopulation had a chest trauma and 57.1% had an AIS score ≥3 points for chest trauma. The incidence of early-onset VAP increased in patients who had more systems injured with TBI.

The data from this study demonstrated that a GCS <9 on admission was associated with a higher incidence of developing VAP, which can be explained by the severity of the brain injury, the need for emergency intervention, and prolonged sedation with MV. It was also demonstrated that 60% of patients who developed early-onset VAP had pulmonary contusions on admission, which is significant, particularly when compared with those who developed late-onset VAP (23.7%).

The high incidence of MDR remains a problem and a burden of regional centres and ICUs and depends on the local ecology.[21,22] Antimicrobials used in empirical regimens should be selected based on the local pattern of susceptibility. Despite the fact that most MDR bacteria are isolated from patients with late-onset VAP, there is growing evidence that resistance is also a problem in patients who develop early-onset VAP.[16]

Another important finding of this study was the lack of a difference between isolated pathogens. This is a new problem, particularly concerning empirical antimicrobial therapy, because the pathogens that cause early- and late-onset VAP are similar.[23] *Staphylococcus aureus* appears to be a typical pathogen of early-onset pneumonia in younger patients with head trauma, due to the incidence of *S. aureus* nasal carriage on admission.[24,25] In the

Table 3
Factors associated with late-onset of VAP

	β (SE)	OR (95% CI)	*p*-Value
Age	0.04 (0.02)	1.04 (1.02–1.07)	0.002
ISS	0.08 (0.02)	1.09 (1.04–1.13)	0.000
Coma	1.35 (0.50)	3.84 (1.44–10.28)	0.007

VAP, ventilator-associated pneumonia; SE, standard error; OR, odds ratio; CI, confidence interval; ISS, Injury Severity Score.

Table 4
Distribution of causative agents of VAP, isolated from respiratory samples

Pathogen	Early-onset VAP	Late-onset VAP
Acinetobacter spp	24 (47.2)	29 (51.8)
Klebsiella pneumoniae	8 (15.7)	10 (17.9)
Pseudomonas aeruginosa	5 (9.8)	9 (16.1)
Staphylococcus aureus (MSSA)	6 (11.7)	-
Staphylococcus aureus (MRSA)	2 (3.9)	4 (7.1)
Serratia spp	3 (5.9)	1 (1.8)
Citrobacter spp	2 (3.9)	1 (1.8)
Enterobacter spp	-	1 (1.8)
Stenotrophomonas maltophilia	1 (1.9)	1 (1.8)
Total	51 (100%)	56 (100%)

VAP, ventilator-associated pneumonia; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, MSSA, methicillin-resistant *Staphylococcus aureus*.

present study, *Acinetobacter spp* was the most prevalent microorganism isolated from patients with early- and late-onset VAP (47.2% and 51.8%), followed by *Klebsiella pneumoniae* (15.7% and 17.9%) and *Pseudomonas aeruginosa* (9.8% and 16.1%). Methicillin-sensitive *S. aureus* was isolated only from patients with early-onset VAP. However, the incidence of methicillin-resistant *S. aureus* in both subgroups was similar: two cases in early-onset VAP (3.9% of isolates) and four cases in late-onset VAP (7.1% of isolates).

The present findings regarding the incidence of isolation of pathogens are not applicable to other centres. Despite growing evidence that there is no difference between the clinical courses of early- and late-onset VAP,[26] a significant association was found between severe TBI associated with a chest injury and early pulmonary infection as a serious complication, with no difference in mortality rate. Geographic variation may potentiate the likelihood of a patient developing VAP, and possibly other types of nosocomial infection. The environmental characteristics of patients may predispose certain populations to infection in the setting of trauma, and the prevention of such infections may not be possible.[27]

The proportion of patients who developed VAP in this study was slightly higher than reported previously.[28,15] The VAP rate observed occurred after implementing a regional and multidisciplinary VAP preventive program with standardized diagnostic algorithms and a revised regional policy according to evidence-based recommendations for preventing VAP.

The secondary analysis had several limitations that should be addressed. First, a high mortality rate was reported, primarily due to sepsis, which was either a consequence of extensive brain injury, VAP, or infection of other organs. Second, factors not included in the study may have contributed to the high incidence of VAP, such as alcohol abuse, severity of fall or motor vehicle collision, and ICU work patterns and setting. Third, distinguishing infectious pneumonia (IP), aspiration pneumonia (AP), and VAP in patients with TBI is difficult,[31] especially in an administrative dataset. The lack of microbiological data and the likely presence of multiple other confounders could not be identified or controlled for in this study.[30] Many of the factors associated with an increased risk of VAP are inherent comorbidities in patients with TBI that place this unique group at high risk.[30]

The results of the present study demonstrate that patients with TBI are at increased risk of developing pneumonia and that a significant portion of this risk is associated with an extended time on MV, as such patients may be ventilated for days or weeks.[31]

The ISS and coma were independent predictors of early- and late-onset VAP in patients with TBI. Additionally, young age and chest trauma were predictors of early-onset VAP, whereas older age was a predictor of late-onset VAP.

In summary, patients with severe TBI and a chest injury represent a specific subgroup of patients with a higher risk of developing early-onset VAP, possibly caused by antibiotic-resistant pathogens. These patients are a specific target population for studies examining the prevention and treatment of pneumonia. *Acinetobacter spp* was the leading cause of pneumonia in patients with severe TBI in this study. In conclusion, the results of this study suggest that the extent of TBI and trauma of other organs influence the development of early VAP, while the extent of TBI and age influence the development of late VAP. Patients with early- and late-onset VAP harboured the same pathogens.

Acknowledgement

This work was supported by the Ministry of Science and Technological Development of Serbia (contract number 175046, 2011–2014).

Conflict of interest: There is no conflict of interest.

References

1. Tagliaferri F, Compagnone C, Korsic M, Servadei F, Kraus J. A systematic review of brain injury epidemiology in Europe. *Acta Neurochir* 2006;**148**:255–68.
2. Lockey DJ, Costas T, Parr MJ. Aspiration in severe trauma: a prospective study. *Anaesthesia* 1999;**54**:1097.
3. Adnet F, Baud F. Relation between Glasgow Coma Scale and aspiration pneumonia. *Lancet* 1996;**348**:123–4.
4. Mannick JA, Rodrick ML, Lederer JA. The immunologic response to injury. *J Am Coll Surg* 2001;**193**:237–44.
5. Hedrick TL, Smith RL, McElearney ST, Evans HL, Smith PW, Pruett TL, et al. Differences in early- and late-onset ventilator-associated pneumonia between surgical and trauma patients in a combined surgical or trauma intensive care unit. *J Trauma* 2008;**64**:714–20.
6. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002;**165**:867–903.
7. Garnacho-Montero J, Corcia-Palomo Y, Amaya-Villar R. How to treat VAP due to MDR pathogens in ICU patients. *BMC Infect Dis* 2014;**14**:135.
8. Anthony DC, Couch Y. The systemic response to CNS injury. *Exp Neurol* 2014;**258**:105–11.
9. Hukkelhoven CW, Steyerberg EW, Habbema JD, Farace E, Marmarou A, Murray GD, et al. Predicting outcome after traumatic brain injury: development and validation of a prognostic score based on admission characteristics. *J Neurotrauma* 2005;**22**:1025–39.
10. Plurad DS, Kim D, Bricker S, Lemesurier L, Neville A, Bongard F, Putnam D. Ventilator-associated pneumonia in severe traumatic brain injury: the clinical significance of admission chest computed tomography findings. *J Surg Res* 2013;**183**:371–6.
11. Browne E, Hellyer TP, Baudouin SV. A national survey of the diagnosis and management of suspected ventilator-associated pneumonia. *BMJ Open Respir Res* 2014;**1**:e000066.
12. Morris AC, Hay AW, Swann DG, Everingham K, McCulloch C, McNulty J, et al. Reducing ventilator-associated pneumonia in intensive care: impact of implementing a care bundle. *Crit Care Med* 2011;**39**:2218–24.
13. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare associated pneumonia. *Am J Respir Crit Care Med* 2005;**171**:388–416.
14. Nair GB, Niederman NS. Ventilator-associated pneumonia: present understanding and ongoing debates. *Intensive Care Med* 2015;**41**:34–48.
15. Zygun DA, Zuege DJ, Boiteau PJ, Laupland KB, Henderson EA, Kortbeek JB, Doig CJ. Ventilator-associated pneumonia in severe traumatic brain injury. *Neurocrit Care* 2006;**5**:108–14.
16. Kalanuria AA, Zai W, Mirski M. Ventilator-associated pneumonia in the ICU. *Crit Care* 2014;**18**:208.
17. Ferguson N, Fan E, Camporota L. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012;**38**:1573–82.
18. Civil ID, Schwab CW. The Abbreviated Injury Scale, 1985 revision: a condensed chart for clinical use. *J Trauma* 1988;**28**:87–90.
19. MacKenzie EJ, Shapiro S, Eastham JN. The Abbreviated Injury Scale and Injury Severity Score. Levels of inter- and intrarater reliability. *Med Care* 1985;**23**:823–35.
20. Baker SP, O'Neill B, Haddon Jr W, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* 1974;**14**:187–96.
21. Garnacho-Montero J, Ortiz-Leyba C, Fernández-Hinojosa E, Aldabó-Pallás T, Cayuela A, Marquez-Vácaro JA, et al. *Acinetobacter baumannii* ventilator-associated pneumonia: epidemiological and clinical findings. *Intensive Care Med* 2005;**31**:649–55.
22. Martin-Loeches I, Deja M, Koulenti D, Dimopoulos G, Marsh B, Torres A, et al. Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors. *Intensive Care Med* 2013;**39**:672–81.
23. Gastmeier P, Sohr D, Geffers C, Rüden H, Vonberg RP, Welte T. Early and late-onset pneumonia: is this still a useful classification? *Antimicrob Agents Chemother* 2009;**53**:2714–8.
24. Bronchard R, Albaladejo P, Brezac G, Geffroy A, Seince PF, Morris W, et al. Early onset pneumonia: risk factors and consequences in head trauma patients. *Anesthesiology* 2004;**100**:234–9.
25. Tilahun B, Faust AC, McCorstin P, Ortegon A. Nasal colonization and lower respiratory tract infections with methicillin-resistant *Staphylococcus aureus*. *Am J Crit Care* 2015;**24**:8–12.
26. Giantsou E, Liratzopoulos N, Efraimidou E, Panopoulou M, Alepopoulou E, Kartali-Ktenidou S, et al. Both early-onset and late-onset ventilator-associated pneumonia are caused mainly by potentially multiresistant bacteria. *Intensive Care Med* 2005;**31**:1488–94.
27. Zarzaur LB, Bell T, Croce AM, Fabian CT. Geographic variation in susceptibility to ventilator-associated pneumonia after traumatic injury. *J Trauma Acute Care Surg* 2013;**75**:234–40.
28. Hsieh AH, Bishop MJ, Kubilis PS, Newell DW, Pierson DJ. Pneumonia following closed head injury. *Am Rev Respir Dis* 1992;**146**:290–4.
30. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma* 1993;**34**:216–22.
31. Hui X, Haider AH, Hashmi ZG, Rushing AP, Dhiman N, Scott VK, et al. Increased risk of pneumonia among ventilated patients with traumatic brain injury: every day counts! *J Surg Res* 2013;**184**:438–43.