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ORIGINAL RESEARCH

Risk factors and microbiological profile of ventilator-associated pneumonia in a tertiary intensive care unit in Tuzla: a prospective observational study

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Running title: Bećirović et al. Ventilator-associated pneumonia in ICU

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ABSTRACT

Aim: To determine the prevalence and microbiological profile of ventilator-associated pneumonia (VAP) in mechanically ventilated patients and to assess clinical and laboratory parameters associated with its development, with emphasis on C-reactive protein (CRP) levels and duration of mechanical ventilation.

Methods: This single-centre prospective observational cohort study included 118 adult patients who required invasive mechanical ventilation for more than 48 hours in the intensive care unit of the University Clinical Centre Tuzla. Patients were classified into VAP and non-VAP groups. Demographic, clinical, laboratory, and microbiological data were collected, and in-hospital outcomes were recorded. Statistical analysis included between-group comparisons, univariate logistic regression, and receiver operating characteristic (ROC) curve analysis.

Results: VAP was diagnosed in 41 patients (34.7%). Gram-negative pathogens predominated (≈85%), with *Acinetobacter baumannii* identified most frequently (43.9%), followed by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Patients with VAP had significantly longer durations of mechanical ventilation (12.5 vs. 7.3 days, $p<0.001$) and hospitalisation (19.6 vs. 12.2 days, $p<0.001$), as well as higher CRP levels (178.2 vs. 126.4 mg/L, $p<0.001$). Reintubation, elevated CRP, leukocytosis, hypercapnia, and prolonged mechanical ventilation were associated with VAP. CRP demonstrated good-to-moderate discriminative ability for VAP (AUC=0.83).

Conclusion: VAP remains a common and clinically significant complication in mechanically ventilated patients. Elevated CRP levels and prolonged mechanical ventilation may support early clinical suspicion using routinely available parameters.

Keywords: *Acinetobacter baumannii*; C-reactive protein; intensive care unit; mechanical ventilation; ventilator-associated pneumonia

INTRODUCTION

Ventilator-associated pneumonia (VAP) is a severe nosocomial infection that develops in patients receiving invasive mechanical ventilation for more than 48 hours and remains one of the most common infectious complications in intensive care units (ICUs) worldwide (1). It is associated with increased morbidity, prolonged duration of mechanical ventilation, extended hospital stay, and high mortality (2). Reported incidence rates vary widely, typically ranging from 10% to over 40%, reflecting differences in patient populations, disease severity, diagnostic criteria, and preventive strategies (3).

The pathogenesis of VAP is closely linked to the disruption of normal host defence mechanisms, including endotracheal intubation, impaired mucociliary clearance, and microaspiration, which leads to colonization of the lower respiratory tract by pathogens (4). Patients requiring invasive mechanical ventilation represent a particularly vulnerable population, as critical illness, repeated invasive procedures, and antimicrobial exposure collectively create an ecological environment that favours infection by hospital-adapted organisms (5).

The microbiological spectrum of VAP is closely related to the timing of pneumonia onset and the presence of risk factors for multidrug-resistant (MDR) pathogens (6). Early-onset VAP, typically occurring within the first four to five days of hospitalisation, is more commonly caused by antibiotic-susceptible organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and methicillin-sensitive *Staphylococcus aureus* (4). In contrast, late-onset VAP is more frequently associated with hospital-adapted gram-negative bacteria and MDR pathogens, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus* (8).

International guidelines emphasize the importance of distinguishing between patients at low and high risk for MDR pathogens to guide empirical antimicrobial therapy (9). Patients

without septic shock, without recent antimicrobial exposure, and treated in ICUs with a low prevalence of resistant organisms may be candidates for narrower-spectrum empirical regimens (9). Conversely, patients with late-onset pneumonia, severe clinical presentation, or established risk factors for resistance often require initial broad-spectrum antimicrobial coverage to ensure adequate treatment (10).

In contemporary ICU settings, gram-negative organisms such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* are frequently isolated in VAP, as repeated antibiotic usage tends to eliminate susceptible bacteria while allowing hospital-adapted organisms to persist (11). Several clinical factors have been consistently associated with the development of VAP, including prolonged duration of mechanical ventilation, reintubation, prior antibiotic exposure, and severity of critical illness (12). In addition to clinical variables, routinely available laboratory and respiratory parameters, such as leukocytosis, elevated C-reactive protein (CRP) levels, and hypercapnia, may reflect early inflammatory and ventilatory deterioration. Among these, CRP concentration and mechanical ventilation duration are of particular interest because they are readily available in daily clinical practice and may help identify patients at increased risk of VAP (13).

Despite advances in intensive care management and the implementation of preventive measures, VAP continues to contribute substantially to adverse clinical outcomes. Understanding local VAP epidemiology, including its microbiological profile and associated clinical and inflammatory characteristics, remains essential for optimising surveillance, prevention, and antimicrobial management strategies (14). However, data from Bosnia and Herzegovina and similar healthcare settings remain limited.

This study aimed to determine the incidence and microbiological spectrum of VAP in mechanically ventilated adult patients, identify clinical and laboratory variables associated

with its development, and evaluate the discriminative performance of CRP levels and mechanical ventilation duration for VAP.

MATERIAL AND METHODS

Patients and study design

This prospective observational cohort study was conducted between January 1, 2023, and December 31, 2024, in the Intensive Care Unit of the Clinic for Internal Medicine at the University Clinical Centre Tuzla. The study was non-interventional, and all diagnostic and therapeutic decisions were made by the treating physicians in accordance with routine clinical practice.

The study included 118 adult patients (≥18 years) who required invasive mechanical ventilation for more than 48 hours. Exclusion criteria included clinical or radiological signs of pneumonia prior to mechanical ventilation, known immunosuppressive conditions (including active malignancy, long-term corticosteroid therapy, or immunosuppressive treatment), and incomplete clinical or laboratory documentation.

Patients were classified into two groups based on whether they developed VAP during their ICU stay.

Methods

VAP was defined in accordance with the international European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Latin American Thoracic Association guidelines (ALAT) as pneumonia occurring ≥ 48 hours after initiation of invasive mechanical ventilation (15). The diagnosis required radiographic evidence of new or progressive pulmonary infiltrates on chest imaging that could not be explained by alternative causes, in combination with at least two clinical criteria, including body temperature >38°C or <36°C, leukocytosis or leukopenia, purulent tracheal secretions, or worsening oxygenation.

Microbiological findings were used to support the clinical diagnosis in selected cases but were not required as an independent diagnostic criterion. Alternative causes of pulmonary infiltrates, including pulmonary oedema, atelectasis, and non-infectious inflammatory conditions, were systematically considered during the diagnostic evaluation. VAP diagnosis was established by the treating intensive care physicians in accordance with institutional clinical practice and contemporary international guideline recommendations.

Mechanical ventilation was delivered using intensive care ventilators from the Savina™ series (Dräger, Germany), operating in pressure-controlled or volume-controlled modes, in accordance with institutional protocols. Standard ventilator care bundles and infection prevention measures were applied throughout the study period. Single-use ventilator circuits were employed for each patient and were not reused.

All patients received standard intensive care management, including antimicrobial therapy. Empirical antimicrobial therapy for suspected VAP was initiated in accordance with institutional protocols and contemporary guideline recommendations, with subsequent adjustment based on clinical response and, when available, microbiological results.

Demographic data, including age and gender, and clinical variables, including length of hospital stay, duration of mechanical ventilation, need for reintubation, and in-hospital mortality, were recorded for all patients. Laboratory parameters included complete blood count, serum biochemical markers, and arterial blood gas measurements. Baseline laboratory values were obtained within 24 hours of ICU admission, and follow-up laboratory measurements were collected during mechanical ventilation. In patients who developed VAP, laboratory values used for analysis were measured at or immediately before the time of clinical diagnosis.

Leukocytosis was defined as a leukocyte count >12 $\times 10^9$/L, and hypercapnia as an arterial partial pressure of carbon dioxide ($PaCO_2$) >45 mmHg. CRP was analysed as a marker of

systemic inflammation and was not used as a primary diagnostic criterion for VAP.

Peripheral venous blood samples were collected into K_2EDTA tubes and analysed using the Sysmex XN-1000 automated haematology analyser (Sysmex Corporation, Kobe, Japan). C-reactive protein (CRP) and routine biochemical parameters were measured using the Beckman Coulter DxC 700 AU analyser (Beckman Coulter Diagnostics, Switzerland). Serum biochemical parameters, including glucose, high-density lipoprotein cholesterol, and CRP, were measured using standard automated chemistry analysers. Arterial blood gas analysis, including $PaCO_2$ measurement, was performed in accordance with routine institutional procedures.

In patients diagnosed with VAP, microbiological samples were obtained from lower respiratory tract specimens, including tracheal aspirates or bronchoalveolar lavage, as clinically indicated. Pathogen identification was performed using gram staining and conventional culture techniques. Respiratory specimens consisted primarily of tracheal aspirates and bronchoalveolar lavage samples obtained according to clinical indication and routine intensive care practice. Conventional qualitative culture methods were used in routine microbiological analysis, whereas quantitative culture thresholds were not systematically applied within the institutional protocol. Whenever clinically feasible, respiratory samples were obtained before escalation or modification of antimicrobial therapy. Isolated microorganisms were classified according to standard microbiological criteria and categorised as gram-negative or gram-positive bacteria.

Statistical analysis

Categorical variables were presented as absolute numbers and percentages, while continuous variables were expressed as mean ± standard deviation (SD). Normality of data distribution was assessed using the Kolmogorov-Smirnov test. Between-group comparisons for categorical variables were performed using Pearson's χ^2 test. Continuous variables were

compared using the independent-samples t-test for normally distributed variables or the Mann-Whitney U test for non-normally distributed variables. To identify clinical and laboratory variables associated with the development of ventilator-associated pneumonia, univariate logistic regression analysis was performed, and results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). The following dichotomized variables were included in the regression analysis: duration of mechanical ventilation >7 days, length of hospital stay >14 days, CRP >150 mg/L, leukocyte count >12 $\times 10^9$/L, hypercapnia ($PaCO_2$ >45 mmHg), and reintubation.

Receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminative ability of selected variables for ventilator-associated pneumonia, with the area under the curve (AUC) quantifying overall diagnostic performance. Multivariate logistic regression was not performed due to the limited number of VAP events, which reduces the risk of model overfitting. All statistical tests were two-sided, and p-values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Among 118 adult patients, VAP was diagnosed in 41 patients, yielding an overall prevalence of 34.7%. The mean age was comparable between patients who developed VAP and those who did not (64.2±13.1 vs. 59.8±14.6 years; p=0.080), and male gender predominated in both groups (p=0.630) (Table 1).

The duration of mechanical ventilation was significantly longer in the VAP group compared with non-VAP patients (12.5±5.8 vs. 7.3±3.9 days; p<0.001), as was the overall length of hospital stay (19.6 ± 7.2 vs. 12.2 ± 5.4 days; p<0.001). Reintubation occurred more frequently among patients with VAP than among those without VAP (29.3% vs. 10.4%; p=0.001).

At the time of clinical suspicion or diagnosis of VAP, patients in the VAP group exhibited a significantly higher inflammatory and respiratory burden. CRP levels were markedly elevated compared with non-VAP patients (178.2±55.3 vs. 126.4±40.1 mg/L; p<0.001), as were leukocyte counts (13.4±4.2 vs. 10.9±3.1×10⁹/L; p=0.014) and $PaCO_2$ (48.2±8.3 vs. 42.6±6.4 mmHg; p=0.002).

Microbiological analysis of respiratory samples from patients with VAP showed a predominance of gram-negative pathogens (90.2% of all isolates). *Acinetobacter baumannii* was the most frequently identified microorganism (43.9%), followed by *Pseudomonas aeruginosa* (22.0%) and *Klebsiella pneumoniae* (14.6%). Other gram-negative bacteria accounted for 9.8% of isolates, while gram-positive bacteria represented 9.8% (Table 2).

In univariate analysis, several clinical variables were associated with VAP (Table 3). Reintubation was associated with a substantially increased likelihood of VAP (OR 4.12; 95%CI 1.62-10.48; p=0.002). Elevated inflammatory and respiratory markers were also associated with VAP, including CRP levels greater than 150 mg/L (OR 3.45; 95%CI 1.58-7.52; p=0.002), leukocyte counts exceeding 12 ×10⁹/L (OR 2.18; 95%CI 1.03-4.63; p=0.041), and hypercapnia defined as $PaCO_2$ values above 45 mmHg (OR 2.55; 95%CI 1.18-5.49; p=0.018).

The overall in-hospital mortality rate among mechanically ventilated patients was 61.0%. Mortality was higher among patients who developed VAP compared with those without VAP (73.2% vs. 55.8%); however, this difference did not reach statistical significance (p = 0.065) (Figure 1).

ROC analysis demonstrated good discriminative performance of CRP measured at the time of clinical suspicion for VAP (AUC = 0.83, 95% CI 0.75-0.91). The optimal cut-off value was 150 mg/L, yielding a sensitivity of 77% and specificity of 72% (Figure 2).

DISCUSSION

The main findings of this study were that VAP occurred in 34.7% of mechanically ventilated patients and was associated with longer mechanical ventilation, longer hospital stay, higher inflammatory markers, and more frequent reintubation. The microbiological profile was dominated by gram-negative pathogens, particularly *Acinetobacter baumannii*, while CRP showed good discriminative performance for VAP in ROC analysis. Similar rates have been reported in other high-acuity intensive care settings, ranging from approximately 25% to 40% (16).

Once VAP developed, patients required extended mechanical ventilation and remained hospitalised for significantly longer periods (17,18). Mechanical ventilation compromises normal airway defence mechanisms, promotes microaspiration, and facilitates biofilm formation on artificial airways (19). Continued exposure of the lower respiratory tract to invasive devices and hospital flora creates favourable conditions for colonization by opportunistic pathogens and progression to infection (20).

The microbiological profile was dominated by gram-negative pathogens, with *Acinetobacter baumannii* most frequently isolated, followed by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The predominance of gram-negative organisms in our cohort is consistent with observations from intensive care settings characterised by prolonged mechanical ventilation and extensive antimicrobial exposure (21). This distribution reflects sustained ecological selection rather than sporadic infection and is largely shaped by local antimicrobial practices and ICU microbial ecology (22). Prolonged mechanical ventilation, broad-spectrum antimicrobial exposure, and invasive airway devices favour colonization by hospital-adapted organisms capable of biofilm formation and persistence (23).

The predominance of these pathogens has direct therapeutic implications, supporting prompt empiric gram-negative coverage in suspected VAP and reinforcing the need for microbiology-guided therapy and timely de-escalation based on local resistance patterns (24). Reintubation and hypercapnia were more common among patients who developed VAP, reflecting airway instability and impaired ventilatory control (25). Repeated airway instrumentation and compromised ventilation facilitate aspiration and introduction of hospital flora into the lower respiratory tract, promoting progression from colonization to infection (26). These variables are best interpreted as markers of increased susceptibility to VAP rather than independent causal factors (27).

Inflammatory markers, particularly CRP and leukocyte count, were significantly elevated in patients with VAP (28). The observed discriminative performance of CRP in ROC analysis suggests that this marker reflects the systemic inflammatory response associated with evolving pulmonary infection and critical illness (29). Because these parameters were assessed at the time of clinical suspicion or diagnosis of VAP, they should primarily be interpreted as markers of evolving infection and respiratory deterioration rather than baseline predisposing factors.

However, CRP lacks disease specificity and should be interpreted in conjunction with clinical findings, radiological assessment, and ventilatory parameters, and should primarily be used as a supportive rather than diagnostic marker (30).

In our cohort, prolonged mechanical ventilation, extended hospital stay, reintubation, elevated inflammatory markers, leukocytosis, and hypercapnia were associated with VAP. Similar findings have been reported in previous studies of mechanically ventilated patients (31). Although multivariate analysis was not performed due to the limited number of VAP events, these associations are biologically plausible and consistent with established VAP pathophysiology (32). Together, they delineate a clinical and microbiological phenotype

characterised by prolonged critical illness, sustained systemic inflammation, and continuous exposure to ICU-specific pathogens (33).

In-hospital mortality among mechanically ventilated patients in this cohort was numerically higher among patients who developed VAP; however, this difference did not reach statistical significance The high overall mortality likely reflects the advanced age, high burden of comorbidities, severe respiratory failure, and frequent multiorgan dysfunction in this tertiary-care ICU population (34).

This study has several limitations. Its single-centre design limits generalisability, as findings likely reflect local ICU ecology and antimicrobial practices. Clinically indicated rather than systematic sampling, incomplete susceptibility data, and limited information on illness severity, comorbidities, ICU admission indications, prior antimicrobial exposure, and ventilator bundle adherence constrained assessment of resistance patterns, stewardship implications, transmission dynamics, confounding, and prevention-related factors. Finally, the observational design and univariate analysis preclude causal inference and identification of independent predictors, with potential residual confounding.

CONCLUSION

VAP remains a common, clinically significant complication of prolonged invasive mechanical ventilation. In this cohort, it was associated with longer ventilatory support, extended hospitalisation, and predominance of gram-negative hospital-adapted pathogens. Elevated inflammatory markers and ventilatory instability may aid early suspicion within an integrated clinical–microbiological framework. These findings highlight the need for continuous surveillance, infection prevention, individualized antimicrobial stewardship, and locally informed VAP diagnosis, prevention, and treatment.

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Conflicts of interest: None to declare.

Author contributions (CRediT): Conceptualization: M.B., E.B. Methodology: M.B., E.B., J.H. Formal analysis: E.B. Investigation: M.B., E.B., J.H., A.B. Data curation: M.B., E.B. Writing – original draft: E.B., M.B., R.G. Writing – review and editing: M.B., E.B., J.H., A.B., E.M., A.A. Supervision: E.B. Project administration: M.B., E.B.

Ethics statement: The study protocol was reviewed and approved by the Ethics Committee of the University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Due to the observational and non-interventional nature of the study, all diagnostic and therapeutic procedures were performed as part of routine clinical care.

Data availability statement: The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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TABLES AND FIGURES

Table 1. Demographic, clinical, and laboratory characteristics of patients with and without ventilator-associated pneumonia (VAP)

Variable	VAP (n = 41)	Non-VAP (n = 77)	p
	Mean ± SD		
Age (years)	64.2 ± 13.1	59.8 ± 14.6	0.080
Duration of mechanical ventilation (days)	12.5 ± 5.8	7.3 ± 3.9	<0.001
Length of hospital stay (days)	19.6 ± 7.2	12.2 ± 5.4	<0.001
C-reactive protein (mg/L)	178.2 ± 55.3	126.4 ± 40.1	<0.001
Leukocyte count ($\times 10^9$/L)	13.4 ± 4.2	10.9 ± 3.1	0.014
$PaCO_2$ (mmHg)	48.2 ± 8.3	42.6 ± 6.4	0.002
	N (%)		
Male gender	26 (63.4%)	45 (58.4%)	0.630
In-hospital mortality	30 (73.2%)	43 (55.8%)	0.065

VAP, ventilator-associated pneumonia; SD, standard deviation; $PaCO_2$, arterial partial pressure of carbon dioxide.

Table 2. Microbiological isolates identified in patients with ventilator-associated pneumonia (VAP)

Pathogen	Number of isolates (n)	Proportion among VAP patients (%)
Acinetobacter baumannii	18	43.9
Pseudomonas aeruginosa	9	22.0
Klebsiella pneumoniae	6	14.6
Other gram-negative bacteria	4	9.8
Gram-positive bacteria	4	9.8

VAP, ventilator-associated pneumonia. Percentages are calculated based on the total number of VAP patients (n = 41), with each patient having a single predominant pathogen identified.

Table 3. Univariate analysis of clinical factors associated with ventilator-associated pneumonia (VAP)

Predictor	Odds ratio (95% CI)	p-value
Reintubation (yes)	4.12 (1.62-10.48)	0.002
CRP >150 mg/L	3.45 (1.58-7.52)	0.002
Leukocyte count >12 $\times 10^9$/L	2.18 (1.03-4.63)	0.041
$PaCO_2$ >45 mmHg	2.55 (1.18-5.49)	0.018

VAP, ventilator-associated pneumonia; CRP, C-reactive protein; $PaCO_2$, arterial partial pressure of carbon dioxide; CI, confidence interval.

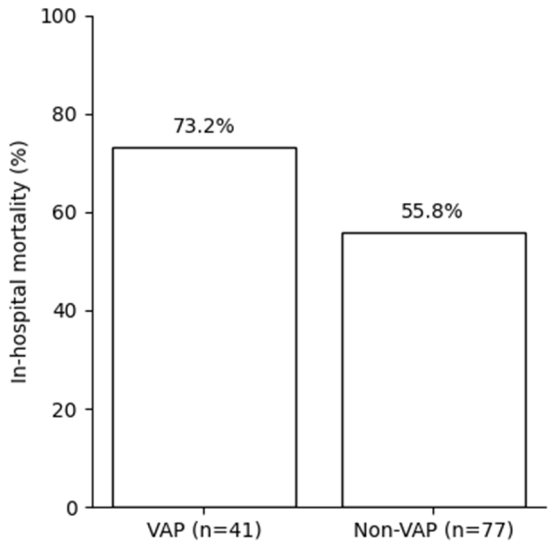

Figure 1. In-hospital mortality according to ventilator-associated pneumonia (VAP) status.

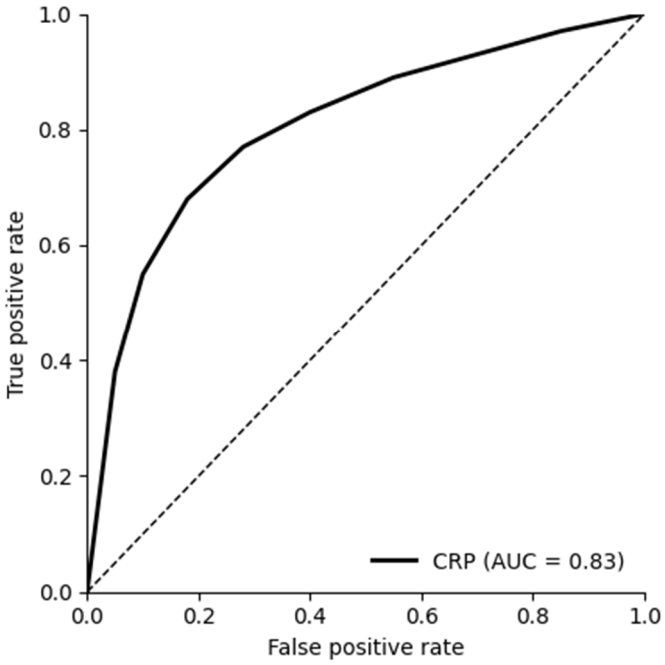

Figure 2. Receiver operating characteristic (ROC) curve of C-reactive protein for the identification of ventilator-associated pneumonia (VAP). The area under the curve (AUC) was 0.83 (95% CI 0.75-0.91), indicating good discriminative performance.