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Independent Determinants of Ventilator-Associated Pneumonia in Critically Ill Mechanically Ventilated Patients: A Prospective Multicenter Cohort Study

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ABSTRACT

Introduction: Ventilator-associated pneumonia (VAP) remains a major source of morbidity and mortality among critically ill patients requiring mechanical ventilation, contributing to prolonged intensive care unit (ICU) stays, increased healthcare costs, and worse clinical outcomes. Early identification of patients at high risk for VAP is essential for strengthening preventive strategies and optimizing critical care management.

Methods: We conducted a prospective multicenter cohort study involving adult patients who required invasive mechanical ventilation for > 48 h. Demographic, clinical, and ventilatory data were systematically collected from ICU admission until extubation or death. The primary outcome was VAP, which was defined according to standardized clinical and microbiological criteria. Multivariable logistic regression analysis was performed to identify the independent determinants of VAP after adjusting for clinically relevant confounders.

Results: Among 512 patients on mechanical ventilation, 126 (24.6%) developed VAP. The independent determinants of VAP included prolonged duration of mechanical ventilation, higher baseline severity scores, reintubation, supine positioning, and inadequate oral hygiene practices. In contrast, early initiation of enteral nutrition and strict adherence to ventilator care bundles were associated with a significantly lower risk of VAP development. The predictive model demonstrated good discrimination, thereby supporting its clinical utility.

Conclusion: VAP remains a frequent and clinically significant complication in patients on mechanical ventilation, driven by identifiable and potentially modifiable determinants. Early risk stratification based on these factors may enable targeted preventive interventions, reduce the burden of VAP, and improve outcomes in critically ill patients.

Keywords

Ventilator-Associated Pneumonia, Mechanical Ventilation, Risk Factors, Intensive Care Unit, Infection, Critical Care

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INTRODUCTION

Ventilator-associated pneumonia (VAP) remains one of the most prevalent and clinically consequential healthcare-associated infections among critically ill patients requiring invasive mechanical ventilation, typically developing after 48 h of endotracheal intubation [1]. Despite substantial advances in critical care management, antimicrobial stewardship, and infection prevention practices, VAP continues to impose a major burden on patients and healthcare systems, being strongly associated with increased morbidity and mortality, prolonged duration of mechanical ventilation, extended intensive care unit (ICU) stay, and escalating healthcare costs [2]. Although the reported incidence of VAP varies according to patient case mix, diagnostic criteria, and institutional practices, it remains a persistent and unresolved challenge, even in highly resourced

ICUs with established preventive protocols. The pathogenesis of VAP is complex and multifactorial in nature. It is primarily driven by the microaspiration of contaminated oropharyngeal and gastric secretions into the lower respiratory tract, impaired host immune defenses, and biofilm formation on endotracheal tubes, which together create a favorable environment for bacterial colonization and infection [3]. These pathogenic mechanisms are further amplified by critical illness–related conditions, such as deep sedation, suppression of protective airway reflexes, impaired mucociliary clearance, and prolonged exposure to invasive devices.

Consequently, mechanically ventilated patients represent a particularly vulnerable population in which even subtle variations in clinical management may substantially alter the risk of pulmonary infection. Over the past two decades, considerable efforts have been directed toward preventing VAP, most notably through the implementation of ventilator care bundle. These bundles commonly include head-of-bed elevation, daily sedation interruption, assessment of readiness for extubation, oral hygiene with antiseptic agents, and early mobilization [4]. Adherence to these evidence-based measures has been shown to reduce the incidence of VAP in various settings [5]. Nevertheless, the effectiveness of such preventive strategies in routine practice remains inconsistent, as adherence to individual bundle components often varies across institutions and clinical teams [6]. VAP continues to occur even in ICUs where prevention protocols are formally established, underscoring the need for more precise identification of patients at the greatest risk. A growing body of literature has sought to define the clinical predictors and risk factors associated with VAP incidence. These include patient-related characteristics, such as advanced age, comorbidities, and severity of illness, as well as treatment-related variables, including prolonged duration of mechanical ventilation, reintubation, sedation exposure, enteral feeding practices, and patient positioning [7]. However, existing evidence remains heterogeneous and methodologically limited in many cases. A substantial proportion of prior studies have been retrospective or single-center in design, with variable diagnostic definitions and inconsistent capture of time-dependent intensive care unit (ICU) variables. Moreover, relatively few prospective multicenter investigations have simultaneously evaluated both baseline patient characteristics and modifiable ICU care practices as independent determinants of VAP incidence. This gap is clinically important because several potential determinants of VAP are modifiable and may serve as actionable targets for prevention. Suboptimal oral hygiene, prolonged supine positioning, delayed initiation of enteral nutrition, and inconsistent adherence to ventilator care bundles have all been implicated in the development of VAP [8]. Identifying the relative contributions of these factors is essential not only for improving risk stratification but also for informing quality-improvement initiatives, protocol-based preventive strategies, and resource allocation in the ICU. A multicenter approach is particularly important in this context, as the risk of VAP may be influenced by inter-institutional differences in patient populations, ventilatory practices, infection control measures, and staffing patterns. Given these limitations, there is a compelling need for robust prospective multicenter data to better define the independent determinants of VAP in critically ill, mechanically ventilated patients. Prospective observational studies provide a more rigorous framework for systematic data collection, temporal assessment of exposure-outcome relationships, and evaluation of dynamic clinical variables than retrospective studies [9]. By prospectively examining a broad range of clinical and care-related factors across multiple centers, stronger and more generalizable evidence may be generated to guide preventive strategies in contemporary ICU practices. Therefore, this study aimed to identify the independent clinical determinants of ventilator-associated pneumonia in critically ill patients undergoing invasive mechanical ventilation using a prospective multicenter cohort design. By integrating both modifiable and non-modifiable factors, this study seeks to provide clinically actionable insights to refine early risk stratification, strengthen preventive interventions, and ultimately improve outcomes in patients undergoing MV [10].

METHODS

This prospective multicenter observational cohort study was conducted across several tertiary care intensive care units (ICUs) to identify the independent clinical determinants of ventilator-associated pneumonia (VAP) in critically ill patients requiring invasive mechanical ventilation. This study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

statement to ensure methodological rigor, transparency, and reproducibility. Participating centers applied standardized protocols for mechanical ventilation, infection surveillance, and routine intensive care unit (ICU) care to minimize inter-institutional variation and enhance the comparability of clinical data. Adult patients aged ≥ 18 years who required invasive mechanical ventilation for at least 48 h were eligible for inclusion. Consecutive enrollment was used to reduce selection bias and improve the representativeness of the study population. VAP-free status at the time of intubation was confirmed both clinically and radiologically. Patients were excluded if they had pre-existing pneumonia, documented pulmonary infection prior to intubation or within the first 48 h of mechanical ventilation, or if they were admitted for palliative or end-of-life care. In patients with multiple ICU admissions during the study period, only the first eligible admission was included to avoid within-patient clustering and to preserve statistical independence.

Clinical and demographic data were prospectively collected using a standardized case report form by trained investigators at each site. Baseline variables included age, sex, body mass index, smoking status, and relevant comorbidities, including chronic obstructive pulmonary disease, chronic kidney disease, heart failure, diabetes mellitus, and other chronic illnesses. The severity of illness at ICU admission was assessed using validated scoring systems, particularly the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Ventilation-related variables were recorded longitudinally and included ventilator mode, tidal volume, positive end-expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2), use of sedation, and total duration of mechanical ventilation. Care-related variables with plausible relevance to VAP prevention were systematically documented, including head-of-bed positioning, oral hygiene practices, sedation interruption strategies, timing of enteral nutrition initiation, adherence to ventilator care bundle components, reintubation events, tracheostomy, and exposure to broad-spectrum antibiotics. These variables were selected based on prior literature and clinical relevance as potential determinants of VAP. The primary outcome was the development of ventilator-associated pneumonia during the ICU stay. VAP was defined using a combination of clinical, radiological, and microbiological criteria. Specifically, diagnosis required the presence of a new or progressive pulmonary infiltrate on chest imaging occurring after at least 48 h of invasive mechanical ventilation, together with at least two of the following: fever, leukocytosis or leukopenia, purulent tracheal secretions, or positive microbiological culture from respiratory specimens. To enhance diagnostic consistency and clinical validity, VAP cases were adjudicated by attending intensivists, according to predefined criteria. Patients were followed prospectively from the initiation of invasive mechanical ventilation until extubation, ICU discharge, death, or the occurrence of VAP, whichever occurred first. The timing of VAP onset was recorded to distinguish early-and late-onset events, where appropriate. The secondary outcomes included the duration of mechanical ventilation, length of ICU stay, and in-hospital mortality.

Continuous variables were summarized as medians with interquartile ranges or means with standard deviations, as appropriate according to the data distribution, whereas categorical variables were presented as frequencies and percentages. Comparisons between patients who developed VAP and those who did not were performed using the Mann–Whitney U test or Student's t-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables as appropriate. Multivariable logistic regression analysis was performed to identify the independent determinants of VAP. Variables considered clinically relevant, together with those demonstrating a p-value of <0.10 in the univariable analysis, were entered into the multivariable model. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each outcome. Model discrimination was assessed using the area under the receiver operating characteristic (ROC) curve, whereas calibration was evaluated using goodness-of-fit testing. Prior to model construction, multicollinearity among candidate predictors was examined, and interaction terms were explored for clinically plausible variable combinations. Sensitivity analyses were performed to test the robustness of the findings, including the exclusion of patients with very early extubation and adjustment for center-level clustering using mixed-effects modeling, where appropriate. The study protocol was reviewed and approved by the institutional review boards and ethics committees of all participating centers. Written informed consent was obtained from the patients or their legally authorized representatives whenever required by local regulations. All collected data were

anonymized prior to analysis, and patient confidentiality was maintained throughout the study in accordance with the applicable ethical standards and the principles of the Declaration of Helsinki.

RESULTS

During the study period, 548 mechanically ventilated patients were screened for eligibility. After applying the predefined inclusion and exclusion criteria, 512 patients were included in the final analysis. Among them, 126 patients developed ventilator-associated pneumonia (VAP), corresponding to an overall incidence of 24.6%. The median age of the study population was 61 years (interquartile range [IQR], 49–71 years), and 290 patients (56.6%) were men. Patients who developed VAP required significantly longer durations of mechanical ventilation than those who did not develop VAP (median, 10 days [IQR, 7–16] vs. 5 days [IQR, 3–8]; p<0.001). In addition, patients in the VAP group demonstrated greater baseline illness severity, as reflected by higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores upon ICU admission.

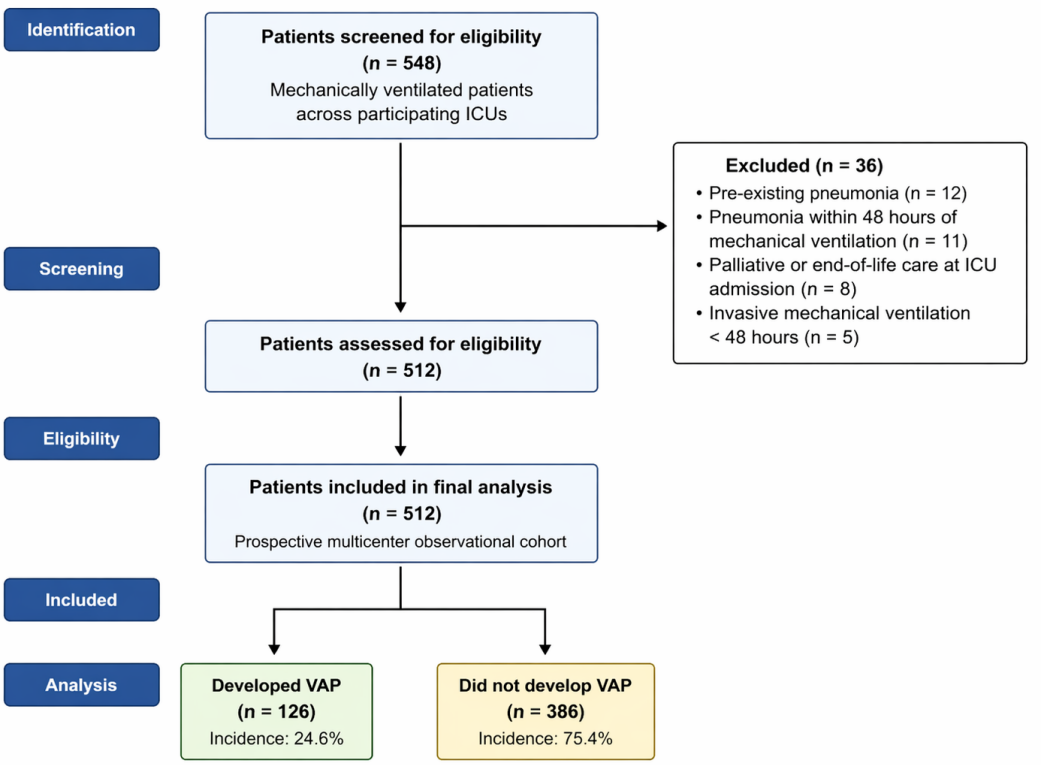

Figure 1. Flow diagram of patient screening, eligibility assessment, and final cohort inclusion.

Compared with patients who did not develop VAP, those who developed VAP were more likely to have higher severity-of-illness scores, prolonged ventilatory support, and higher incidence of reintubation. Modifiable care-related factors, including supine positioning and inadequate oral hygiene practices, were more frequently observed in the VAP group. In contrast, early initiation of enteral nutrition was more common in patients who did not develop VAP. Most VAP episodes occurred after prolonged exposure to mechanical ventilation, with a median onset of 6 days (IQR, 4‑9 days) following intubation. Early onset VAP (≤5 days) accounted for 42.1% of the cases, whereas late-onset VAP (>5 days) accounted for 57.9%, indicating a higher burden of infection associated with an extended ventilatory duration. Patients who developed VAP experienced significantly worse clinical outcomes than those who did not. In-hospital mortality was significantly higher in the VAP group (28.6% vs 19.4%; p=0.02). Furthermore, VAP was associated with prolonged ICU length of stay and extended mechanical ventilation duration.

Table 1. Baseline Characteristics of the Study Population

Variable	VAP (n=126)	Non-VAP (n=386)	p-value
Age (years), median (IQR)	62 (50–72)	60 (48–70)	0.21

Male sex, n (%)	72 (57.1)	218 (56.5)	0.89
APACHE II score, median (IQR)	20 (16–25)	17 (14–22)	<0.001
Duration of mechanical ventilation (days), median (IQR)	10 (7–16)	5 (3–8)	<0.001
Reintubation, n (%)	38 (30.2)	52 (13.5)	<0.001
Supine positioning, n (%)	54 (42.9)	102 (26.4)	0.001
Poor oral hygiene, n (%)	61 (48.4)	118 (30.6)	<0.001
Early enteral nutrition, n (%)	68 (54.0)	258 (66.8)	0.01

In the multivariable logistic regression analysis adjusted for clinically relevant confounders, several variables remained independently associated with the development of VAP. Prolonged duration of mechanical ventilation (>7 days) emerged as the strongest determinant, followed by reintubation. Among the modifiable care-related factors, supine positioning and poor oral hygiene were independently associated with an increased risk of VAP. Conversely, early initiation of enteral nutrition was independently associated with a reduced likelihood of developing VAP.

Table 2. Multivariable Logistic Regression Analysis of Independent Determinants of VAP

Variable	Adjusted OR (95% CI)	p-value
Duration of mechanical ventilation >7 days	2.41 (1.68–3.46)	<0.001
Reintubation	2.87 (1.79–4.61)	<0.001
Supine positioning	1.76 (1.15–2.68)	0.009
Poor oral hygiene	1.94 (1.27–2.96)	0.002
Early enteral nutrition	0.68 (0.45–0.98)	0.041

The final multivariable model demonstrated good discriminative ability, with an area under the receiver operating characteristic curve (AUC) of 0.78, indicating an acceptable predictive performance. Calibration analysis showed good agreement between the predicted and observed probabilities of VAP, supporting the robustness and clinical applicability of the model.

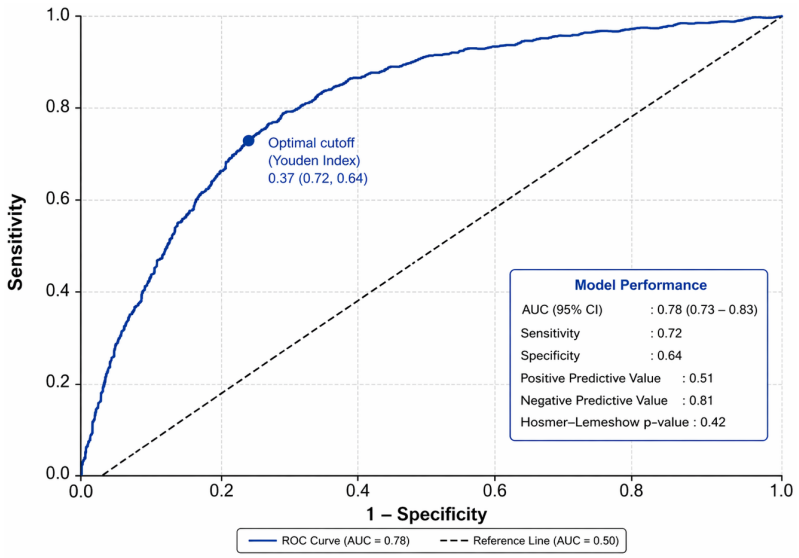

Figure 2. Receiver operating characteristic (ROC) curve of the final multivariable model for the prediction of ventilator-associated pneumonia.

Subgroup analyses demonstrated that the association between the identified determinants and VAP was more pronounced in patients requiring prolonged mechanical ventilation and those with higher baseline severity scores. Notably, the protective effect of early enteral nutrition remained consistent across all examined subgroups, suggesting a stable benefit, irrespective of illness severity or duration of ventilatory support. Sensitivity analyses excluding patients with early extubation (<72 hours) yielded results comparable to those of the primary analysis, confirming the robustness of the findings. Additional analyses incorporating adjustments for center-level variability using mixed-effects modeling did not materially alter the magnitude or

direction of the observed associations, indicating that inter-center differences had minimal impact on the primary outcomes.

DISCUSSION

In this prospective multicenter cohort study, we identified several independent determinants of ventilator-associated pneumonia (VAP), including prolonged duration of mechanical ventilation, reintubation, supine positioning, and inadequate oral hygiene, while early enteral nutrition showed a significant protective effect. These findings reinforce the multifactorial pathogenesis of VAP and underscore the critical interplay between baseline illness severity and modifiable ICU care practices in shaping the infection risk. Prolonged mechanical ventilation emerged as the most influential determinant of VAP, a finding strongly supported by existing evidence demonstrating that extended exposure to endotracheal intubation facilitates bacterial colonization, biofilm formation, and microaspiration into the lower respiratory tract [11,12]. The cumulative risk associated with prolonged ventilation highlights the importance of early liberation strategies, including daily assessment of readiness for extubation and protocolized weaning. In parallel, reintubation is independently associated with a substantially increased risk of VAP, likely reflecting repeated disruption of airway defenses, increased aspiration events, and heightened exposure to contaminated secretions during airway manipulation [13]. Our findings emphasize the pivotal role of modifiable ICU practices in preventing VAP. Supine positioning and inadequate oral hygiene were both independently associated with increased VAP risk, supporting prior studies demonstrating that head-of-bed elevation reduces aspiration risk and that structured oral care, particularly with antiseptic agents, significantly decreases VAP incidence [14,15]. Despite strong guideline recommendations, adherence to these preventive measures remains inconsistent in real-world practice, suggesting that implementation gaps continue to contribute to preventable VAP cases.

The protective association of early enteral nutrition further highlights the importance of systemic physiological support for infection prevention. Early nutritional intervention has been linked to the preservation of gut mucosal integrity, reduction of bacterial translocation, and enhancement of host immune responses in critically ill patients [16]. This finding reinforces the concept that VAP prevention should not be confined to airway management alone but should be approached as part of a comprehensive multidisciplinary critical care strategy. When contextualized within the broader literature, our results are consistent with prior studies evaluating ventilator care bundles, which have demonstrated a reduction in VAP incidence with the systematic implementation of evidence-based practices [17,18]. However, the persistent incidence of VAP observed in our cohort suggests that standard bundle-based strategies may be insufficient in high-risk populations such as ours. This underscores the need for more refined risk-adapted approaches that incorporate both patient-specific and care-related determinants. From a clinical perspective, these findings support a shift toward individualized risk stratification for VAP prevention. Early identification of high-risk patients may enable targeted intensification of preventive strategies, including optimized patient positioning, enhanced oral hygiene protocols, and proactive ventilator management aimed at minimizing ventilatory duration and avoiding unnecessary reintubation [19]. The acceptable discriminative performance of the final model further suggests that these determinants may have practical value for early bedside risk stratification, although external validation is still required before broader clinical implementation can be achieved. Several limitations should be acknowledged. Although the prospective design enhances temporal validity and data accuracy, residual confounding cannot be excluded entirely. Intercenter variability in clinical practice may have influenced the observed associations, although the multicenter design enhanced the generalizability of our findings. In addition, the diagnosis of VAP remains inherently challenging, with potential misclassification due to overlap with other pulmonary conditions, such as atelectasis or pulmonary edema [20].

Despite these limitations, this study had several important strengths, including its prospective multicenter design, standardized data collection, and simultaneous evaluation of both baseline patient characteristics and modifiable ICU care practices. These features strengthen the internal validity and real-world applicability of our findings. Collectively, our results provide clinically relevant evidence that may inform more precise, targeted, and effective VAP prevention strategies for patients who are mechanically

ventilated. Future studies should focus on the external validation of this predictive framework, evaluation of center-specific implementation strategies, and assessment of whether risk-adapted preventive interventions can translate into measurable reductions in VAP incidence, resource utilization, and mortality in critically ill populations.

CONCLUSION

In this prospective multicenter cohort study, ventilator-associated pneumonia remained a frequent and clinically significant complication among patients who were mechanically ventilated, driven by both underlying disease severity and modifiable ICU care practices. Prolonged mechanical ventilation, reintubation, supine positioning, and inadequate oral hygiene were identified as independent determinants, whereas early enteral nutrition demonstrated a protective effect. These findings highlight that VAP is not merely an inevitable consequence of critical illness but is a potentially preventable condition. Incorporating these determinants into early risk stratification frameworks may enable targeted, patient-specific preventive strategies beyond standard care bundles, thereby reducing VAP incidence, optimizing clinical outcomes, and improving the quality of care in critically ill populations.

DECLARATIONS

None

CONSENT FOR PUBLICATION

The Authors agree to the publication in the Journal of Society Medicine.

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COMPETING INTERESTS

All authors have reviewed and approved the final version of the manuscript and agreed to its publication in the Journal of Society Medicine.

AUTHORS' CONTRIBUTIONS

I.M. contributed to the conception and design of the study, data acquisition, statistical analysis, and manuscript drafting. F.B. contributed to data interpretation, methodological supervision, and critical revision of the manuscript for the important intellectual content. C.O. provided clinical expertise, contributed to the data validation, and critically reviewed and approved the final manuscript. All authors have read and approved the final version of the manuscript and agree to be held accountable for all aspects of the work.

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