E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.48047/ijprt/16.02.266

Research Article

Prospective Longitudinal Study of Inflammatory Biomarker Trajectories and Clinical Outcomes in Patients with Ventilator-Associated Pneumonia

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Abstract

Ventilator-associated pneumonia (VAP) remains one of the most frequent healthcare-associated infections among critically ill patients receiving mechanical ventilation and is associated with prolonged intensive care unit (ICU) stay, increased healthcare costs, and substantial mortality. Although inflammatory biomarkers are routinely used in the assessment of infection severity, limited evidence exists regarding the prognostic significance of longitudinal biomarker trajectories throughout the clinical course of VAP. This prospective longitudinal study evaluated the association between serial inflammatory biomarker patterns and clinical outcomes among mechanically ventilated patients diagnosed with VAP.

A total of 180 adult ICU patients with confirmed VAP were followed prospectively for 14 days after diagnosis. Serum C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), and neutrophil-to-lymphocyte ratio (NLR) were measured on days 0, 3, 7, and 14. The primary outcomes included 28-day mortality, duration of mechanical ventilation, and ICU length of stay. Patients with favorable outcomes demonstrated significant reductions in CRP (142.6 ± 34.8 to 48.9 ± 20.4 mg/L), PCT (4.8 ± 1.9 to 0.9 ± 0.6 ng/mL), and IL-6 (126.4 ± 38.7 to 42.1 ± 18.5 pg/mL) over the observation period ($p < 0.001$). Non-survivors exhibited persistently elevated biomarker levels. Multivariate analysis identified failure of

PCT reduction by more than 50% within seven days (OR 4.2, 95% CI 2.1–8.4, $p < 0.001$) and persistently elevated IL-6 (OR 3.7, 95% CI 1.9–7.2, $p < 0.001$) as independent predictors of mortality.

These findings suggest that dynamic inflammatory biomarker trajectories provide clinically meaningful prognostic information beyond baseline measurements and may improve risk stratification and treatment monitoring in patients with ventilator-associated pneumonia.

Keywords: Ventilator-associated pneumonia, inflammatory biomarkers, procalcitonin, C-reactive protein, intensive care

Introduction

Ventilator-associated pneumonia is among the most common nosocomial infections encountered in critically ill patients requiring invasive mechanical ventilation. Defined as pneumonia developing at least 48 hours after endotracheal intubation, VAP continues to represent a major challenge in intensive care medicine due to its association with prolonged hospitalization, increased healthcare expenditure, antimicrobial resistance, and significant mortality [1–3].

The pathogenesis of VAP involves a complex interaction between host immune responses, microbial colonization, aspiration of contaminated secretions, and mechanical disruption of normal airway defense mechanisms. Mechanical ventilation alters mucociliary clearance and facilitates bacterial adherence to endotracheal tubes, thereby increasing susceptibility to lower respiratory tract infections. Despite improvements in infection prevention strategies, VAP remains a leading cause of ICU-acquired morbidity worldwide [2–5].

Inflammatory biomarkers have emerged as important tools in the diagnosis, monitoring, and prognostic assessment of infectious diseases. Among these biomarkers, C-reactive protein and procalcitonin are most frequently utilized due to their accessibility and responsiveness to systemic inflammation. Recent investigations have also highlighted the potential value of cytokines such as interleukin-6 and hematologic indices including the neutrophil-to-lymphocyte ratio as indicators of disease severity and treatment response [4–8].

Traditionally, clinical decisions have relied on single biomarker measurements obtained at diagnosis. However, baseline biomarker values often demonstrate substantial overlap between survivors and non-survivors, limiting their predictive utility. Increasing evidence suggests that the trajectory of biomarker changes over time may provide more clinically relevant information than isolated measurements. Dynamic reductions in inflammatory

markers may reflect successful infection control and resolution of systemic inflammation, whereas persistently elevated levels may indicate treatment failure or ongoing immune dysregulation [6–10].

The concept of biomarker trajectories has gained attention in sepsis research, where serial measurements have demonstrated superior prognostic performance compared with baseline values alone. Similar approaches may be valuable in VAP, yet prospective longitudinal investigations remain limited. Understanding temporal patterns of inflammatory biomarkers may facilitate earlier identification of patients at risk for adverse outcomes and support individualized therapeutic decision-making [8–12].

Furthermore, the heterogeneity of VAP pathogens and host responses complicates prognostication using conventional clinical parameters. Biomarker trajectory analysis may provide a more objective and biologically meaningful assessment of disease progression. Such information could assist clinicians in optimizing antimicrobial therapy, evaluating treatment response, and identifying patients requiring intensified supportive interventions [10–14].

Given these considerations, the present study was designed to prospectively evaluate longitudinal changes in inflammatory biomarkers among patients with ventilator-associated pneumonia and determine their relationship with mortality, duration of mechanical ventilation, and ICU length of stay.

Methodology

This prospective longitudinal observational study was conducted in the adult intensive care units at Nawaz Sharif Social Security Hospital, Lahore of a tertiary care teaching hospital over a 24-month period. Adult patients aged 18 years or older who developed ventilator-associated pneumonia after at least 48 hours of mechanical ventilation were eligible for inclusion.

VAP diagnosis was established using clinical, radiological, and microbiological criteria, including new or progressive pulmonary infiltrates, fever, leukocytosis or leukopenia, purulent respiratory secretions, and positive quantitative respiratory cultures. Patients with pre-existing pneumonia prior to intubation, severe immunosuppression, active malignancy receiving chemotherapy, autoimmune disorders, or incomplete follow-up data were excluded.

Sample size estimation was performed using Epi Info software. Assuming a mortality rate of approximately 25%, a confidence level of 95%, statistical power of 80%, and an anticipated odds ratio of at least 2.0 for biomarker-associated mortality risk, the minimum sample size was

estimated at 170 patients. To compensate for potential losses, 180 patients were enrolled.

Venous blood samples were collected on day 0 (VAP diagnosis), day 3, day 7, and day 14. Biomarkers analyzed included CRP, PCT, IL-6, and NLR. Clinical data collected included demographic characteristics, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, microbiological findings, duration of mechanical ventilation, ICU length of stay, and mortality.

Written informed consent was obtained from legally authorized representatives. Ethical approval was granted by the institutional review board before study commencement.

Data analysis was performed using SPSS version 27. Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were presented as frequencies and percentages. Longitudinal changes were analyzed using repeated-measures ANOVA. Logistic regression was used to identify independent predictors of mortality. Statistical significance was defined as $p < 0.05$.

Results

Table 1. Baseline Demographic and Clinical Characteristics (n = 180)

Variable	Value
Age (years)	59.8 ± 15.1
Male sex	112 (62.2%)
Female sex	68 (37.8%)
APACHE II score	21.4 ± 6.2
SOFA score	8.9 ± 3.1
Diabetes mellitus	72 (40.0%)
Chronic kidney disease	31 (17.2%)
COPD	45 (25.0%)
Septic shock at diagnosis	39 (21.7%)
28-day mortality	46 (25.6%)

Table 1 demonstrates that the study population consisted predominantly of older critically ill patients with significant comorbidity burden and moderate-to-severe illness severity at VAP diagnosis.

Table 2. Longitudinal Biomarker Trends According to Clinical Outcome

Biomarker	Day 0	Day 3	Day 7	Day 14	p-value
CRP Survivors (mg/L)	142.6 ± 34.8	118.4 ± 29.1	79.7 ± 25.6	48.9 ± 20.4	<0.001
CRP Non-survivors	148.9 ± 39.2	146.1 ± 36.7	141.2 ± 35.8	138.6 ± 33.9	<0.001
PCT Survivors (ng/mL)	4.8 ± 1.9	3.1 ± 1.4	1.8 ± 0.9	0.9 ± 0.6	<0.001
PCT Non-survivors	5.1 ± 2.1	5.3 ± 2.2	5.0 ± 2.0	4.8 ± 2.1	<0.001
IL-6 Survivors (pg/mL)	126.4 ± 38.7	92.1 ± 30.5	63.8 ± 24.1	42.1 ± 18.5	<0.001
IL-6 Non-survivors	131.8 ± 41.2	129.4 ± 39.1	126.7 ± 38.8	121.6 ± 35.4	<0.001

Patients with favorable outcomes demonstrated progressive reductions in all inflammatory biomarkers, whereas persistently elevated levels were observed among non-survivors.

Table 3. Multivariate Predictors of 28-Day Mortality

Variable	Odds Ratio	95% CI	p-value
PCT reduction <50% by Day 7	4.2	2.1–8.4	<0.001
Persistently elevated IL-6	3.7	1.9–7.2	<0.001
APACHE II score >25	3.3	1.7–6.5	0.001
Septic shock	2.8	1.4–5.6	0.004
CRP reduction <30%	2.5	1.3–4.8	0.008

Discussion

The present prospective longitudinal study demonstrates that dynamic inflammatory biomarker trajectories are strongly associated with clinical outcomes in patients with ventilator-associated pneumonia. While baseline biomarker concentrations showed only modest differences between outcome groups, serial measurements revealed distinct patterns that accurately reflected disease progression and treatment response.

Among the biomarkers evaluated, procalcitonin exhibited the strongest prognostic performance. Patients who survived demonstrated rapid and sustained

reductions in serum PCT levels, whereas persistently elevated concentrations were associated with significantly increased mortality risk. These findings support previous evidence suggesting that serial PCT monitoring may provide a valuable indicator of infection resolution and antimicrobial treatment effectiveness [11–13].

Interleukin-6 also emerged as a powerful predictor of adverse outcomes. Persistent elevation of IL-6 likely reflects ongoing systemic inflammation and dysregulated host immune responses. The cytokine's association with mortality observed in this study aligns with contemporary research identifying excessive inflammatory activation as a key contributor to organ dysfunction and poor outcomes in severe infections [14–16].

The results further indicate that biomarker trajectories provide greater prognostic information than baseline values alone. This observation has important clinical implications because initial inflammatory responses may vary considerably among individuals. Longitudinal assessment captures dynamic changes in disease activity and may therefore offer a more reliable reflection of therapeutic response [16–18].

CRP demonstrated significant reductions among survivors but appeared less predictive than PCT and IL-6. This finding may be attributable to CRP's slower biological kinetics and reduced specificity compared with newer biomarkers. Nevertheless, serial CRP monitoring remains clinically useful due to its widespread availability and low cost [17–19].

The study also identified illness severity and septic shock as independent mortality predictors. These findings reinforce the multifactorial nature of VAP outcomes and highlight the importance of integrating biomarker information with established clinical risk assessment tools.

Several strengths distinguish this investigation, including its prospective design, serial biomarker measurements, and comprehensive outcome assessment. However, the study was conducted in a single center and therefore may have limited generalizability. Future multicenter studies are warranted to validate these findings and explore biomarker-guided treatment strategies.

Overall, the results suggest that inflammatory biomarker trajectories provide valuable prognostic information and may support personalized management approaches in patients with ventilator-associated pneumonia.

Conclusion

Longitudinal monitoring of inflammatory biomarkers provides clinically meaningful prognostic information in ventilator-

associated pneumonia. Persistently elevated procalcitonin and interleukin-6 levels were independently associated with increased mortality and prolonged critical illness. Incorporation of biomarker trajectory analysis into routine ICU practice may improve risk stratification and facilitate earlier identification of patients requiring intensified therapeutic interventions.

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