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Evaluation of Serum Inflammatory Biomarkers in Ventilator Associated Pneumonia: A Study from Tertiary Care Hospitals in Islamabad, Pakistan

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ABSTRACT

Background: Ventilator-associated Pneumonia (VAP) is one of the most common infections in critically ill patients receiving mechanical ventilation. It remains a major cause of increased mortality among these patients and contributes to prolonged hospital stay. Early diagnosis of VAP is often difficult because commonly used clinical and laboratory findings can also appear in other respiratory conditions and lack specificity. Serum inflammatory biomarkers such as Pro-calcitonin (PCT), C-reactive Protein (CRP) and White Blood Cells (WBCs) count may improve diagnostic accuracy and help monitor the disease progression. **Methodology:** This study included 70 mechanically ventilated ICU patients diagnosed with VAP across the selected Tertiary Care Hospitals of Islamabad. Levels of PCT, CRP and WBCs count were measured across three different points of time; during first 48 hours of mechanical ventilation (base-line value), at clinical suspicion of VAP and one week after the diagnosis of VAP. Descriptive and inferential tests including mean, standard deviation, frequency, percentage, Shapiro-Wilk test, Wilcoxon signed-rank test and Friedman test were used (where applicable) for the analysis of data. **Results:** Serum PCT levels showed a significant rise from base-line value to the time of clinical VAP suspicion and then a significant fall, one week after VAP diagnosis ($p < 0.001$). CRP levels also increased at the time of suspicion and then decreased one week after diagnosis but the overall variation in its levels was not statistically significant ($p = 0.116$). WBCs Count only showed minimum fluctuation across the three time points without any statistically significant difference ($p = 0.108$). **Conclusion:** Among the evaluated biomarkers, PCT demonstrated greater diagnostic relevance as compared to CRP and WBCs Count, reflected by its stronger temporal response. Its dynamic changes closely reflected disease's onset, progression and its response to treatment. These findings suggest that PCT has a great clinical usefulness as a biomarker for VAP than CRP and WBCs count. These findings suggest the usefulness of PCT as a clinical adjunct for the diagnosis and monitoring of VAP.

Keywords: Ventilator-associated Pneumonia (VAP), Serum Biomarkers, Pro-calcitonin (PCT), C-reactive Protein (CRP), White Blood Cells (WBCs) count

INTRODUCTION

Ventilator-associated Pneumonia (VAP) remains one of the most frequent and clinically significant healthcare associated infections encountered in the ICUs worldwide. It is defined as pneumonia developing after 48 hours of initiation of mechanical ventilation [1] and contributes to increased mortality, prolonged hospital stays and increased healthcare costs [2]. The reported incidence of VAP varies depending on patient population and diagnostic criteria, ranging from 5 to 40% while estimated

attributable mortality linked to VAP is reported around 10% with higher mortality in surgical ICUs [3]. This burden highlights the urgent need for early recognition and timely intervention to prevent complications.

Despite improvements in intensive care, diagnosis of VAP often remains challenging because its clinical manifestations often overlap with other inflammatory and non-infectious pulmonary conditions observed in critically ill patients. Traditional diagnostic factors such as fever, leukocytosis, purulent secretions and radiographic chest infiltrates frequently lack specificity. A postmortem validation study demonstrated that the presence of infiltrates on the chest radiograph and two of three clinical criteria (leukocytosis, purulent secretions and fever) had a sensitivity of 69% and a specificity of 75% [4]. Similarly, radiographic findings may be difficult to interpret in patients with Acute Respiratory Distress Syndrome (ARDS), pulmonary edema or atelectasis, often resulting in diagnostic uncertainty. Because of these diagnostic uncertainties, serum biomarkers have gained increasing attention as adjunctive tools for improving the diagnostic precision and monitoring of VAP. Among these biomarkers PCT, CRP and WBCs count remain the most widely investigated markers due to their accessibility and potential clinical value.

PCT is a 116-amino acid residue first explained by Le Moullec et al. in 1984; its diagnostic significance was not recognized until 1993 [5]. PCT has emerged as one of the most promising biomarker for the bacterial infections of lower respiratory tract. In a prospective study evaluating patients with VAP, PCT threshold of 2.99 ng/mL demonstrated sensitivity of 78% and specificity of 97%, significantly outperforming CRP for the diagnosis of VAP [6]. Similarly, another study reported the mean PCT concentration of 11.5 ng/mL in confirmed VAP patients as compared to PCT mean concentrations of 1.5 ng/mL in non-VAP mechanically ventilated controls, highlighting the discriminatory diagnostic value of PCT [7]. Meta-analytical evidence further supports its usefulness. A systematic review (including 373 patients and 434 suspected VAP episodes) demonstrated 76% diagnostic sensitivity and 79% specificity associated with increased plasma PCT levels significantly increasing the probability of VAP diagnosis [8]. A retrospective study in COVID-19 patients reported that PCT may be a pertinent biomarker for VAP diagnosis and can be a helpful tool for antibiotic withdrawal [9]. CRP is a typical short-chain PTX member, mainly synthesized in the liver to respond to inflammation [10]. It is another widely used biomarker produced by the hepatocytes in response to IL-6 stimulation. A sequential biomarker assessment among the ventilated patients, reported lower sensitivity (56%) for CRP as compared to PCT despite acceptable specificity (91%) for microbiologically confirmed VAP [6]. This reduced sensitivity limits the reliability of CRP as an isolated diagnostic indicator. WBCs are part of the immune system and participate in innate and humoral immune responses. They circulate in the blood and mount inflammatory and cellular responses to injury or pathogens [11]. WBCs Count remains one of the most used laboratory indicators in intensive care settings. However, its interpretation in VAP is often difficult because WBCs count changes may occur also in response to systematic stress, corticosteroid administration and other non-infectious inflammatory conditions. It is usually interpreted alongside other clinical and laboratory parameters. It is incorporated into CPIS where the abnormal WBCs count contributes to the assessment of infection along with the other parameters such as temperature, tracheal secretions, radiographic findings and microbiological cultures [12].

A comparative diagnostic study by Chen et al. evaluated PCT, CRP and Clinical Pulmonary Infection Score (CPIS) in suspected VAP patients and it reported superior diagnostic performance of PCT as compared to CRP alone [13]. Similarly, another study reported that PCT is associated with the severity of illness in patients with severe pneumonia and appears to be a prognostic marker of morbidity and mortality comparable to the APACHE II score [14]. Despite promising evidence favoring PCT, variability persists across the healthcare settings. Data from local healthcare systems remains limited. Due to conflicting evidence and lack of data, these biomarkers lack the ability to replace current diagnostic methods [15].

Therefore, the present study was conducted to evaluate the changes in the level of serum biomarkers in mechanically ventilated adult ICU patients diagnosed with VAP. By comparing the trends of these biomarkers at pre-defined clinical stages, this study aimed to identify reliability of these biomarkers for early diagnosis of VAP and monitoring the progression of disease, thereby improving the evidence based management of VAP.

METHODOLOGY

This study included 70 adult mechanically ventilated individuals from the ICUs of selected tertiary care hospitals of Islamabad. During the study period, 102 mechanically ventilated ICU patients were assessed across the selected hospitals, of whom 17 developed VAP, giving an estimated prevalence of 16.7%. Sample size was calculated using the Cochran's formula, at 95%

Volume 7, Issue 1, 2026 | https://doi.org/10.53576/bashir.007.01.0316

confidence interval and 5% margin of error. Finite population correction, was applied due to the limited eligible patient population, resulting in a final sample size of 70 patients.

Patients who had received mechanical ventilation for more than 48 hours and subsequently developed clinical features suggestive of lower respiratory tract infection were evaluated for VAP. The diagnosis was based on a combination of clinical and radiological findings, including fever, abnormal WBCs count, purulent tracheal secretions and new or progressive infiltrate on chest radiography after excluding other potential causes of these findings. Microbiological investigations, when available were considered as supportive evidence for the diagnosis of VAP in conjunction with clinical and radiological findings. Time duration of this study was about four months from October 2025 to January 2026. Individuals with pre-existing pneumonia or any other major established infection, those who (or their legally authorized representatives) refused consent or those who were below 18 years of age were excluded from the study.

Data Collection Procedure

Data were collected prospectively using a pre-structured questionnaire, documenting patients' demographics, co-morbidities, risk factors and serum biomarker levels: PCT, CRP and WBCs count. Levels of PCT, CRP and WBCs count were measured across three different points of time; during first 48 hours of mechanical ventilation (base-line value), at clinical suspicion of VAP and one week after the diagnosis of VAP.

Analysis of Data

Data were analysed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive and inferential tests including mean, standard deviation, frequency, percentage, Shapiro-Wilk test, Wilcoxon signed-rank test and Friedman test were applied (where applicable). The distribution of continuous variables, including body temperature, serum PCT, CRP, and WBCs count was assessed using the Shapiro-Wilk test. The normality assessment indicated that the repeated measurements did not satisfy the assumption of normal distribution; therefore, non-parametric statistical methods were used. Changes in body temperature, serum PCT, CRP, and WBCs count across the three study time points were assessed using the Friedman test for related samples. Pairwise comparisons between individual time points were performed using the Wilcoxon signed-rank test. A p value of less than 0.05 was considered significant. Continuous variables were presented as mean ± standard deviation (S.D) to facilitate interpretation and comparison with previous studies, while non-parametric tests were used for statistical inference because the data did not fully satisfy the assumptions for parametric analysis.

Ethical approval was obtained from the hospital (RD # 2025-24), informed consent was ensured, patient confidentiality was maintained and all data were securely stored, adhering strictly to institutional ethical guidelines and international research standards. Ethical approval was also obtained from the Institutional Review Board (IRB) of Bashir Institute of Health Sciences.

RESULTS

The demographics and baseline clinical characteristics of the study population are presented in Figure 1. The figure illustrates the distribution of patients according to the gender (Figure 1(a)), age group (Figure 1(b)) and primary diagnosis profile at the time of ICU admission (Figure 1(c)).

Volume 7, Issue 1, 2026 | https://doi.org/10.53576/bashir.007.01.0316

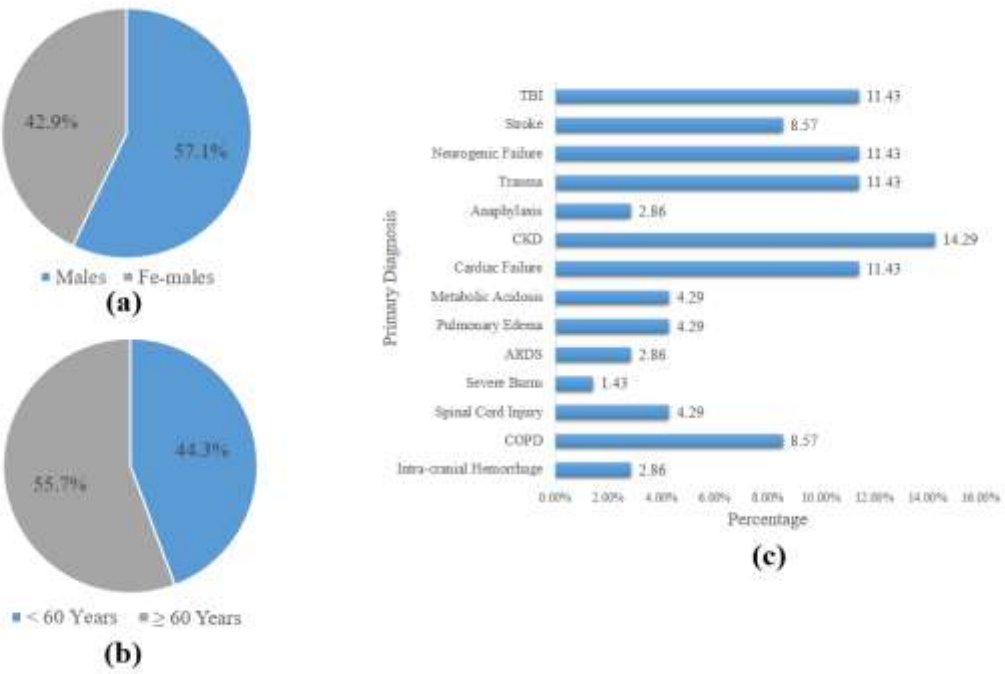

Figure 1: Demographics and baseline clinical characteristics of the study population (n = 70). **(a)** Gender distribution. **(b)** Age distribution. **(c)** Primary diagnosis profile at the time of ICU admission.

The distribution of identified risk factors demonstrated considerate variability among the study participants. Each risk factor was recorded as present or absent based on documented clinical history and procedures performed during the hospital stay before the diagnosis of VAP. The most prevalent risk factor among the participants was NG tube placement, observed in 75.71% of the patients at the time of VAP development. This was followed by Age above 60 years (55.71%), Diabetes (documented in 48.57% of the participants) and Emergency Intubation (38.57%). Notably, three risk factors; Tracheostomy, Blood transfusion and previous surgery exhibited identical prevalence of 28.57% indicating a comparable contribution to VAP susceptibility in this study. The least prevalent risk factor in this study was CVC replacement documented in 14.29% cases. Figure 2 demonstrates the prevalence of risk factors among study population.

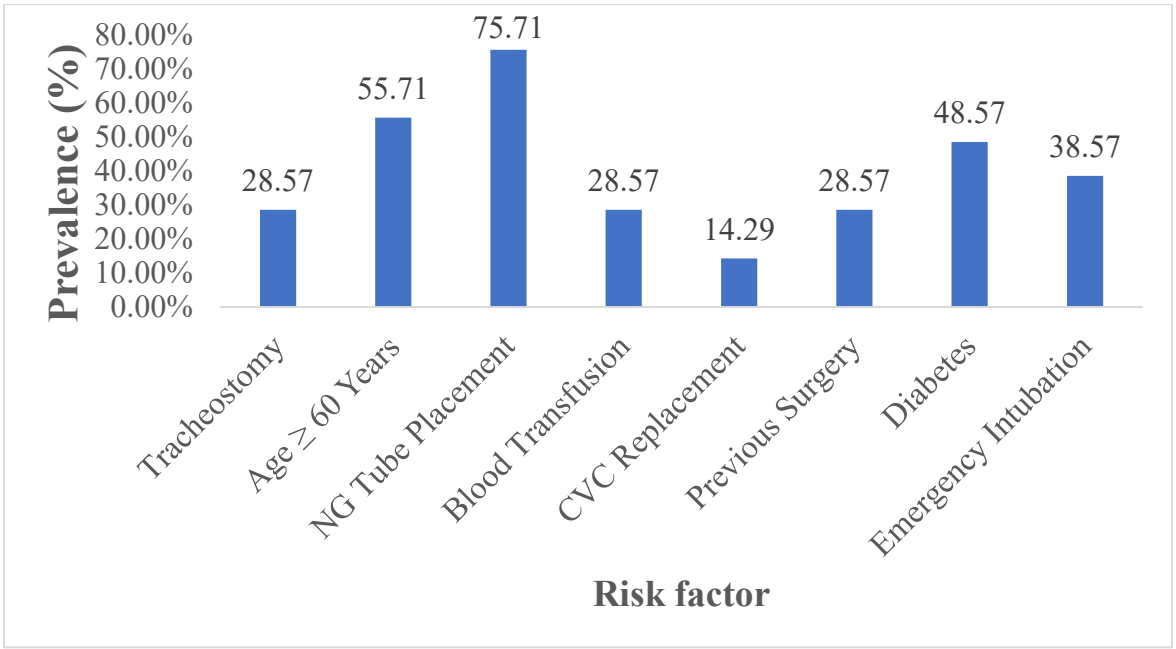

Figure 2: Prevalence of Risk Factors among Study Population (n = 70).

Volume 7, Issue 1, 2026 | https://doi.org/10.53576/bashir.007.01.0316

Temperature:

The mean temperature of study participants during the first 48 hours of mechanical ventilation was 99.81±1.21^{o}F. The mean temperature at clinical suspicion of VAP was calculated 100.51±1.49^{o}F, representing an absolute change of 0.7 ^{o}F and a 0.70% increase from the baseline value. The rise was statistically significant according to the Wilcoxon signed-rank test ($p = 0.007$). One week after VAP diagnosis, the mean temperature was 99.59±1.18^{o}F. It shows an absolute change of 0.92 ^{o}F and a 0.91% decrease when compared with the mean value recorded at the time of VAP suspicion. This change was statistically significant ($p < 0.001$). The mean temperature values across the three time points are illustrated in Figure 3(a).

Overall comparison of temperature values across the three time points using the Friedman test confirmed a statistically significant difference over time (Friedman $\chi^2 = 9.814$, $p = 0.007$). This indicates that absolute changes were modest but the pattern of change was consistent across the study participants.

Serum Bio-markers

Ⅰ. Pro-calcitonin:

The mean pro-calcitonin level during the first 48 hours of mechanical ventilation was 0.83±0.54 ng/mL representing the baseline value in the study. At the time of clinical suspicion of VAP, mean PCT was recorded to be 1.97±0.86 ng/mL. This shows a rise of 1.14 ng/mL corresponding to a 137.3% rise from the baseline value recorded during the first 48 hours of mechanical ventilation. This increase was statistically significant according to the Wilcoxon signed-rank test ($p < 0.001$). One week after the diagnosis of VAP, the mean value of PCT was recorded to be 1.32 ± 0.77 ng/mL showing a decrease of 32.9% (0.65 ng/mL) compared with the mean value of pro-calcitonin recorded at the time of clinical suspicion of VAP. This change was statistically significant according to Wilcoxon signed-rank test ($p < 0.001$). Figure 3(b) demonstrates the mean levels of Serum PCT across the three time points.

Overall PCT demonstrated a clear pattern of rise at the onset of VAP followed by a decline with time. The difference of mean PCT levels across the three points of time were confirmed by the Friedman test (Friedman $\chi^2 = 67.229$, $p < 0.001$). This shows a statistically significant variation in serum PCT levels across time, along the course of VAP.

Ⅱ. C-reactive protein:

The descriptive statistics showed that the mean CRP value during the first 48 hours of mechanical ventilation was 41.46 ± 17.11 mg/L, which increased to 52.66 ± 18.88 mg/L at the time of clinical suspicion of VAP. This shows a rise of about 27.01% (11.2 mg/L) from the baseline value recorded during the first 48 hours of mechanical ventilation. This increase was statistically significant according to the Wilcoxon signed-rank test ($p = 0.004$). One week after the diagnosis of VAP, the mean value of CRP was 46.03 ± 25.09 mg/L. The change between the CRP value at clinical VAP suspicion and the value calculated 1 week after VAP diagnosis is 6.63 mg/L. This indicates a 12.6% decrease in CRP value across these two time points. This change was not statistically significant ($p = 0.112$) according to the Wilcoxon signed-rank test. The mean values of CRP across the three different predefined time points are described in Figure 3(c).

The overall comparison of CRP levels using the Friedman test did not demonstrate any statistically significant difference across the three time points, Friedman $\chi^2 = 4.314$, $p = 0.116$.

Ⅲ. WBCs Count:

WBCs levels were also evaluated at three points; during first 48 hours of mechanical ventilation (baseline value), at clinical suspicion of VAP and then one week after the diagnosis of VAP. The mean WBCs count during first 48 hours was 14.31±2.92×10^9/L. This mean value increased to 15.31±2.29×10^9/L at the time of suspicion of VAP representing an approximate rise of 6.99% (1.00×10^9/L). One week after VAP diagnosis, the mean value of WBCs count was recorded to be 15.24±3.38×10^9/L. This shows a decrease in mean value of WBCs count by 0.45% (0.07×10^9/L). Intergroup comparison using the Wilcoxon sign-ranked test showed that the increase in WBCs count at the time when VAP was clinically suspected from the baseline value (recorded during first 48 hours of mechanical ventilation) was not statistically significant ($p = 0.117$). The change observed by comparison between VAP levels at clinical suspicion and 1 week after VAP diagnosis was also not statistically

Volume 7, Issue 1, 2026 | https://doi.org/10.53576/bashir.007.01.0316

significant (p = 0.898) indicating persistence of the inflammation. Figure 4(d) illustrates the mean WBCs count recorded among the study population across the three time points.

When all these three time points were analyzed using the Friedman test (for the repeated non-parametric measures), it was observed that the change in the levels of WBCs count along the course of VAP was statistically non-significant (Friedman χ^2 = 4.457, p = 0.108), confirming that WBCs count showed no significant overall shift across the time period of the study.

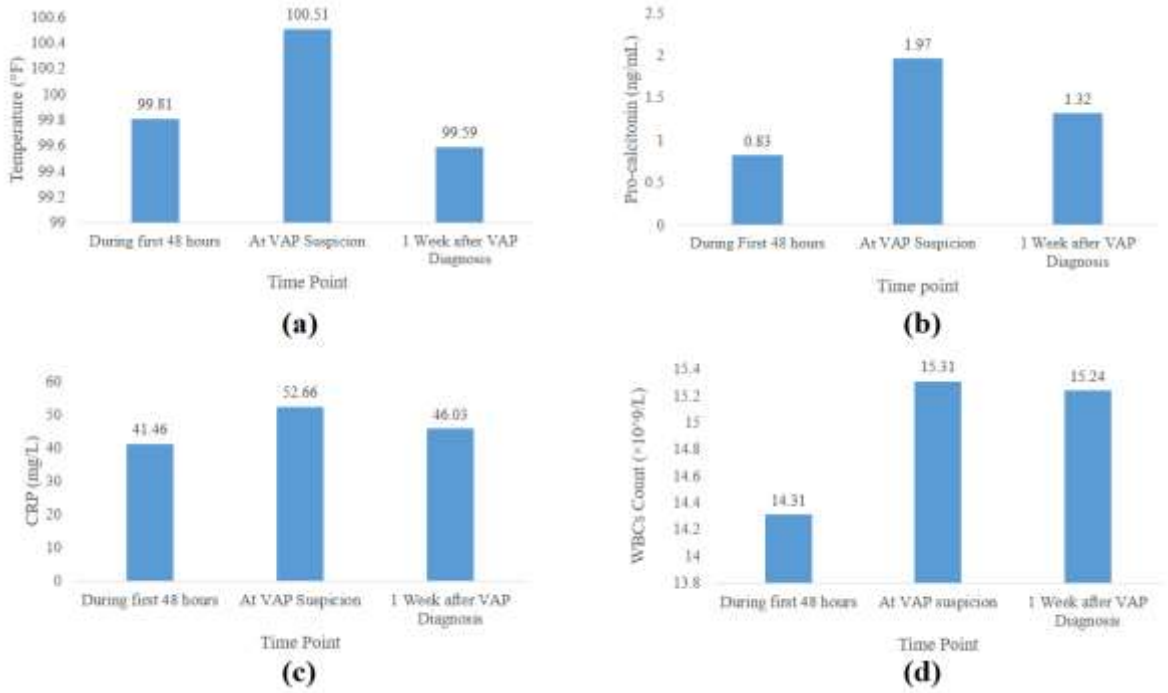

Figure 3: Mean values of Temperature and Serum biomarkers recorded at three predefined time points among the study population (n = 70). **(a)** Mean body temperature of study participants. **(b)** Mean Serum PCT levels of study participants. **(c)** Mean CRP levels of study participants. **(d)** Mean WBCs count of participants.

DISCUSSION

In this study, 70 adult mechanically ventilated ICU individuals diagnosed with VAP were included. Most participants were older, with 55.7% participants, who had age above 60 years and males constituted 57.1%. These demographics are consistent with previous findings that advanced age and male gender are common VAP risk factors likely due to immune changes and co-morbidity burden in ICU population [16, 17]. Several risk factors were prevalent in the study group including NG tube placement (75.7%), age above 60 years (55.7%), diabetes (48.5%), emergency intubation (38.5%), blood transfusion (28.6%), previous surgery (28.5%), tracheostomy (28.5%) and CVC replacement (14.3%) [18].

Body temperature showed a modest but statistically significant variation. Although the absolute change was < 1^{o}F, the overall trend was significant (Friedman χ^2 = 9.814, p = 0.007). Similar mild elevations have also been reported in other ICU infections where temperature is influenced by many other non-infectious factors [19]. Previous studies have also reported poor performance of body temperature in the prediction of VAP diagnosis [20].

Pro-calcitonin demonstrated a significant marked dynamic pattern. The changes in mean PCT levels (rise from the baseline level and then decrease one week after VAP diagnosis) were statistically significant (p < 0.001, for both comparisons using Wilcoxon signed-rank test). Overall variation in its level were also statistically significant (Friedman χ^2 = 67.229, p < 0.001). These findings support PCT as a dynamic biomarker for VAP. Luyt et al. reported similar doubling of PCT at the time of VAP diagnosis as compared to the baseline [21]. Similarly, a study published in *Thorax* reported that PCT may be utilized as a diagnostic biomarker for paediatric VAP following cardiac surgery [22]. Another study conducted at the intensive care unit (ICU) of the Department of Cardiothoracic Surgery at the Second Xiangya Hospital of Central South University (Changsha, China) reported that serum PCT

Volume 7, Issue 1, 2026 | https://doi.org/10.53576/bashir.007.01.0316

may be used as diagnostic marker for VAP in patients following cardiac surgery [23]. The rise at suspicion and fall after 1 week suggests usefulness of PCT for the monitoring of infection course and response to antibiotic therapy [6, 8, 13].

Mean CRP value demonstrated an increase of 27% at the time of clinical suspicion of VAP as compared to the baseline value showing a statistically significant difference across the two time points ($p = 0.004$). Its levels decreased after one week without any statistically significant difference ($p=0.112$). Overall change in CRP value was not significant (Friedman $\chi^2 = 4.314$, $p = 0.116$). Although CRP rises with inflammation, it is influenced by surgery, trauma and other ICU stressors. Povoa et al. observed persistent CRP elevation during the ICU infections [20]. This suggests that CRP may be sensitive to infection and an elevation in its level may indicate a new infection development but it may be less specific as compared to PCT for VAP detection or monitoring its resolution [13, 24].

WBCs count showed minimal, non-significant changes in this study. Mean WBCs count had an increase of about 6.99% at the time of clinical VAP suspicion as compared to the baseline value without any statistically significant difference ($p = 0.117$), and then had a decrease of 0.45% without any statistically significant difference ($p = 0.898$). Overall trend of WBCs count was also not statistically significant according to the Friedman test ($\chi^2 = 4.457$, p 0.108). This suggests that WBCs count may not be reliable for reflecting the onset and progression of VAP [20]. These findings align with prior studied showing WBCs count variability due to multiple non-infectious ICU factors [25].

Overall, PCT showed the most consistent and significant trend, rising at VAP suspicion and then declining after one week. This indicates a greater diagnostic relevance of PCT compared with CRP and WBCs count for diagnosis and monitoring of VAP [13, 26]. However, no biomarker should be assessed alone for VAP diagnosis and all must complement clinical assessment.

Limitations and Recommendations

The study had several limitations that should be considered. The sample size was relatively small which may reduce the statistical power and accuracy of the results. This was a multi-institutional study within a single metropolitan area (Islamabad), the results may not represent the broader ICU population with the different patient characteristics or clinical practices. The biomarkers were measured at fixed time points which may not have captured all the dynamic changes of these biomarkers along the course of illness. Microbiological confirmation was not always available which may have affected the diagnostic comparison. Additionally, factors such as co-morbidities, concurrent infections and non-infectious inflammatory conditions could have influenced the levels of these biomarkers.

Future studies should try to include larger and multi-center populations to improve generalizability. More frequent serial measurements of these biomarkers can better define their trends along the course of VAP. Future researches should also explore the emerging biomarkers such as Soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1) and other host-response markers (such as IL-6), which may offer improved diagnostic accuracy as compared to these traditional inflammatory bio-markers. Absence of microbiological and pathogen distribution data limited etiological stratification; this should be addressed in future prospective studies. Future studies should also comprehensively evaluate the independent impact of pre-existing co-morbid conditions on the incidence, severity, therapeutic response and clinical outcomes of VAP.

CONCLUSION

This study evaluated the dynamics of PCT, CRP and WBCs count in mechanically ventilated patients with VAP. Our findings demonstrate that PCT exhibited more pronounced temporal changes as compared to CRP and WBCs count. PCT levels showed a significant increase at the time of clinical suspicion of VAP and then a significant decrease one week after diagnosis. CRP exhibited a less significant increase at VAP suspicion and its value remained high even after one week reflecting general systemic inflammation. CRP levels did not show a significant statistical difference across the time. Despite this, CRP retains clinical value as a widely available inflammatory biomarker particularly when interpreted alongside the PCT trends. Its interpretation should be cautious when used alone. WBCs count remained highly variable across the patients, limiting its diagnostic utility for VAP. Overall, results suggest that PCT exhibited a stronger temporal response as compared to CRP and WBCs count suggesting its potential utility as a supportive biomarker in the clinical assessment of the infection and it may have potential utility in monitoring inflammatory activity in patients with VAP.

Volume 7, Issue 1, 2026 | https://doi.org/10.53576/bashir.007.01.0316

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Author's Contribution

All authors contributed equally to the conception and planning of the study, data collection, statistical analysis, interpretation of the results and drafting the manuscript. All authors critically reviewed the final manuscript and approved it for publication.

Conflicts of Interest

None declared.

Ethical Approval and Consent to Participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was granted ethical approval by the Ethical Review Committee of Bashir Institute of Health Sciences (IRB/BIHS/2025/VII/01).

Use of Artificial Intelligence

No AI-based writing assistance was used during preparation of this manuscript.

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Data Availability Statement

The datasets generated and analysed in this study are available from the corresponding author on reasonable request.

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