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Monaldi Archives for Chest Disease

Monaldi Archives for Chest Disease 2026; 96:3225
doi: 10.4081/monaldi.2025.3225

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Pentraxin-3 as a novel biomarker in predicting outcomes of nosocomial pneumonia: a prospective observational study

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Abstract

Pneumonia, among all nosocomial infections, is known for its dismal prognosis, imposing substantial morbidity and mortality. While the diagnostic performance of various blood biomarkers has undergone scrutiny, their prognostic implications remain relatively unexplored. This study aimed to evaluate the prognostic significance of clinical factors, microbial etiology, and blood biomarkers, including procalcitonin, C-reactive protein (CRP), and pentraxin-3, in determining the outcome of nosocomial pneumonia. We enrolled 72 patients with microbiologically confirmed hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). Patient data comprising demographics, comorbidities, duration of hospitalization, isolated pathogen, and laboratory parameters, including CRP, procalcitonin, and pentraxin-3 levels, were compiled to assess their correlation with 28-day survival outcomes. The study included 58 VAP and 14 HAP patients. The mean age was 52.78±16.98 years, and the majority were males (68.06%). Out of 72, 30 (41.67%) died. Carbapenem-resistant *Acinetobacter baumannii* (44.44%) and Carbapenem-resistant *Enterobacteriaceae* (25%) were the most common isolated pathogens. On univariate analysis, male gender, smoking, opium addiction, underlying neurological condition as comorbidity, presence of septic shock, elevated blood urea, and serum pentraxin-3 levels were significantly associated with 28-day mortality. However, multivariate analysis of subgroup data revealed serum pentraxin-3 levels to be an independent risk factor for mortality in VAP patients. Serum pentraxin-3 levels may be a potential and superior prognostic marker compared to CRP and procalcitonin in predicting mortality in VAP patients.

Key words: C-reactive protein, nosocomial pneumonia, pentraxin-3, procalcitonin.

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Introduction

Nosocomial pneumonia is among the most prevalent hospital-acquired infections (HAI), comprising 22% of all cases. These infections worsen patient outcomes, extending hospital stay by 1-2 weeks, thereby incurring higher costs. Ventilator-associated pneumonia (VAP) lengthens the duration of mechanical ventilation by 7.6 to 11.5 days and hospitalization by 11 to 13.1 days [1]. The overall mortality associated with VAP has been reported between 20% and 50%. However, a meta-analysis of randomized studies on VAP prevention estimated the attributable mortality to be around 13% [2]. While hospital-acquired pneumonia (HAP) is generally considered less severe than VAP, about 50% of HAP patients experience serious complications such as respiratory failure, septic shock, pleural effusions, renal failure, and empyema [3]. Both VAP and HAP caused by high-risk pathogens such as *Pseudomonas aeruginosa, Acinetobacter spp., Stenotrophomonas maltophilia* significantly elevate morbidity and mortality [4].

Given the high mortality associated with nosocomial pneumonia, early prognostic blood biomarkers can offer a promising alternative to traditional complex scoring systems. Various inflammatory markers and their kinetics, particularly procalcitonin (PCT) and C-reactive protein (CRP) have been studied to predict treatment outcomes in sepsis and VAP with additional potential in indicating sepsis severity, antimicrobial efficacy and in-hospital mortality [5-9]. Both markers can be influenced by non-infectious inflammation, organ dysfunction and prior antibiotic use, leading to potential misinterpretation [10]. Furthermore, PCT levels vary by infection site, peaking in those with positive blood cultures and lowest with pulmonary infections, limiting its prognostic value in pneumonia [7,11]. Although serial trends in PCT and CRP levels may provide some moderate prognostic information, relying solely on their

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absolute values at a single point of time is insufficient for assessing outcomes in HAP and VAP cases [10].

Pentraxin-3 (PTX3), an emerging biomarker, is an acute-phase protein with low blood levels in normal conditions (<2 ng/mL in humans). It rises earlier than conventional markers in response to inflammation and infections. Many studies have been conducted depicting its significant association with disease severity and mortality in sepsis and septic shock [12-17]. Elevated PTX3 levels strongly correlate with the severity of lung infection, warranting further research to ascertain their prognostic value in nosocomial pneumonia [18]. Given the paucity of literature on prognostic biomarkers of hospital-acquired pneumonia, this study seeks to determine the value of various blood biomarkers, such as PCT, CRP, and PTX3, in anticipating outcomes of nosocomial pneumonia.

Materials and Methods

This prospective observational study was conducted at a tertiary care center in western India from March 2022 to December 2023. After obtaining informed consent, patients aged 18 years and above with microbiologically confirmed HAP or VAP were recruited and followed up for 28 days. Culture proven HAP and VAP was defined as "isolation of known nosocomial microbes with new lung infiltrate plus clinical evidence that infiltrate is of infectious origin, which included new onset fever, purulent sputum/secretions, leucocytosis, and decline in oxygenation" after 48 hours of admission and mechanical ventilation, respectively [3]. Only the first VAP/HAP episode was included. Patients with community-acquired pneumonia; other concurrent HAI like urinary tract infection or bloodstream infection; history of malignancy; neutropenic patients; those who received chemotherapy or radiotherapy within 4 weeks; patients with HIV/AIDS; and pregnant females were excluded from the study. Institute ethics committee approval was taken prior to the commencement of the study (AIIMS/IEC/2022/3940).

Data and sample collection

Data was collected according to a predesigned structured proforma. Admitted patients were being daily evaluated for clinical diagnostic criteria of HAP or VAP. Microbiological culture results of respiratory samples like sputum or endotracheal aspirate (ETA) or bronchoalveolar aspirate, collected under sterile precautions, were recorded. Basic demographics, comorbidities, reasons for admission, duration of intensive care unit (ICU) or ward stay, and routine investigations like complete blood count, liver function tests and kidney function tests, and serum samples for CRP, PCT, and PTX3 levels were obtained on the day of microbiological confirmation. HAP and VAP were managed according to clinical practice guidelines of Infectious Diseases Society of America and American Thoracic Society 2016 [3] and the latest guidance for the management of multidrug-resistant organisms [19].

Patient's venous samples were collected to measure serum PTX-3 levels. Thirty minutes after drawing blood, tubes underwent centrifugation for 8 minutes at 4000 rpm. Samples were then aliquoted, and serum portions were preserved at -80°C. Serum PTX-3 levels were measured using a commercial enzyme-linked immunosorbent assay kit (Human PTX 3/ TSG-14; Elabscience Bionovation Inc., Texas, USA) according to the manufacturer's instructions. Serum PCT levels were measured by chemiluminescence immunoassay on Siemens Advia Centaur XP; serum CRP levels were determined by immunoturbidimetric assay on Beckman Coulter AU series (AU 680). The patients were followed for 28 days to assess the outcome. Depending on the outcomes, patients were grouped into survivors and non-survivors. Those who died within 28 days were grouped as non-survivors, and those who survived for at least 28 days after the diagnosis of pneumonia or were discharged from the ICU or ward within 28 days were considered survivors.

Statistical analysis

Categorical variables were presented as number and percentage (%) whereas quantitative data were presented as means ± standard deviation. The final analysis was done *via* SPSS software version 25.0 (IBM, Chicago, IL, USA). The comparison of not normally distributed quantitative variables was analyzed using the Mann-Whitney test, and normally distributed quantitative variables were analyzed *via* the independent *t*-test. Qualitative variables were analyzed using the chi-square test. Receiver operating characteristic (ROC) curves were obtained to assess the cut-off point, sensitivity, specificity, positive predictive value, and negative predictive value of PCT, CRP, and PTX3 for predicting nosocomial pneumonia mortality. Multivariate logistic regression was utilized to find out significant risk factors of VAP non-survivors. For statistical significance, $p<0.05$ was considered statistically significant.

Results

In this study, 58 VAP and 14 HAP patients were included, out of which 58.33% (n=42) survived while 41.67% (n=30) died. The mean age of study subjects was 52.78±16.98 years, and the majority (68.06%) were males. The most common pathogen isolated was Carbapenem-resistant *Acinetobacter baumannii* (CRAB) (44.44%), followed by Carbapenem-resistant *Enterobacteriaceae* (CRE) *Klebsiella pneumoniae* (25%), followed by extended-spectrum β-lactamase (ESBL) (20.83%). The demographic, clinical, and laboratory parameters are compiled and represented in Table 1. The average day of expiry was 11.03±6.58 days.

In univariate analysis, male gender, smoking, opium addiction, neurological diseases as comorbidity, septic shock during pneumonia, raised blood urea and high serum PTX3 levels were significantly associated with 28-day mortality. Multivariate regression showed none of the above variable as significant risk factors of mortality. However, after subgroup analysis in VAP patients, in multivariate analysis, PTX3 was found to be a significant independent risk factor of mortality after adjusting for confounding factors with adjusted odds ratio of 1.038 (1.001 to 1.076) (Table 2).

ROC curves above the diagonal line are considered to have reasonable discriminating ability to predict mortality. Discriminatory power of PTX-3 [area under the curve (AUC) 0.833; 95% confidence interval (CI): 0.727 to 0.911] was excellent (Figure 1). On the other hand, the discriminatory power of PCT (AUC 0.587; 95% CI: 0.465 to 0.702) (Figure 2) and CRP (AUC 0.629; 95% CI: 0.507 to 0.740) was non-significant (Figure 3). Amongst all biomarkers, PTX-3 was the best predictor of mortality at the cut-off point of >62.657 pg/mL with an AUC of 0.8333 and high sensitivity and specificity of 76.67% and 83.33%, respectively.

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Table 1. Comparison of demographic, clinical and laboratory parameters between survivors and non-survivors.

Variable	Overall (n=72)	Survivors (n=42)	Non-survivors (n=30)	p
Demographics				
Age (mean ± SD)	52.78±16.98	50.45±16.63	56.03±17.21	0.171
Male, n (%)	49 (68.06)	23 (54.76)	26 (86.67)	0.005
Female, n (%)	23 (31.94)	19 (45.24)	4 (13.33)	
Addiction, n (%)				
Nil	29 (40.28)	25 (59.52)	4 (13.33)	<0.0001
BMFE	8 (11.11)	5 (11.90)	3 (10)	1
Smokers	24 (33.33)	7 (16.67)	17 (56.67)	0.0004
Opium	9 (12.50)	2 (4.76)	7 (23.33)	0.029
Tobacco	7 (9.72)	3 (7.14)	4 (13.33)	0.44
Alcoholic	6 (8.33)	1 (2.38)	5 (16.67)	0.076
Comorbidities, n (%)				
Diabetes	26 (36.11)	13 (30.95)	13 (43.33)	0.281
Hypertension	24 (33.33)	18 (42.86)	6 (20)	0.043
Respiratory problems	29 (40.28)	18 (42.86)	11 (36.67)	0.597
CKD	7 (9.72)	5 (11.90)	2 (6.67)	0.692
Neurological	23 (31.94)	9 (21.43)	14 (46.67)	0.024
Cardiac	7 (9.72)	4 (9.52)	3 (10)	1
Post-operative	9 (12.50)	7 (16.67)	2 (6.67)	0.288
Post-trauma	6 (8.33)	6 (14.29)	0 (0)	0.037
Complications, n (%)				
No complications	43 (59.72)	27 (64.29)	16 (53.33)	0.35
Septic shock	15 (20.83)	5 (11.90)	10 (33.33)	0.027
AKI	12 (16.67)	9 (21.43)	3 (10)	0.336
Thrombocytopenia	10 (13.89)	6 (14.29)	4 (13.33)	1
MODS	3 (4.17)	1 (2.38)	2 (6.67)	0.567
Encephalopathy	2 (2.78)	0 (0)	2 (6.67)	0.17
Microbes, n (%)				
CRAB	32 (44.44)	15 (35.71)	17 (56.67)	0.078
CRE	18 (25)	10 (23.81)	8 (26.67)	0.783
DTR Pseudomonas	4 (5.56)	2 (4.76)	2 (6.67)	1
ESBL	15 (20.83)	15 (35.71)	0 (0)	<0.0001
Serratia	1 (1.39)	0 (0)	1 (3.33)	0.417
MRSA	1 (1.39)	0 (0)	1 (3.33)	0.417
Stenotrophomonas	1 (1.39)	0 (0)	1 (3.33)	0.417
Lab parameters, (mean ± SD)				
TLC (/µL)	18750±7202.7	1770±7544	20210±6539	0.147
Platelet (thousand/µL)	244.82±167.77	255±143	230±198	0.16
Total bilirubin (mg/dL)	1.04±1.47	0.88±1.11	1.26±1.86	0.068
Albumin (g/dL)	2.44±0.6	2.54±0.61	2.32±0.58	0.13
Urea (mg/dL)	67.91±50.18	56.37±43.2	84.07±55.34	0.008
Creatinine (mg/dL)	1.63±1.61	1.44±1.46	1.9±1.79	0.095
CRP (mg/L)	132.98±80.43	118.97±78.56	152.58±80.18	0.063§
Procalcitonin (ng/mL)	9.32±20.58	6.31±14.37	13.55±26.71	0.211§
Pentraxin-3 (pg/mL)	62.12±39.2	44.98±20.93	86.12±46.07	<0.0001
Day of expiry (mean)	-	-	11.03±6.58	

SD, standard deviation; BMFE, biomass fuel exposure; CKD, chronic kidney disease; AKI, acute kidney injury; MODS, multiorgan dysfunction syndrome; CRAB, Carbapenem resistant *Acinetobacter baumannii*; CRE, Carbapenem resistant *Enterobacteriaceae*; DTR, difficult to treat resistant; ESBL, extended spectrum β-lactamases; MRSA, methicillin resistant Staphylococcus aureus; TLC, total leucocyte count; CRP, C-reactive protein.

Table 2. Multivariate logistic regression to find out significant risk factors of ventilator-associated pneumonia non-survivors.

Variables	Odds ratio (95% CI)	p
Urea (mg/dL)	1.006 (0.989-1.024)	0.485
Pentraxin 3 (pg/mL)	1.038 (1.001-1.076)	0.043
Gender		
Female (reference)	1.000	-
Male	4.367 (0.790-24.132)	0.091
Neurological	4.532 (0.862-23.824)	0.074
Trauma	0.499 (0.015-16.731)	0.698
Organism		
ESBL	0.521 (0.026-10.320)	0.669

CI, confidence interval; ESBL, extended spectrum β-lactamases.

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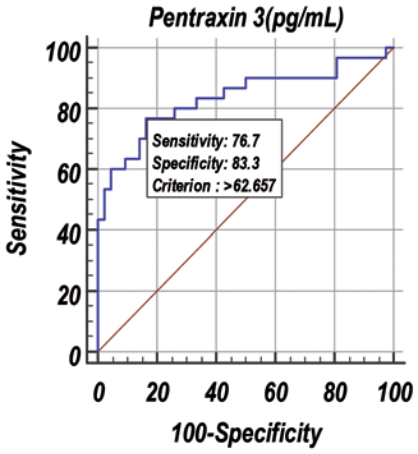


Figure 1. Receiver operating characteristic curve of pentraxin 3 (pg/mL) for predicting mortality.

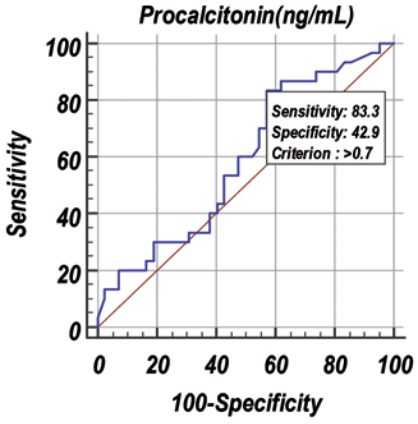


Figure 2. Receiver operating characteristic curve of procalcitonin (ng/mL) for predicting mortality.

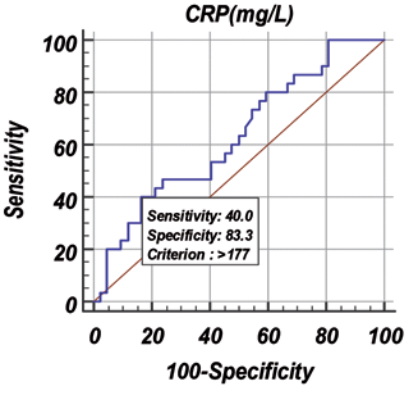


Figure 3. Receiver operating characteristic curve of C-reactive protein (CRP) (mg/L) for predicting mortality.

Discussion

Nosocomial pneumonia remains a significant contributor of morbidity and mortality despite advancements in antimicrobial therapy [20]. Early identification of individuals at high risk of mortality due to hospital-acquired pneumonia is crucial for improving patient care and outcomes and optimizing healthcare resource utilization. Exploring inflammatory biomarkers as prognostic tools could offer more practical advantages over complex severity indices like Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation II and highlights the need for further research to validate the effective application of blood biomarker measurement in clinical decision-making. CRP and PCT are widely studied parameters for diagnosing infections and monitoring clinical response in VAP [5,20-23]. However, their uncertain prognostic relevance calls for additional research into alternative biomarkers.

PTX3, an acute phase secretory protein of the long pentraxin subfamily, is produced by the innate immune system at various inflammatory sites. Particularly, in the lungs, it is produced by leukocytes, endothelial cells, and epithelial cells. In contrast to CRP, rapid elevation of PTX-3 following lung infection emphasizes its significance in early diagnosis and assessment of disease severity [24]. PTX3 levels correlate with acute lung injury, acute respiratory distress syndrome severity, and systemic involvement [25]. High plasma PTX3 levels have been shown to predict poor outcomes in sepsis and septic shock [12-17]. Furthermore, the diagnostic significance of PTX3 levels in serum, pleural fluid, and alveoli has been investigated in patients with pneumonia [24-26]. Bronchoalveolar lavage PTX3 levels demonstrated greater diagnostic potential, showing significantly higher levels and an earlier peak in VAP patients compared to serum CRP, highlighting PTX3's superior potential among various biomarkers [25]. Similarly, research identified that a PTX3 threshold level of >16.43 ng/ml yielded 74.0% specificity and 68.6% sensitivity for diagnosing VAP [23]. However, its role as a prognostic marker in nosocomial pneumonia needs further exploration.

This study comprehensively analyzed the prognostic role of demographic profile, comorbidities, laboratory parameters, microbiological results, and blood biomarkers such as CRP, PCT, and PTX3 in predicting the outcomes of nosocomial pneumonia.

We found that male gender, smoking, opium addiction, neurological comorbidities, septic shock, and elevated blood urea and serum PTX3 levels were significantly higher in non-survivors. Conversely, favorable outcomes were associated with female gender, absence of addictive behavior, trauma as a cause of hospitalization, and ESBL microorganisms as infectious etiologies. Multivariate analysis revealed raised serum PTX3 levels as an independent risk factor for mortality in VAP patients. The overall mortality of nosocomial pneumonia was 41.67%, aligning with previous reports where the mortality rate ranged from 9.2 to 53.3% [20].

Higher in-hospital mortality among men was observed, consistent with prior literature. Gender significantly impacts the incidence and outcomes of CAP (community-acquired pneumonia), HAP, and VAP, with higher mortality observed in males [27]. This can be attributed to men's higher addictive potential and more severe existing comorbidities relative to women. Substance abuse, particularly smoking and opium addiction, correlated with higher mortality rates, possibly due to the detrimental effects on the immune system and respiratory function. Mechanically ventilated patients with opioid use disorders require higher sedative and analgesic doses, resulting in excessive sedation and respiratory depression, thereby prolonging

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ventilatory support [28]. Prior research has similarly observed extended ventilation and hospitalization among opioid users, although their results did not translate into higher mortality [29]. Implementing opioid-sparing agents for sedation might be beneficial for these patients.

Neurological comorbidities were associated with an increased mortality risk, likely due to complications like immobility, dysphagia, and respiratory muscle weakness. Prior studies have consistently reported a higher incidence of hospital-acquired pneumonia, particularly from multi-drug resistant gram-negative bacteria (GNB), in neurological patients [30]. Septic shock has emerged as a significant contributor to mortality, also evidenced by research showing that 60% of ICU admissions with nosocomial infections had septic shock with exceptionally high mortality rates [31].

Drug-resistant GNB, notably CRAB, emerged as the predominant pathogen (44.44%), followed by CRE (25%) and ESBL organisms (20.83%). Several studies have highlighted that GNB accounted for 89% of VAP infections, with *A. baumannii* being the most frequently isolated pathogen, followed by *P. aeruginosa* [32-34]. Overall mortality was higher for *A. baumannii infections* (83.33%) and *K. pneumoniae* (71.42%), consistent with our findings [35,36]. In our study, ESBL organisms were significantly less prevalent among non-survivors compared to survivors, likely influenced by the widespread use of carbapenems as the empirical antibiotic for nosocomial infections, which are also recommended for ESBL infections [37].

Amongst various laboratory parameters, elevated blood urea levels significantly predicted mortality outcomes. This observation corroborates previous studies that highlighted the mortality association with blood urea nitrogen levels exceeding 11 mmol/L and serum creatinine levels above 1.1 mg/dL, further emphasizing the clinical relevance of monitoring renal function in assessing patient outcomes [38,39].

CRP is a highly sensitive inflammatory biomarker, however not specific, and increases in both infectious and non-infectious inflammation. Although our study revealed higher mean CRP levels in non-survivors compared to survivors, it was not statistically significant. Similar results were reported where no significant association between serial CRP measurements was found between two groups of VAP patients [40].

PCT is widely acknowledged as a specific biomarker in diagnosing bacterial infections [41]. Its association with severity of infection has been extensively studied in community-acquired pneumonia, with higher levels as a predictor of mortality [42]. Research into PCT and CRP kinetics in VAP highlighted that elevated PCT levels by day 4 of VAP strongly correlate with higher mortality, whereas CRP levels did not significantly affect mortality rates [40,43]. In our study, PCT demonstrated a sensitivity of 83.33% as a mortality predictor, consistent with previous findings, albeit with a lower specificity of 42.86%. Another study [44] reported no significant differences in the mean serum PCT or CRP levels at ICU admission between VAP survivors and non-survivors. Thus, serial measurements of PCT rather than the single value at the onset of nosocomial pneumonia were found to carry prognostic value [45].

PTX3 emerged as a significant independent risk factor for mortality, outperforming CRP and PCT in VAP patients, however not in nosocomial pneumonia, possibly due to higher inflammation in more critically ill VAP patients. Amongst all parameters, PTX3 was found to be the best predictor of mortality with a high specificity of 83.33%, the highest positive predictive value, and the highest negative predictive value of 76.70% and 83.30%, respectively, as compared to PCT and CRP in predicting VAP mortality. Our results support previous research indicating that PTX3 is strongly associated with lung injury [46,47]. As a single unique biological marker, PTX3 emerged superior in predicting mortality as compared to frequently used other markers, including CRP, interleukin-6, and tumor necrosis factor-α [48]. Recent findings have highlighted significantly elevated levels of PTX3 and other inflammatory proteins in individuals previously infected with COVID-19, supporting the validity of PTX3 as a systemic biomarker in prolonged systemic inflammatory responses [49]. These results emphasize the potential of PTX3 as a valuable tool in assessing prognosis and guiding therapeutic interventions in severe cases.

Our study extensively examined the prognostic value of a single measurement of PTX3 in patients with nosocomial pneumonia, complemented by comprehensive demographic, clinical, and microbiological profiles. The prospective design of our study ensured complete data capture until the end of follow-up, enhancing the study's reliability. However, it is important to acknowledge certain limitations. Conducted at a single center, our findings may have limited generalizability across broader regional populations. Being a single-center study, the spectrum of microbiological profile was limited, as it does not reflect the variability in microbial prevalence and resistance patterns in different settings. More research involving pooled data from multiple centers would enhance the robustness of the results. Another limitation was the lack of consideration of baseline disease severity, which could impact mortality outcomes. Furthermore, the absence of baseline PTX-3 level measurements before VAP onset highlights the need for comprehensive baseline assessments in future studies for better understanding of predictive biomarkers.

Notwithstanding these constraints, PTX-3 has demonstrated a strong association with mortality in pneumonia, surpassing CRP and PCT. Therefore, as a dynamic inflammatory marker, PTX3 levels could complement traditional scoring systems, providing a real-time indicator of worsening infection and guiding timely antibiotic stewardship. This further emphasizes the need for additional research to establish optimal threshold of PTX-3 levels for accurately predicting mortality risk in cases of HAI and informing decisions on antibiotic de-escalation strategies. This research holds promise for refining clinical practices and optimizing treatment outcomes in patients with hospital-acquired pneumonia.

Conclusions

PTX3 emerged as a novel biomarker, offering promising prognostic value in nosocomial pneumonia, outperforming traditional markers like PCT and CRP. This emphasizes the importance of future research to validate its application and further broaden our understanding of morbidity and mortality in nosocomial infections.

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Received: 15 October 2024; Accepted: 18 April 2025; Early view: 12 June 2025.

Contributions: Isha Garg: study design, data collection, manuscript writing. Nishant Kumar Chauhan: concept and study design, manuscript editing. Harsh Vardhan: manuscript editing. Shrimanjunath Sankanagoudar: data collection, sample handling. Naveen Dutt: manuscript editing, expert consultation. Gopal Durgeshwar, Hariharan Iyer: expert consultation. Nikhil Kothari: manuscript editing. Ravisekhar Gadepalli: statistical analysis. Deepak Kumar: manuscript review. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: the study protocol was approved by the Institutional Ethics Committee of All India Institute of Medical Sciences, Jodhpur, Rajasthan (AIIMS/IEC/2022/3940).

Informed consent: written informed consent was obtained from all participating individuals or their authorized representatives for information to be used in an anonymized manner and for scientific publication.

Patient consent for publication: the consent for publication of patient's data was obtained.

Availability of data and materials: the datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of generative artificial intelligence and artificial intelligence-assisted technologies in the writing process: during the preparation of this revised manuscript, the authors used ChatGPT (OpenAI) to assist with language editing and improving clarity. The authors reviewed and edited the suggested text and take full responsibility for the final content of the manuscript.

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