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Original Article

Association of C-Reactive Protein and Procalcitonin Trajectories with Clinical Outcome in Elderly with Severe Pneumonia

Yuru Fu [a], Yalin Li [a], Hao Li [a], Jia Wang [a], Yuanyuan Wang [b *]

[a] *Department of Critical Care Medicine, Fuyang People's Hospital, Fuyang, Anhui 236000, China,* [b] *Department of Cardiology, Fuyang People's Hospital, Fuyang, Anhui 236000, China*

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SUMMARY

Background: Pneumonia remains a major cause of morbidity and mortality in older adults. Although C-reactive protein (CRP) and procalcitonin (PCT) have established roles in guiding pneumonia treatment, the prognostic value of their serial measurements in elderly patients with severe disease is less defined.
Methods: In this observational cohort study, 200 adults aged ≥ 65 years with severe community- or hospital-acquired pneumonia were enrolled. CRP and PCT levels were measured at ICU admission (Day 0) and on Days 1, 3, 5, and 7. The primary outcome was 30-day mortality. Patients were stratified into rapid-decline (> 50% reduction by Day 3) versus slower-decline groups for both biomarkers.
Results: A ≥ 50% Day-3 decline independently predicted lower 30-day mortality for both CRP (adjusted OR 0.52 [0.24–0.95], AUC 0.78, 95% CI 0.72–0.84) and PCT (adjusted OR 0.56 [0.27–1.00], AUC 0.76, 95% CI 0.69–0.82). Multivariate analysis confirmed that rapid biomarker declines significantly decreased mortality risk, even after adjusting for age, comorbidities, and Acute Physiology and Chronic Health Evaluation II scores. Integrating CRP/PCT trajectories with severity scores improved model discrimination (AUC from 0.73 to 0.82).
Conclusion: In older adults with severe pneumonia, dynamic changes in CRP and PCT provide valuable prognostic information beyond single measurements. Monitoring these biomarker trajectories may facilitate timely, individualized treatment strategies and improve clinical outcomes in this high-risk population.

1. Introduction

Pneumonia remains a leading cause of morbidity and mortality, particularly among older adults. The elderly population is especially vulnerable to pneumonia, with an incidence rate significantly higher than in younger populations.[1] The mortality rates significantly higher in those over 85 years of age.[2] The prevalence of severe pneumonia in older adults is exacerbated by the presence of multiple comorbidities such as chronic obstructive pulmonary disease, heart failure, and diabetes mellitus.[3,4]

Inflammatory biomarkers like C-reactive protein (CRP) and procalcitonin (PCT) play crucial roles in the management of pneumonia. CRP is associated with the severity of infection and clinical outcomes, serving as a useful marker for assessing the inflammatory response.[5] PCT, on the other hand, is particularly valuable in distinguishing bacterial infections and guiding antibiotic use.[5] Single-time-point measurements of pneumonia have historically guided clinical decisions; however, emerging evidence suggests that serial or trajectory-based measurements offer more nuanced insights into disease progression and treatment response.[6] This shift is particularly critical in the elderly population, where age-specific research is scarce, often leading to underpowered studies that fail to analyze older adults separately.[7–9] Research on the trajectories of biomarkers such as CRP and PCT in pneumonia and sepsis has provided valuable insights into their prognostic significance. A slower decline or a lack of decline in CRP levels by day 3 or 4 is associated with worse outcomes in pneumonia.[10,11] Similarly, inadequate early clearance of PCT is linked to increased mortality in sepsis, and serial measurements of PCT can enhance risk stratification in community-acquired pneumonia (CAP).[12] These biomarkers, when monitored over time, offer moderate predictive value for the prognosis of hospitalized CAP patients.[11] However, there remain significant gaps in the understanding of these trajectories. The heterogeneity in the timing of measurements, the cut points for CRP, and the thresholds for high clearance of PCT limit the generalizability of findings across different studies.[13] Furthermore, evidence is sparse regarding older adults with severe CAP or hospital-acquired pneumonia (HAP).[13] Additionally, the incremental value of early CRP and PCT trajectories when added to established risk scores like Acute Physiology and Chronic Health Evaluation II (APACHE II) in this population is not well understood.[13]

In this study, we investigated whether CRP and PCT trajectories predict clinical outcomesin older patients with severe pneumonia. We also examined whether adding these trajectories to standard severity scores, such as APACHE II, improves 30-day mortality prediction. Our central hypothesis is that rapid biomarker declines correlate with better outcomes, even in a high-risk elderly population. Findings may guide clinical decisions, including antibiotic steward-

* Corresponding author. Department of Cardiology, Fuyang People's Hospital, 501 Sanqing Road, Yingzhou District, Fuyang City, Anhui 236000, China.
E-mail address: wangyuanyuancdj@163.com (Y.y. Wang)

ship and resource allocation for aging societies.

2. Materials and methods

This was an observational cohort study conducted between January 2022 and December 2023 in Fuyang People's Hospital. The study protocol was approved by the Institutional Review Boards of Fuyang People's Hospital. All procedures were conducted in accordance with the ethical standards of the responsible committees on human experimentation and with the Helsinki Declaration. Each participant or their legal representative signed an informed consent form. Patient confidentiality was maintained by de-identifying all records.

Inclusion criteria: 1) Adult patients aged ≥ 65 years; 2) diagnosis of severe pneumonia, including severe community-acquired pneumonia (CAP) as defined by ATS/IDSA 2019 major/minor severity criteria, and hospital-acquired/ventilator-associated pneumonia defined by the 2016 IDSA/ATS HAP/VAP guideline;[14,15] 3) requirement for ICU admission due to respiratory failure, sepsis, or septic shock attributed to pneumonia; 4) written informed consent obtained from the patient or a legally authorized representative.

Exclusion criteria: 1) pregnant patients; 2) active malignancy on palliative treatment; 3) known immunosuppression (e.g., HIV/AIDS with CD4 < 200 cells/μL, chronic high-dose steroids); 4) inability to measure CRP or PCT at the specified time points; 5) prior enrollment in this study (to avoid duplicate data).

2.1. Biomarker measurements

2.1.1. CRP

Blood samples were collected in serum tubes at ICU admission (Day 0) and on Days 1, 3, 5, and 7. CRP levels (mg/L) were measured using a high-sensitivity immunoturbidimetric assay (Cobas c501, Roche Diagnostics). The assay's lower detection limit was 0.3 mg/L, with an inter-assay coefficient of variation of < 5%.

2.1.2. PCT

From the same blood draws, plasma was collected and tested for PCT (ng/mL) using a solid-phase sandwich immunoassay (BRAHMS PCT LIA, Thermo Fisher Scientific). The lower detection limit was 0.05 ng/mL, with an inter-assay coefficient of variation of < 8%.

2.2. Clinical data collection

Patient data were recorded in a standardized electronic case report form (CRF). The following variables were collected: Demographics (age, sex, body mass index, smoking history); Comorbidities (diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), chronic kidney disease); Severity Scores (Sequential Organ Failure Assessment (SOFA) and APACHE II scores upon ICU admission); Treatment Modalities (antibiotic regimens, vasopressors, mechanical ventilation requirements, and adjunctive therapies (e.g., corticosteroids)). Severe pneumonia was defined as patients who met at least one major or three minor ATS/IDSA criteria for community-acquired pneumonia or similar criteria for hospital-acquired pneumonia with severe features.

2.3. Outcome measures

The primary outcome was 30-day mortality. Secondary outcomes included ICU LOS, days on mechanical ventilation, and total hospital LOS. Additionally, patients were classified according to whether they experienced a rapid decline in CRP or PCT (separately and in combination) to assess differences in clinical outcomes.

2.4. Sample size calculation

Prior to study initiation, a sample size calculation was performed assuming an expected 25% 30-day mortality rate in severe pneumonia. We hypothesized that patients exhibiting a rapid biomarker decline would have significantly lower mortality (15%). With an alpha of 0.05 and a power of 80%, we estimated a required sample size of approximately 180 patients. To account for potential dropouts and missing data, we enrolled 200 patients.

2.5. Statistical analysis

All analyses were performed using R (version 4.4). A two-sided $p < 0.05$ was considered statistically significant. Continuous variables were presented as mean ± standard deviation (SD) or median [interquartile range, IQR] depending on normality (assessed by Shapiro-Wilk test). Categorical variables were presented as frequencies (%). Independent t-tests or Mann-Whitney U tests were used for continuous outcomes. Chi-square or Fisher's exact tests were used for categorical outcomes. CRP and PCT were evaluated at Days 0, 1, 3, 5, and 7. The relative change (percentage drop from baseline) was calculated, and groups were stratified based on "rapid" vs. "slower" declines. Univariate and multivariate logistic regression was used to identify predictors of 30-day mortality. Covariates included age, sex, APACHE II, comorbidities, and CRP/PCT trajectories. Interaction terms (CRP × PCT) were considered to assess potential synergistic effects. Model fit was evaluated using the Hosmer-Lemeshow test and the Akaike Information Criterion (AIC). Discrimination was assessed with the area under the receiver operating characteristic curve (AUC).

To determine the optimal percentage reduction in CRP and PCT predicting 30-day mortality, receiver-operating-characteristic (ROC) curves were constructed for the Day 0 to Day 3 change. The Youden index (J = sensitivity + specificity – 1) was used to identify the best cut-point, and 95% confidence intervals (CIs) were computed by bootstrap resampling (2,000 iterations).

3. Results

Two-hundred forty-five adults with suspected severe pneumonia were screened; 200 fulfilled eligibility criteria and provided informed consent (Figure 1). In the study, we assessed baseline characteristics and admission biomarker levels in 200 patients with severe CAP and severe HAP. The mean age of the cohort was 72.4 years (SD ± 6.1), with a predominance of males (56%). The average body mass index (BMI) was 23.2 kg/m^2 (SD ± 4.4). The prevalence of comorbid conditions included hypertension (47%), diabetes mellitus (34%), chronic obstructive pulmonary disease (COPD) (30%), and chronic kidney disease (16%) (Table 1). Of the 200 older ICU patients with severe pneumonia, 124 (62%) had CAP and 76 (38%) had HAP (Table 1). Severity of illness was quantified using APACHE II and SOFA scores, with median values of 18 (IQR 15–22) and 7 (IQR 5–9), respectively. Upon admission, the mean C-reactive protein (CRP) level was 138.3 mg/L, and the mean procalcitonin (PCT) level was 7.9 ng/mL (Table 1).

The study tracked the trajectories of CRP and PCT over the initial week of hospitalization in patients with severe pneumonia. Both biomarkers displayed a general decline over time (Table 2). Specifically, CRP levels decreased from 138.3 mg/L at ICU admission to 45.1 mg/L by Day 7 (Table 2). Similarly, PCT levels dropped from 7.9 ng/mL at admission to 1.3 ng/mL by the end of the observation period (Table 2). This pattern suggests that both CRP and PCT could serve as

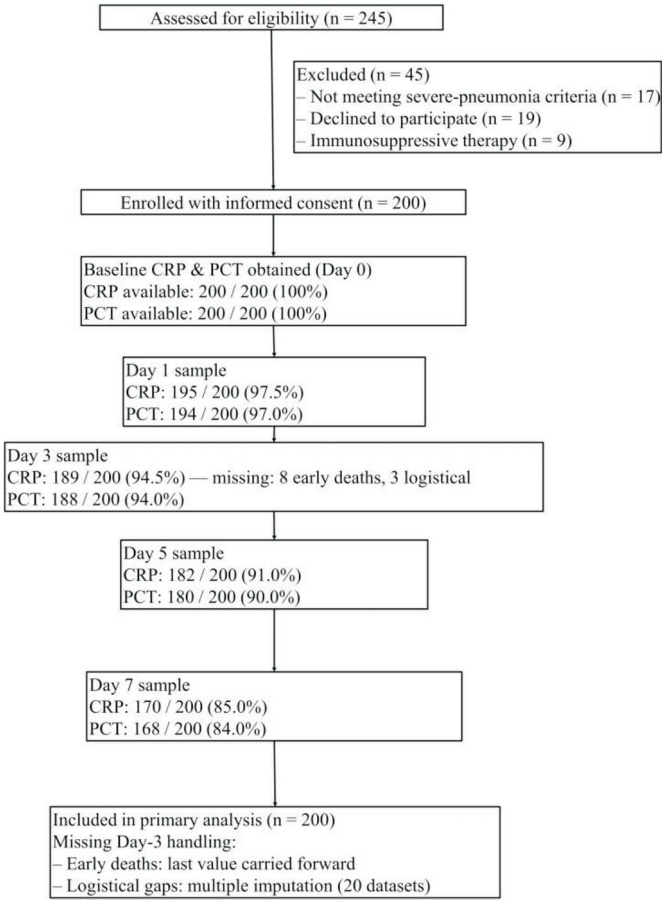

Figure 1. Participant flow and completeness of serial biomarker measurements. Two-hundred forty-five adults with suspected severe pneumonia were screened; 200 fulfilled eligibility criteria and provided informed consent. The diagram details exclusions, enrolment, availability of CRP and PCT samples on study Days 0, 1, 3, 5, 7, and inclusion in the primary 30-day mortality analysis. Day-3 missingness (5.5%) comprised 8 early deaths and 3 logistical gaps; early deaths were conservatively carried forward as "no decline" and logistical gaps were multiply-imputed.

effective indicators of therapeutic response and prognosis in severe pneumonia.

Next, we evaluated if decline of CRP and PCT levels were associated with clinical outcomes. Patients were divided into rapid decline group (> 50% reduction by Day 3) or slower decline group (< 50% reduction by Day 3). Patient with rapid decline of CRP or PCT exhibited significantly better outcomes (Table 3). Specifically, those with rapid biomarker decline had shorter ICU stays (CRP: 6 days, PCT: 5 days), fewer days on mechanical ventilation (CRP: 5 days, PCT: 4 days), and shorter total hospital stays (CRP: 14 days, PCT: 13 days) (Table 3). Additionally, the 30-day mortality rates were lower in these groups (CRP: 12.0%, PCT: 11.5%) compared to those with a slower decline in biomarkers (Table 3).

Table 1
Baseline characteristics of patients with severe pneumonia.

Variables	Value
Age (years), mean ± SD	72.4 ± 6.1
Gender	
Male, n (%)	112 (56%)
Female, n (%)	88 (44%)
Body mass index (kg/m^2), mean ± SD	23.2 ± 4.4
Comorbidities	
Hypertension, n (%)	94 (47%)
Diabetes mellitus, n (%)	68 (34%)
Chronic obstructive pulmonary disease (COPD), n (%)	60 (30%)
Chronic kidney disease, n (%)	32 (16%)
Acquisition setting	
Community-acquired pneumonia (CAP), n (%)	124 (62%)
Hospital-acquired pneumonia (HAP), n (%)	76 (38%)
Severity Scores	
APACHE II Score, median (IQR)	18 (15–22)
SOFA Score, median (IQR)	7 (5–9)
Biomarker levels at admission	
CRP (mg/L), mean ± SD	138.3 ± 36.7
PCT (ng/mL), mean ± SD	7.9 ± 3.8

APACHE II: Acute Physiology and Chronic Health Evaluation II; CRP: C-reactive protein; IQR: interquartile range; PCT: procalcitonin; SOFA: Sequential Organ Failure Assessment.

Table 2
Biomarker trajectories over time.

Time point	CRP (mg/L), Mean ± SD	PCT (ng/mL), Mean ± SD
Day 0	138.3 ± 36.7	7.9 ± 3.8
Day 1	115.6 ± 34.5	5.6 ± 3.5
Day 3	82.2 ± 29.4	3.5 ± 2.3
Day 5	62.5 ± 25.7	2.0 ± 1.4
Day 7	45.1 ± 18.0	1.3 ± 1.0

CRP: C-reactive protein; PCT: procalcitonin.

The Youden-optimized thresholds were a 48.7% decline for CRP (AUC = 0.78, 95% CI 0.72–0.84) and a 52.1% decline for PCT (AUC = 0.76, 95% CI 0.69–0.82). For clinical simplicity and bedside usability, we retained the round-number threshold of ≥ 50% for both biomarkers, which lies within the CIs of the data-driven optima (Supplementary Table S1).

We explored the six comparisons that combine CRP and PCT trajectories with ICU length of stay, ventilation-free days and total hospital stay. Raw p-values were generated from multivariable linear-mixed models (adjusted for age, sex, APACHE II score and major comorbidities) and then corrected for multiplicity with the Benjamini–Hochberg step-up procedure, controlling the false-discovery rate at 10%. After adjustment, a rapid decline in either biomarker remained significantly associated with shorter ICU stay (adjusted p = 0.008 for CRP; 0.011 for PCT), while the favorable associations for ventilation-free days and total hospital stay persisted only for CRP (adjusted p = 0.048 and 0.043, respectively) but not for PCT (adjusted p = 0.14 and 0.13) (Supplementary Table S2).

Table 3
Clinical outcomes by CRP and PCT trajectory.

	CRP			PCT		
	Rapid decline (n = 92)	Slower decline (n = 108)	p-value	Rapid decline (n = 78)	Slower decline (n = 122)	p-value
ICU length of stay (days), median (IQR)	6 (4–8)	9 (6–12)	0.001	5 (3–7)	9 (6–11)	< 0.001
Mechanical ventilation days, median (IQR)	5 (3–8)	8 (5–11)	0.020	4 (2–7)	7 (4–10)	0.015
Total hospital stay (days), median (IQR)	14 (10–17)	18 (14–21)	0.010	13 (9–16)	17 (13–20)	0.005
30-day mortality, n (%)	11 (12.0%)	29 (26.9%)	0.007	9 (11.5%)	30 (24.6%)	0.012

CRP: C-reactive protein; IQR: interquartile range; PCT: procalcitonin.

Univariate and multivariate logistic regression analyses were performed to identifying factors influencing 30-day mortality in severe pneumonia patients. In univariate analysis, each additional year of age increased mortality risk, as did each point increase in the APACHE II score (Table 4). A rapid decline in CRP and PCT significantly reduced mortality risk ($p < 0.05$) (Table 4). In the multivariate analysis, which adjusted for confounders, the risk factors of age (OR: 1.05, $p = 0.016$) and APACHE II score (OR: 1.08, $p = 0.003$) remained significant (Table 4). The protective effect of rapid CRP and PCT decline persisted ($p < 0.05$) (Table 4).

Median values diverged from Day 1 onward, and the IQR bands of survivors and non-survivors showed minimal overlap after Day 3, visually reinforcing the significantly faster biomarker normalization in survivors (mixed-effects quantile-regression $p < 0.01$ for status × time interaction for both markers, Supplementary Figure S1).

Table 5 illustrates the stepwise enhancement of predictive models for 30-day mortality in patients with severe pneumonia by sequentially adding biomarkers to the baseline model. The baseline model, which includes age and APACHE II scores, starts with an AUC of 0.73 and an AIC of 212.5 (Table 5). Adding the CRP trajectory (percentage change from Day 0 to Day 3) improves the AUC to 0.77 and reduces the AIC to 208.3, indicating enhanced model performance (Table 5). Further incorporation of the PCT trajectory results in an AUC of 0.80 and an AIC of 204.1 (Table 5). The model achieves the best performance when adding an interaction term between CRP and PCT, which raises the AUC to 0.82 and lowers the AIC to 201.7 (Table 5). This incremental approach highlights the value of incorporating dynamic biomarker changes in predictive modeling.

In the shared-parameter joint model (Supplementary Table S3), the linear mixed-effects sub-model showed a significant average daily decline for both biomarkers (CRP $\beta = -0.28$ ln-mg L^{-1} day^{-1}; PCT $\hat{\alpha} = -0.26$ ln-ng mL^{-1} day^{-1}), with substantial between-patient heterogeneity captured by the random-intercept variances (0.41 and 0.36, respectively). Crucially, the association (shared-slope) parameters translated these longitudinal slopes into survival effects: each 50% steeper decline over the first week was associated with a 29% reduction in the hazard of 30-day death for CRP (HR 0.71, 95% CI 0.55– 0.92, $p = 0.009$) and a 26% reduction for PCT (HR 0.74, 95% CI 0.58– 0.96, $p = 0.024$), independent of age and APACHE II. Model discrimination improved modestly over the static landmark model (dynamic C-index 0.85 vs. 0.82), and fit statistics were acceptable (AIC 1 842.9 for CRP, 1 777.5 for PCT). These findings corroborate the primary logistic-regression analysis, underscoring that faster biomarker normalization conveys a clinically meaningful survival advantage in severe pneumonia.

4. Discussion

In this study, older adults with severe CAP and HAP who showed a rapid decline in CRP and PCT experienced notably lower mortality and shorter ICU and hospital stays. These findings underscore the particular utility of a trajectory-based approach over single-time-point measurements, especially in elderly populations characterized by higher baseline inflammation and multiple comorbidities. By capturing dynamic changes in biomarker levels, clinicians can gain a more accurate understanding of disease progression and treatment response, thereby offering tailored interventions that ultimately enhance patient outcomes in this vulnerable group.

The present study demonstrated that a ≥ 50% decline in CRP and PCT levels by Day 3 strongly correlates with better clinical outcomes and converges with previous findings in mixed-age cohorts. Reducing CRP to 50% or less of its peak within 48 hours was associated with lower mortality among cancer patients.[16] Similar observations in COVID-19, where a rapid decrease in CRP post-corticosteroid therapy correlated with reduced mortality,[17] and a steep decline in CRP and IL-6 predicted favorable outcomes in patients receiving tocilizumab.[18] By focusing specifically on older adults — who exhibit immunosenescence and frequently harbor multiple comorbidities[19] — this study addresses a gap in existing literature that often overlooks geriatric-specific trajectories. The refinement of the ≥ 50% threshold by Day 3 aligns with this demographic's altered inflammatory profile and complements prior evidence.[20–23] However, variations in measurement intervals, cutoff values, and population characteristics observed across different studies.[20,21,23]

Mechanistically, immunosenescence and chronic low-grade inflammation (inflammaging) characteristic of older age can delay or

Table 4
Logistic regression analysis for 30-day mortality.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (per 1-year increase)	1.06 (1.02–1.10)	0.004	1.05 (1.01–1.10)	0.016
Male sex	1.20 (0.65–2.23)	0.50	1.15 (0.61–2.16)	0.64
APACHE II Score (per 1-point)	1.08 (1.03–1.15)	0.002	1.08 (1.03–1.14)	0.003
Hypertension	1.18 (0.62–2.20)	0.60	1.10 (0.57–2.10)	0.77
Diabetes mellitus	1.50 (0.80–2.80)	0.24	1.38 (0.70–2.73)	0.34
COPD	1.70 (0.90–3.20)	0.10	1.60 (0.84–3.05)	0.16
CRP rapid decline	0.45 (0.23–0.90)	0.021	0.52 (0.24–0.95)	0.032
PCT rapid decline	0.52 (0.27–1.00)	0.050	0.56 (0.27–1.00)	0.050

APACHE II: Acute Physiology and Chronic Health Evaluation II; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; IQR: interquartile range; PCT: procalcitonin.

Table 5
Predictive performance for 30-day mortality of models integrated with CRP/PCT.

Model	Variables Included	AUC (95% CI)	AIC
Baseline model	Age, APACHE II	0.73 (0.68–0.78)	212.5
Baseline + CRP trajectory	+ CRP % Change (Day 0–3)	0.77 (0.72–0.82)	208.3
Baseline + CRP + PCT trajectory	+ PCT % Change (Day 0–3)	0.80 (0.75–0.85)	204.1
Baseline + CRP + PCT + interaction	+ CRP × PCT Term	0.82 (0.77–0.86)	201.7

AIC: Akaike Information Criterion; APACHE II: Acute Physiology and Chronic Health Evaluation II; AUC: area under the curve; CRP: C-reactive protein; PCT: procalcitonin.

dampen CRP and PCT responses to infections such as pneumonia.[24–27] This underscores the rationale for trajectory-focused evaluations, which may capture disease progression more effectively than single-time-point measurements in elderly individuals. Diabetes can exacerbate oxidative stress and inflammatory processes,[28] while COPD's persistent inflammation and immune impairment may similarly skew these markers.[29] Chronic kidney disease also contributes to a pro-inflammatory milieu and can alter the metabolism of CRP and PCT.[28] Together, these insights affirm the importance of individualized, age-specific thresholds and highlight the role of serial CRP/PCT measurements in optimizing clinical management for older adults with severe pneumonia.

Certain limitations in our current study warrant consideration. The single-center setting may reduce generalizability, and variability in treatment regimens could confound the results. Local treatment protocols can modulate both biomarker trajectories and clinical endpoints, potentially limiting the portability of our findings. Additionally, the observational design restricts the ability to infer causality, and the lack of etiology-specific data impedes definitive conclusions regarding pathogen-specific biomarkers. From a clinical standpoint, these findings suggest that monitoring rapid declines in CRP/PCT could inform decisions on antibiotic de-escalation, ICU step-down, and resource allocation to minimize unnecessary antibiotic use in an aging society. Incorporating biomarker trajectories into existing pneumonia or sepsis protocols may further optimize care. Looking ahead, larger multicenter investigations and randomized trials are needed to validate these trajectory-based thresholds, while subgroup analyses should clarify the impact of specific comorbidities and pathogens.

This study highlights how CRP and PCT trajectories offer valuable prognostic insights beyond single-time-point measurements in older adults with severe pneumonia. By dynamically assessing these biomarkers, clinicians may more accurately predict outcomes, optimize treatment decisions, and allocate resources more efficiently. In turn, thoughtful incorporation of trajectory-based assessments into routine care could translate into enhanced patient survival, shorter hospital stays, and better overall management of healthcare resources for this high-risk elderly population.

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Ethical approval

The study was approved by the Ethics Committee of Fuyang People's Hospital.

Conflict of interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary materials for this article can be found at https://www.sgecm.org.tw/ijge/journal/view.asp?id=37.

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