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ORIGINAL RESEARCH

Time-Lagged Effects of Hyperglycemia on Inflammation in Older Adults with Community-Acquired Pneumonia: Nutritional Insights and Personalized Intervention Windows

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Purpose: The dynamic interplay between glucose metabolism and systemic inflammation is increasingly recognized as a pivotal factor influencing outcomes in older adults with community-acquired pneumonia (CAP), yet its temporal patterns and the modifying role of nutritional status remain insufficiently understood.

Patients and Methods: In this retrospective cohort study, 507 older adults (≥65 years) hospitalized with CAP were included. Serial measurements of blood glucose (GLU), C-reactive protein (CRP), and neutrophil-to-lymphocyte ratio (NLR) were obtained at admission, 24 hours, and 72 hours. Cross-correlation function (CCF) analysis was used to characterize lagged temporal relationships among biomarkers, while autoregressive integrated moving average (ARIMA) models predicted biomarker trends. Subgroup analyses were conducted according to 28-day survival, diabetes status, nutritional status, and age.

Results: Patients who died within 28 days had higher CRP, NLR, and GLU levels across all time points compared to survivors, with pronounced delays in normalization of inflammatory markers and persistent hyperglycemia (all $P<0.001$). CCF analyses demonstrated that glucose elevations often preceded increases in CRP and NLR, particularly at a lag of −1, indicating early metabolic perturbations can foreshadow subsequent inflammatory surges. Survivors showed evidence of timely feedback regulation, with negative correlations at subsequent lags, while non-survivors, malnourished patients, and those aged ≥85 years exhibited disrupted, delayed, or reversed cross-correlation patterns. ARIMA models provided robust predictions, identifying critical intervention windows based on biomarker trends.

Conclusion: These findings reveal the systemic impact of hyperglycemia on inflammation and suggest potential benefits of nutritional interventions targeting glucose control to modulate inflammatory responses in elderly CAP patients. Overall, this study underscores the importance of integrating metabolic monitoring with nutritional strategies to improve outcomes in this vulnerable population.

Keywords: older adults, community-acquired pneumonia, inflammation, glucose metabolism, biomarker dynamics, cross-correlation analysis, ARIMA modeling, China

Introduction

Community-acquired pneumonia (CAP) remains a leading cause of morbidity and mortality in older adults, presenting a significant global health challenge.[1] With an increasingly aging population, the burden of CAP among the elderly continues to rise, posing considerable strain on healthcare systems due to high hospitalization rates, extended recovery periods, and poor prognoses in this vulnerable group.[2,3] Older adults are particularly susceptible to severe CAP due to

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age-related immunological decline, or immunosenescence, which weakens their ability to mount effective immune responses against infections.[4] Furthermore, the presence of chronic comorbidities, such as diabetes, cardiovascular disease, and chronic obstructive pulmonary disease (COPD), as well as conditions like malnutrition and frailty, amplifies disease severity and hinders recovery.[5] Despite advancements in diagnostics, therapeutic interventions, and critical care, CAP in this population remains associated with high mortality, especially in patients requiring intensive care or mechanical ventilation.

The pathophysiology of CAP involves intricate interactions between inflammation and metabolic responses. Inflammation is critical for eliminating pathogens and resolving infection; however, dysregulated or excessive inflammation can lead to tissue damage, organ dysfunction, and poor clinical outcomes.[6,7] In older adults, heightened pro-inflammatory responses, compounded by impaired immune regulation, often result in severe complications, prolonged hospital stays, and increased mortality risk.[8] Simultaneously, CAP is frequently accompanied by metabolic disturbances, particularly disruptions in glucose homeostasis. Conditions such as hyperglycemia and insulin resistance—whether pre-existing or infection-induced—can exacerbate systemic inflammation, compromise immune defenses, and worsen patient outcomes.[9] These interconnected processes underscore the need for biomarkers that dynamically reflect both inflammatory and metabolic states, enabling clinicians to better predict outcomes and tailor treatments effectively.

Previous research has explored the predictive value of inflammatory and metabolic biomarkers in CAP, yet most studies rely on static, single-point measurements, typically taken at admission. Commonly studied biomarkers, including C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and blood glucose (GLU), have demonstrated individual prognostic utility but fail to capture the dynamic, rapidly evolving nature of CAP.[10–12] This limitation is particularly problematic for older adults, whose diverse clinical profiles and responses to treatment require more nuanced prognostic assessments. Moreover, most studies have treated these biomarkers in isolation, overlooking the temporal dynamics of their interactions and how these reflect disease progression and patient outcomes, leaving a critical knowledge gap in understanding the interplay between inflammation and glucose metabolism.

CRP, an acute-phase reactant, is widely used to assess systemic inflammation, correlating strongly with CAP severity and serving as a reliable prognostic marker in acute respiratory infections.[13] NLR, calculated from routine blood tests, represents the balance between neutrophil-mediated pro-inflammatory responses and lymphocyte-driven adaptive immunity, emerging as an indicator of immune dysfunction in CAP.[14] Blood glucose levels, in contrast, reflect metabolic dysregulation, with hyperglycemia and insulin resistance strongly linked to worse outcomes, including increased mortality, particularly in older adults with pre-existing diabetes.[15] Although these biomarkers show promise individually, their dynamic behavior during the course of CAP remains poorly understood, and their combined prognostic utility across multiple time points has yet to be thoroughly investigated, particularly in elderly populations.

The interplay between inflammation and glucose metabolism offers critical insights into host responses to CAP. These processes, when studied longitudinally, can provide valuable prognostic information.[16] Older adults often exhibit unique inflammatory and metabolic responses due to the interplay of underlying comorbidities, age-related immune changes, and malnutrition, necessitating individualized assessments beyond standard diagnostic metrics.[17,18] Advances in time-series biomarker analysis, such as cross-correlation function (CCF) analysis and predictive modeling through autoregressive integrated moving average (ARIMA) models, provide new tools for examining the temporal and causal relationships between biomarkers and disease progression.[19] These approaches offer the potential to uncover critical pathophysiological mechanisms, identify windows for targeted intervention, and refine prognostic assessments in this high-risk group.

Elderly individuals exhibit unique metabolic-inflammatory profiles due to aging-related changes, including reduced insulin sensitivity and persistent low-grade inflammation. Therefore, the present study aimed to investigate the dynamic changes in inflammatory markers (CRP and NLR) and glucose metabolism (GLU) in elderly patients with CAP, and to examine how these changes are associated with short-term prognosis. We focused on analyzing temporal trends in these biomarkers at three critical time points (admission, 24 hours, and 72 hours), evaluating the dynamic interactions between inflammatory markers and glucose metabolism using CCF analysis to identify lag effects and potential causal relationships, and applying ARIMA models to predict the progression of metabolic and inflammatory dysregulation. By providing a comprehensive understanding of the interplay between inflammation and glucose metabolism in elderly

CAP patients, our findings may help inform personalized management strategies and potential nutritional interventions to improve clinical outcomes in this vulnerable population.

Materials and Methods

Study Design and Patients

This retrospective cohort study was conducted at the Second People's Hospital of Lianyungang between October 1, 2020, and October 1, 2024. It included adults aged 65 years or older who had been diagnosed with CAP. CAP diagnosis was established based on the 2019 Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines, which require the presence of at least one respiratory symptom (such as cough, sputum, or dyspnea) and new pulmonary infiltrates on chest radiography, with alternative causes excluded by clinical assessment.[20] The main objective was to explore the dynamic changes in inflammatory markers (CRP, NLR) and glucose metabolism (GLU) and their association with short-term prognosis. Patients were grouped according to 28-day survival outcome.

Patient data confidentiality was maintained throughout the study. All records were anonymized and de-identified prior to analysis, and only the research team had access to the secure database. Ethical approval was obtained from the Ethics Committee of the Second People's Hospital of Lianyungang (Approval No. 2022K040). The study complied with the principles of the Declaration of Helsinki. Because the study involved only pre-existing clinical data with no direct patient intervention, the Ethics Committee waived the requirement for informed consent. The data were used solely for the purposes of this research and were handled with strict confidentiality. All patient data were de-identified and anonymized before analysis; any direct identifiers and sensitive personal information were removed.

Older adults were included if they were 65 years of age or above at admission, fulfilled the diagnostic criteria for CAP as outlined above, had complete clinical and laboratory data available at all specified time points (T0: admission, T1: 24 hours, T2: 72 hours), and had recorded 28-day outcomes. Patients were excluded if they were diagnosed with nosocomial or ventilator-associated pneumonia, had a history of autoimmune disease or were receiving immunosuppressive therapy, had severe hepatic failure or end-stage renal disease (CKD stage 5), had incomplete clinical records or missing key laboratory data, or were discharged against medical advice within the first 24 hours after admission.

Data Collection

Data were retrospectively extracted from the hospital's electronic medical records and included demographic and clinical variables such as age, gender, BMI, and comorbidities (hypertension, diabetes, CKD stage 3 or above, COPD, and cerebrovascular disease). The need for mechanical ventilation, including both invasive and non-invasive types, was also recorded.

Nutritional assessment at admission was performed by trained clinicians or nurses using the Mini Nutritional Assessment-Short Form (MNA-SF), after standardized training to ensure consistency. Patients were classified as well-nourished (MNA-SF score ≥12), at risk of malnutrition (score 8–11), or malnourished (score <8).[21]

These included CRP, NLR (calculated as the absolute neutrophil count divided by the absolute lymphocyte count), and WBC. Blood GLU values were collected to reflect glucose metabolism status. Hyperglycemia was defined as a fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL) or a random plasma glucose level ≥ 11.1 mmol/L (200 mg/dL) based on the criteria established by the American Diabetes Association (ADA).[22] Additional laboratory parameters included serum albumin as an indicator of nutritional and inflammatory status, and BUN as a marker of renal function and metabolic stress.

The primary outcome was 28-day survival, with patients classified into survival and death groups. Dynamic changes in CRP, NLR, and GLU over T0, T1, and T2 were analyzed to monitor early inflammatory and metabolic responses during the critical phase of CAP.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 21 and R version 4.4.1. A two-tailed P-value <0.05 was considered statistically significant. Continuous variables were expressed as mean ± standard deviation (SD)

for normally distributed data or median (interquartile range, IQR) for non-normally distributed data. Categorical variables were presented as frequencies and percentages. Differences between the survival and death groups were assessed using the independent *t*-test for normally distributed continuous variables and the Mann–Whitney *U*-test for non-normally distributed continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) curve analyses were performed to evaluate the prognostic accuracy of CRP and NLR at T0, T1, and T2. Mixed-effects models were employed to analyze longitudinal biomarker trends, accounting for within-subject variability over time. Fixed effects included time, survival status, and their interaction, while random effects accounted for individual variability. These analyses utilized the R package "lme4".

Calibration curves were constructed for each model (CRP, NLR, GLU, and the combined model) at T0, T1, and T2 to assess the agreement between predicted and observed event probabilities. Calibration performance was evaluated using the R package "rms", and visualized with calibration plots comparing predicted and observed risks. Decision curve analysis (DCA) was performed for all models at T0, T1, and T2 using the "rmda" package in R to evaluate the clinical utility of each biomarker and the combined model across a range of threshold probabilities. Net benefit was plotted against threshold probability to quantify the clinical value of model-based decision-making, with higher net benefit indicating greater potential for clinical application.

The cross-correlation function (CCF) was used to study the temporal relationships between GLU and inflammatory markers (CRP, NLR, WBC) across subgroups based on survival, nutritional, and diabetes status. Cross-correlation coefficients (r) were calculated at varying time lags to determine whether changes in GLU preceded or followed alterations in inflammatory markers. Lag 0: Correlation at the same time point. Positive lags (eg, lag 1): Inflammatory marker changes follow GLU changes. Negative lags (eg, lag −1): GLU changes precede inflammatory marker changes. Peaks in correlation coefficients (values near ±1) were visualized using line plots, indicating strong temporal relationships.

Dynamic trends in CRP, NLR, and GLU were analyzed for observed time points (T0, T1, T2) and predicted time points (eg, T3*T4*T5*) using autoregressive integrated moving average (ARIMA) models. Autoregressive Integrated Moving Average (ARIMA) models were used to predict biomarker trends beyond the observed time points, providing insights into the progression of inflammatory and metabolic dysregulation. Model parameters (*p*, *d, q*) were determined using automated selection algorithms, where: *p* represents the order of autoregression, *d* represents the degree of differencing, and *q* represents the order of the moving average. Model selection was automated via the "auto.arima" function in the "forecast" package, with model fit evaluated by Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).[23,24] Line plots were used to visualize observed and predicted trends. Predicted trends highlight the progression of inflammatory and metabolic dysregulation, offering potential early intervention points for high-risk patients. Predicted and observed biomarker trajectories were plotted with "ggplot2".

Additionally, a post hoc power analysis was conducted to assess whether the sample size was sufficient to detect significant differences in the primary outcome (28-day mortality). Based on the total sample of 507 patients, including 425 survivors and 82 non-survivors (28-day mortality rate: 16.2%), and using the observed effect size (Cohen's d, estimated from the distribution of NLR), the statistical power to detect differences between groups was calculated to be greater than 99.9% (using the R package "pwr", $\alpha = 0.05$). These results demonstrate that the current sample size is adequate to ensure sufficient statistical validity for the analyses performed in this study.

Handling Missing Data

All datasets underwent thorough reviews to ensure completeness and accuracy. Variables with more than 20% missing data across the cohort were excluded from the analysis to minimize the risk of introducing potential biases. For the remaining variables with missing data, the multiple imputation by chained equations (MICE) method, implemented via the R mice package (version 4.4.1), was employed. Appropriate imputation models were specified for each variable based on its data type. Continuous variables (eg, CRP, lymphocyte count, neutrophil count, and GLU) were imputed using predictive mean matching (PMM), while categorical variables (eg, gender) were imputed using logistic regression.

To ensure variability and reduce potential biases in the imputation process, five imputed datasets were generated. The imputation process was set to run for 50 iterations to allow for the convergence of the algorithm toward stable imputed

values. After imputation, each of the five datasets underwent separate statistical analyses using methods appropriate for each variable. Results from these datasets were then pooled according to Rubin's rules to compute combined estimates and standard errors, ensuring unbiased and robust conclusions.

For time series variables such as CRP, NLR, and GLU, missing values at different time points were addressed within a longitudinal framework using the MICE method. Time was explicitly included as a covariate in the imputation models to preserve the temporal structure of the data, allowing the imputed values to reflect the inherent dynamics of the variables over time. This approach was critical for maintaining data integrity for ARIMA modeling and cross-correlation analysis, as both methods rely on complete and temporally consistent datasets.

Results

Clinical Characteristics Among Different Groups

A total of 507 older adults with CAP were included in the study based on the predefined inclusion and exclusion criteria, as illustrated in Figure 1. As shown in Table 1, patients in the death group were significantly older than those in the survival group (81.33 ± 5.21 vs 77.14 ± 6.57 years, $P < 0.001$). Gender distribution and BMI showed no significant differences between the groups ($P = 0.325$ and $P = 0.110$, respectively). However, the need for mechanical ventilation was significantly higher in the death group (46.3% vs 15.3%; $P = 0.001$). Comorbidities, including hypertension,

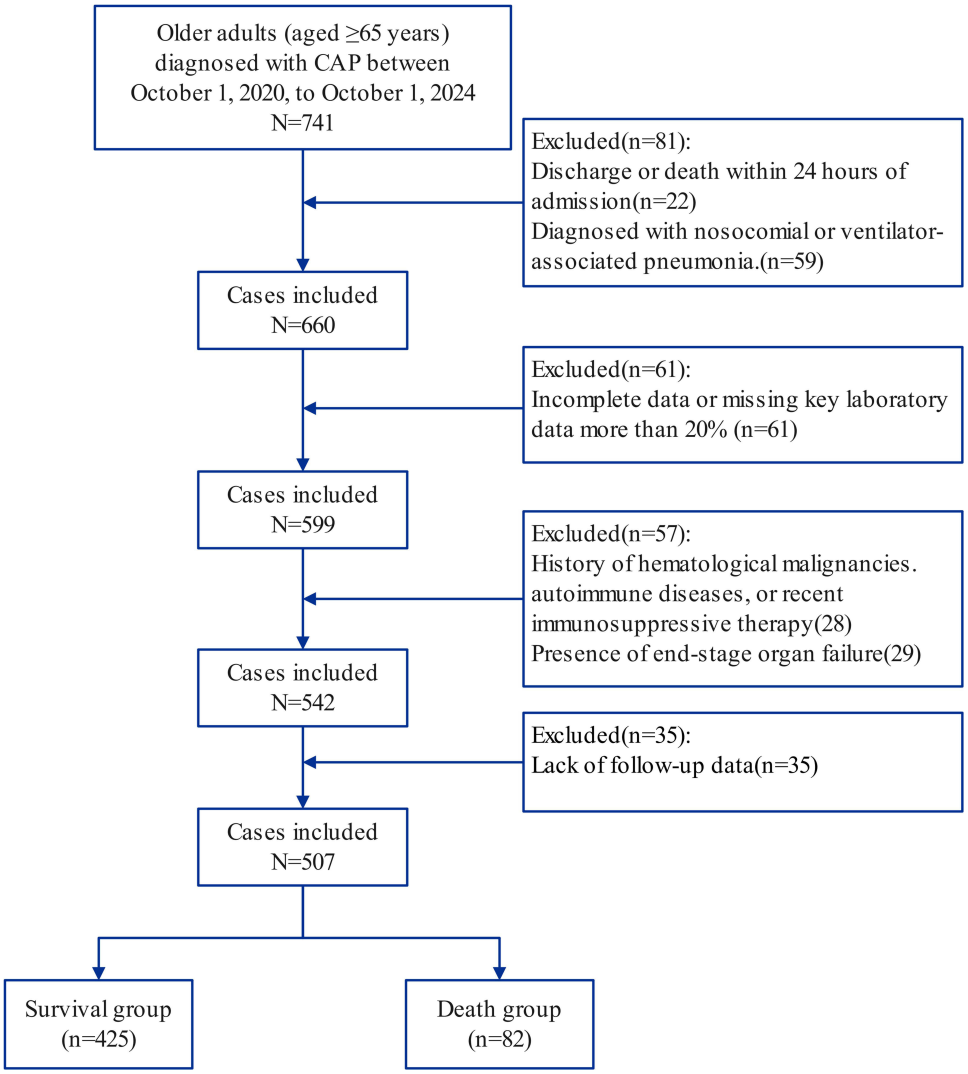

Figure 1 Flow diagram displaying the progress of all participants through the study.

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Table 1 Clinical Characteristics Among Different Groups

Variables	Total (n=507)	Survival Group (n=425)	Death Group (n=82)	*P*
Gender				0.325
Male, n (%)	264(52.1)	225(52.9)	39(47.6)	
Female, n (%)	243(47.9)	200(47.1)	43(52.4)	
Age, mean (SD)	77.98(6.54)	77.14(6.57)	81.33(5.21)	<0.001
BMI, kg/m², mean (SD)	22.85(2.72)	22.96(2.67)	22.39(2.91)	0.110
Mechanical Ventilation				0.001
Yes, n (%)	103(20.3)	65(15.3)	38(46.3)	
No, n (%)	404(79.7)	360(84.7)	44(53.7)	
Underlying diseases				
Hypertension, n (%)	196(38.7)	160(37.6)	36(43.9)	0.379
Diabetes, n (%)	187(36.9)	151(35.5)	36(43.9)	0.158
Chronic Kidney Disease (CKD Stage 3 and above), n (%)	129(25.4)	105(24.7)	24(29.3)	0.480
COPD, n (%)	138(27.2)	115(27.1)	23(28.0)	0.890
Cerebrovascular disease, n (%)	171(33.7)	141(33.2)	30(36.6)	0.602
Etiology				0.725
Bacteria, n (%)	193(38.1)	161(37.9)	32(39.0)	
Virus, n (%)	140(27.6)	119(28.0)	21(25.6)	
Unknown, n (%)	105(20.7)	89(20.9)	16(19.5)	
Mixed infection, n (%)	69(13.6)	56(13.2)	13(15.9)	
Nutritional status				<0.001
Well-nourished group, n (%)	152(30.0)	146(34.4)	6(7.3)	
At-risk-of-malnutrition group, n (%)	198(39.1)	173(40.7)	25(30.5)	
Malnourished group, n (%)	157(31.0)	106(24.9)	51(62.2)	
Hemoglobin, g/L, mean (SD)	111.96(17.82)	111.86(18.18)	112.33(16.39)	0.832
Albumin, g/L, mean (SD)	32.81(3.94)	33.29(3.95)	30.89(3.27)	<0.001
BUN, mg/dl, mean (SD)	22.00(6.71)	21.43(6.68)	24.29(6.37)	<0.001
WBC T0,×109/L, mean (SD)	13.40(3.62)	13.25(2.55)	14.00(3.87)	0.095
WBC T1,×109/L, mean (SD)	13.76(4.05)	13.63(4.10)	14.28(3.82)	0.198
WBC T2,×109/L, mean (SD)	12.50(3.57)	11.88(3.35)	14.98(3.33)	<0.001
NLR T0, median (IQR)	6.89(5.39,9.40)	6.29(5.13,8.27)	8.94(7.72,10.52)	<0.001
NLR T1, median (IQR)	7.36(5.82,10.09)	6.78(5.44,9.01)	9.80(7.47,13.19)	<0.001
NLR T2, median (IQR)	5.17(3.70,8.20)	4.63(3.42,6.13)	11.31(8.62,15.18)	<0.001
CRP T0, mg/L, median (IQR)	56.60(37.70,76.20)	55.30(35.80,75.40)	66.55(43.00,78.80)	0.005
CRP T1, mg/L, median (IQR)	63.84(47.31,80.10)	60.75(46.60,77.16)	77.65(55.15,89.49)	<0.001
CRP T2, mg/L, median (IQR)	43.30(32.20,65.50)	41.10(31.10,56.55)	66.65(45.50,89.50)	<0.001
Glu T0, mmol/L, mean (SD)	8.27(2.02)	8.09(1.88)	8.95(2.36)	0.003
Glu T1, mmol/L, mean (SD)	7.93(1.98)	7.72(1.82)	8.75(2.35)	<0.001
Glu T2, mmol/L, mean (SD)	8.02(2.64)	7.27(1.84)	10.97(3.22)	0.001

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CRP, C-reactive protein; NLR, Neutrophil-to-Lymphocyte Ratio; BUN, blood urea nitrogen; IQR, Interquartile Range; SD, standard deviation; T0, At the time of admission; T1, 24 hours after admission; T2, 72 hours after admission.

diabetes, CKD (stage ≥3), COPD, and cerebrovascular disease, did not differ significantly between groups (all $P > 0.05$). Similarly, the distribution of CAP etiology was comparable ($P = 0.725$).

Malnutrition was more prevalent in the death group (62.2% vs 24.9%; $P < 0.001$). The death group also exhibited significantly lower albumin levels (30.89 ± 3.27 g/L vs 33.29 ± 3.95 g/L, $P < 0.001$) and higher blood urea nitrogen (BUN) levels (24.29 ± 6.37 mg/dL vs 21.43 ± 6.68 mg/dL, $P < 0.001$), indicating poorer nutritional and metabolic status. Inflammatory and glucose metabolism markers revealed significant trends: NLR and CRP: Both markers were consistently higher in the death group at all time points (T0, T1, T2; $P < 0.001$), with CRP showing the greatest difference at T2. Blood Glucose (GLU): GLU levels were significantly elevated in the death group at T0, T1, and T2 ($P < 0.01$). At

T2, the gap was especially pronounced (10.97 ± 3.22 mmol/L vs 7.27 ± 1.84 mmol/L, $P = 0.001$). These findings highlight a strong association between persistent inflammatory and metabolic dysregulation and poor short-term prognosis in elderly CAP patients.

Dynamic Changes in Diagnostic Performance of CRP and NLR Across Time Points

The ROC curve analysis across three time points—T0 (admission), T1 (24 hours post-admission), and T2 (72 hours post-admission)—revealed distinct temporal variations in the diagnostic performance of CRP and NLR (Figure 2). CRP demonstrated a gradual increase in diagnostic accuracy over time, with AUC values improving from 0.60 at T0 to 0.64 at T1, peaking at 0.78 at T2. This pattern indicates a delayed but progressively stronger association with systemic inflammation as CAP advances. In contrast, NLR consistently outperformed CRP at all time points. At T0, NLR achieved an AUC of 0.77, indicating its high sensitivity to inflammation at admission. Although the AUC slightly decreased at T1 (0.72), NLR demonstrated its strongest diagnostic performance at T2, with an AUC of 0.92, underscoring its robustness in identifying advanced inflammatory states.

Comparative analysis highlights the superior diagnostic utility of NLR, particularly at T0 and T2, where it significantly outperformed CRP. These findings underscore the value of NLR as a reliable marker for both early risk stratification and late-phase monitoring of inflammatory progression. CRP, while less sensitive initially, serves as a complementary marker with increasing diagnostic potential during the later stages of the disease.

Results of Calibration and Decision Curve Analyses at T0, T1, and T2

The predictive performance of the CRP, NLR, GLU, and combined (CRP+NLR+GLU) models was comprehensively evaluated at three time points (T0, T1, and T2) using calibration plots and decision curve analysis (DCA).

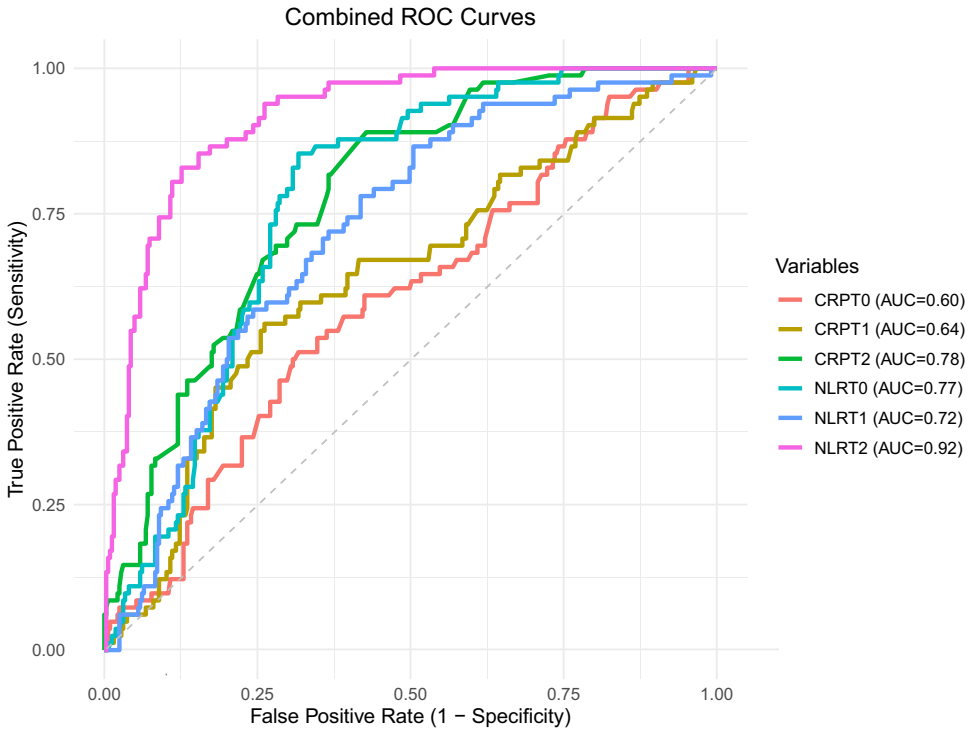


Figure 2 Dynamic Changes in Diagnostic Performance of CRP and NLR Across Time Points.
Notes: The ROC curves highlight that CRP's diagnostic capacity improves consistently over time, while NLR demonstrates superior and reliable performance across all time points, particularly at T0 and T2.
Abbreviations: CRP, C-Reactive Protein; NLR, Neutrophil-to-Lymphocyte Ratio; AUC, Area Under the Curve; T0, Admission Time; T1, 24 Hours After Admission; T2, 72 Hours After Admission.

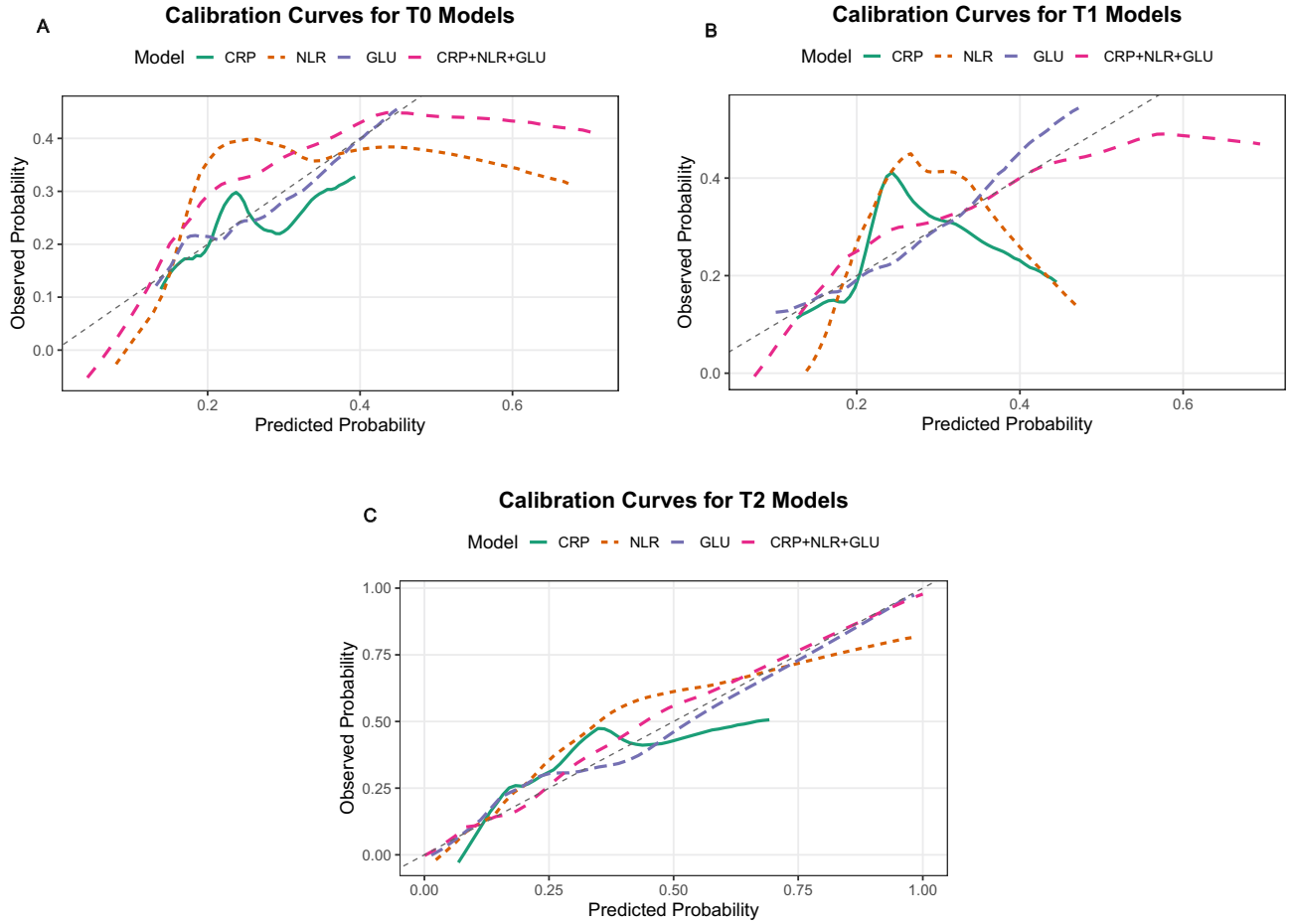
Calibration plots at each time point (Figures 3A–C) demonstrated that the combined model consistently exhibited excellent agreement between the predicted and observed probabilities across all three time points, with calibration curves closely aligning with the ideal reference line. Among the single-indicator models, NLR demonstrated favorable calibration at T1, whereas the CRP model displayed notable deviation from ideal calibration particularly at T2. The GLU model exhibited moderate calibration performance throughout. These findings indicate that, overall, the combined model provided the most reliable and stable probability estimates across the time course.

The decision curve analyses (Figures 3D–F) further revealed that the net benefit of the combined model was superior to that of any single biomarker model over a broad range of threshold probabilities at each time point. While the single-indicator models (especially NLR at T1) provided some clinical net benefit within specific threshold ranges compared to the treat-all or treat-none strategies, the combined model consistently displayed greater clinical utility over a wider range. Together, these results emphasize the advantage of integrating multiple biomarkers for risk prediction, supporting the clinical value of the combined model at distinct clinical stages.

Linear Mixed-Effects Model Analysis Highlighting Temporal and Prognostic Dynamics of CRP, NLR, and GLU

The temporal and prognostic dynamics of CRP, NLR, and GLU during disease progression were assessed using linear mixed-effects models, revealing significant effects of time, prognosis, and their interaction for all biomarkers.

CRP levels exhibited significant temporal changes and prognostic relevance, with a decline over time ($\beta = -5.777$, $P < 0.001$). Initially rising from T0 to T1 due to acute inflammation, CRP levels significantly decreased by T2, reflecting therapeutic response or inflammation resolution. Non-survivors had consistently higher CRP levels compared to



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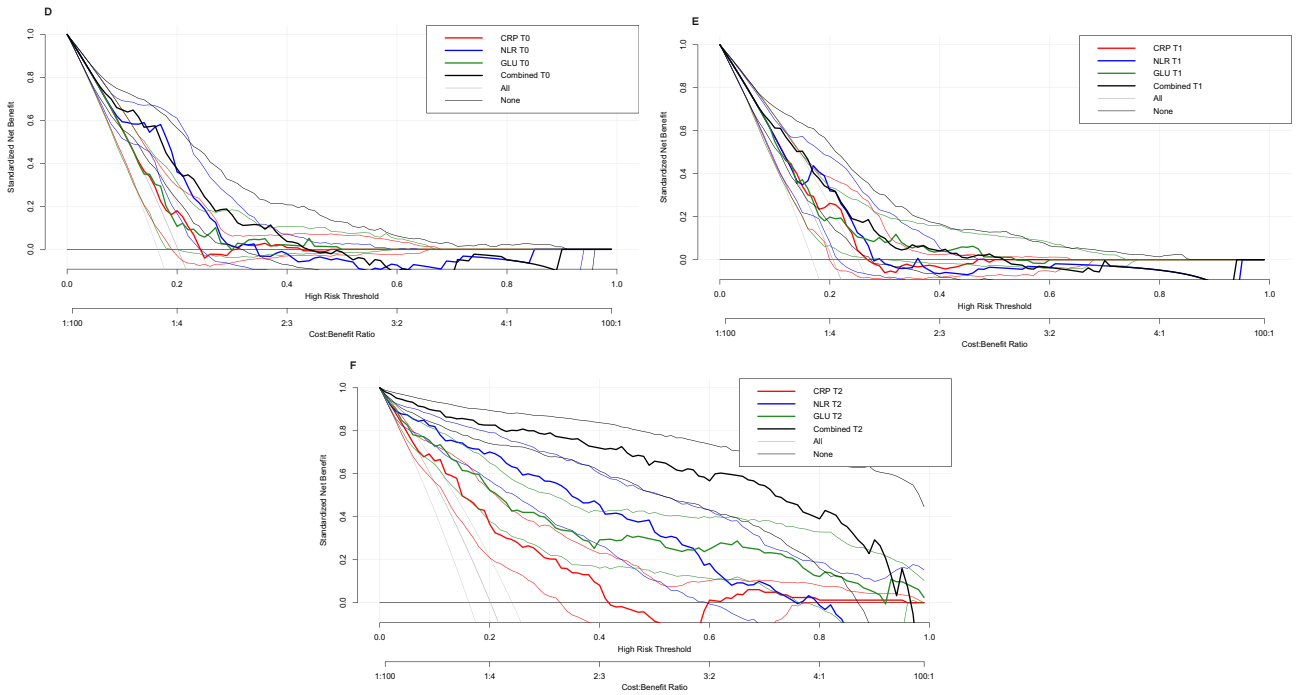

Figure 3 Calibration curves and decision curve analyses for CRP, NLR, GLU, and combined models at T0, T1, and T2.
Notes: Calibration curves (**A**–**C**) demonstrate the concordance between predicted and observed probabilities for each model at three time points. The ideal reference line indicates perfect calibration. Decision curve analyses (**D**–**F**) display the net benefit for each model across a range of threshold probabilities at T0, T1, and T2. Curves situated above the "treat-all" and "treat-none" strategies denote superior clinical utility.
Abbreviations: CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; GLU, glucose; Combined, model including, NLR, and GLU; T0, Admission Time; T1, 24 Hours After Admission; T2, 72 Hours After Admission; DCA, decision curve analysis.

survivors ($\beta = 7.456$, $P = 0.027$), and the time-prognosis interaction was significant ($\beta = 8.351$, $P < 0.001$). While CRP levels declined in survivors by T2, they remained elevated in non-survivors, indicative of unresolved inflammation linked to poor outcomes (Figure 4A).

NLR displayed strong prognostic accuracy and consistent trends across time. Levels declined significantly over time ($\beta = -0.936$, $P < 0.001$), indicating gradual resolution of systemic inflammation. Non-survivors showed higher NLR levels than survivors ($\beta = 1.621$, $P = 0.001$), and a significant time-prognosis interaction was observed ($\beta = 2.233$, $P < 0.001$). Survivors exhibited more pronounced decreases in NLR, whereas non-survivors experienced slower reductions, reflecting persistent inflammatory activity in critically ill patients (Figure 4B).

GLU levels demonstrated declining trends across time ($\beta = -0.410$, $P < 0.001$), reflecting metabolic stabilization. Non-survivors tended to have higher GLU levels compared to survivors, with this trend nearing significance ($\beta = 0.441$, $P = 0.079$). The time-prognosis interaction was significant ($\beta = 1.419$, $P < 0.001$), as non-survivors displayed persistently elevated GLU levels at T2, whereas survivors showed marked declines, indicating improved metabolic regulation during recovery (Figure 4C).

These results highlight distinct temporal and prognostic trends for CRP, NLR, and GLU. CRP reflected acute and unresolved inflammation, with high inter-individual variability, necessitating personalized evaluation. NLR demonstrated consistent temporal patterns and strong prognostic value, serving as a stable indicator of systemic inflammation and mortality risk. GLU persistently elevated levels in non-survivors linked glucose dysregulation to adverse outcomes, emphasizing its role in monitoring metabolic recovery. Together, these findings underscore the clinical utility of CRP, NLR, and GLU in assessing disease progression and guiding personalized treatment strategies in critically ill patients.

Longitudinal Trends of Inflammatory Biomarkers Across Prognosis Groups

This study investigated longitudinal trends in inflammatory (WBC, CRP, NLR) and metabolic (GLU) biomarkers across prognosis groups at observed (T0, T1, T2) and predicted (T3*T4*T5*) time points using Autoregressive Integrated

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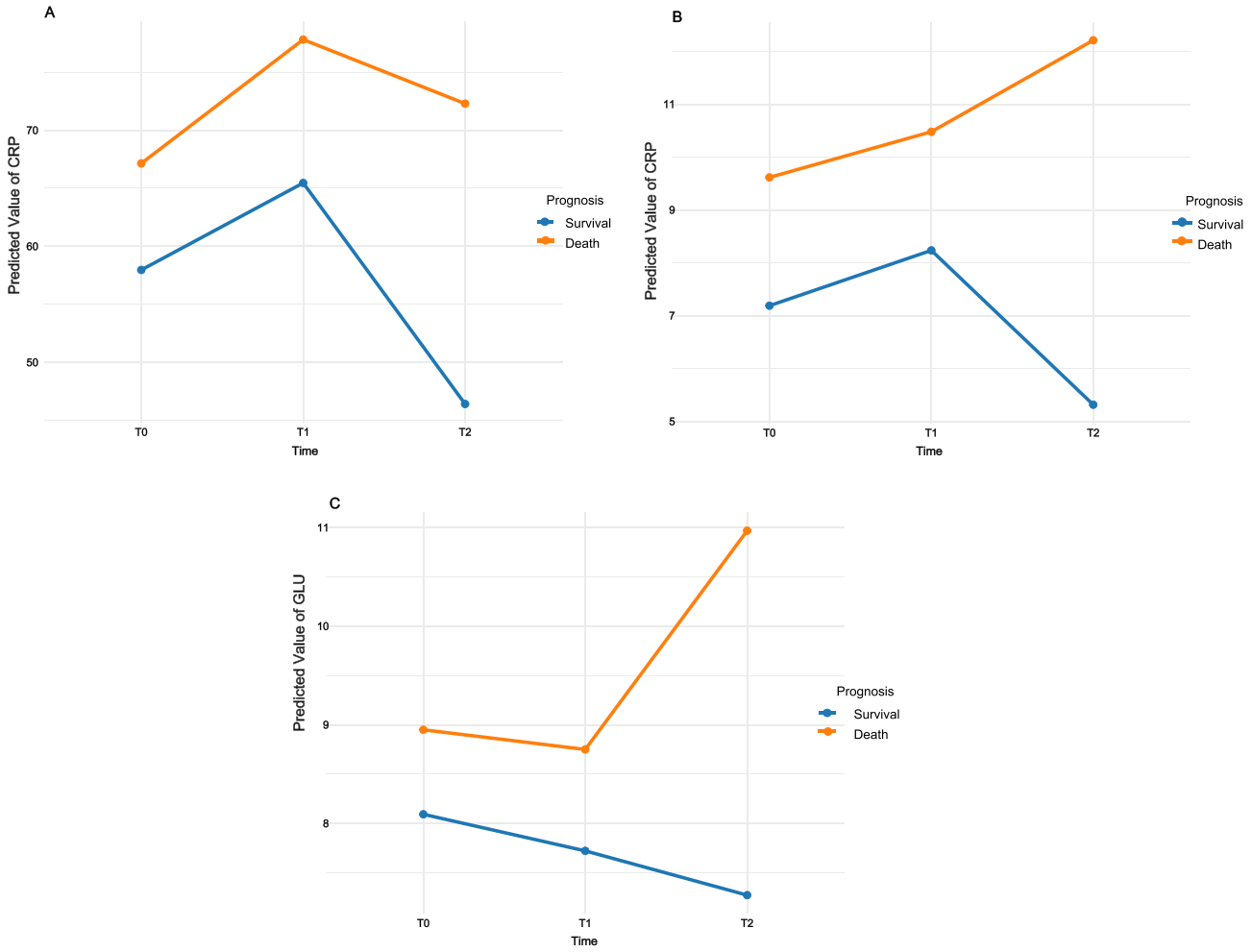

Figure 4 Dynamic Changes in Biomarkers (CRP, NLR, and GLU) Over Time.
Notes: (**A**) shows that CRP declines over time but remains elevated in non-survivors. (**B**) demonstrates that NLR decreases more steeply in survivors than in non-survivors. (**C**) highlights persistent hyperglycemia in non-survivors, linking glucose dysregulation to poorer outcomes.
Abbreviations: CRP, C-Reactive Protein; NLR, Neutrophil-to-Lymphocyte Ratio; GLU, Blood Glucose Level; REML, Restricted Maximum Likelihood; β, Regression Coefficient; T0, Admission Time; T1, 24 Hours After Admission; T2, 72 Hours After Admission.

Moving Average (ARIMA) models. The results in Figure 5 reveal progressive worsening of these biomarkers in the death group, while trends in the survival group remained stable.

CRP and NLR levels in the death group increased significantly from T0 to T2 and further rose at the predicted time points (T3*T4*T5*), indicating persistent and worsening inflammation. In contrast, levels in the survival group exhibited minimal fluctuations and stabilized over time. Similarly, GLU levels in the death group rose sharply between T0 and T2 and continued to rise at the predicted time points, while levels in the survival group remained consistently lower, with minor variations. Levels of CRP and NLR were higher in the death group compared to the survival group, which may indicate a more pronounced inflammatory state; however, this inference must be interpreted with caution, as we did not directly assess inflammatory cytokines.The worsening trajectories at predicted time points highlight the progression of disease in non-survivors, supporting the importance of early biomarker-driven interventions.

CRP and NLR showed significant increases in the death group over time, with predicted trajectories indicating persistent inflammation in non-survivors. GLU levels in the death group continued to rise at predicted time points, linking hyperglycemia to adverse outcomes. Stable trends in the survival group for all biomarkers underscore their importance in monitoring disease progression and stratifying risk.

ARIMA models for each biomarker were based on observed data (T0, T1, T2), with optimal parameters automatically selected to minimize the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for model fit. Table 2 summarizes the parameters and model fit for each biomarker. For example, the CRP model was fitted with

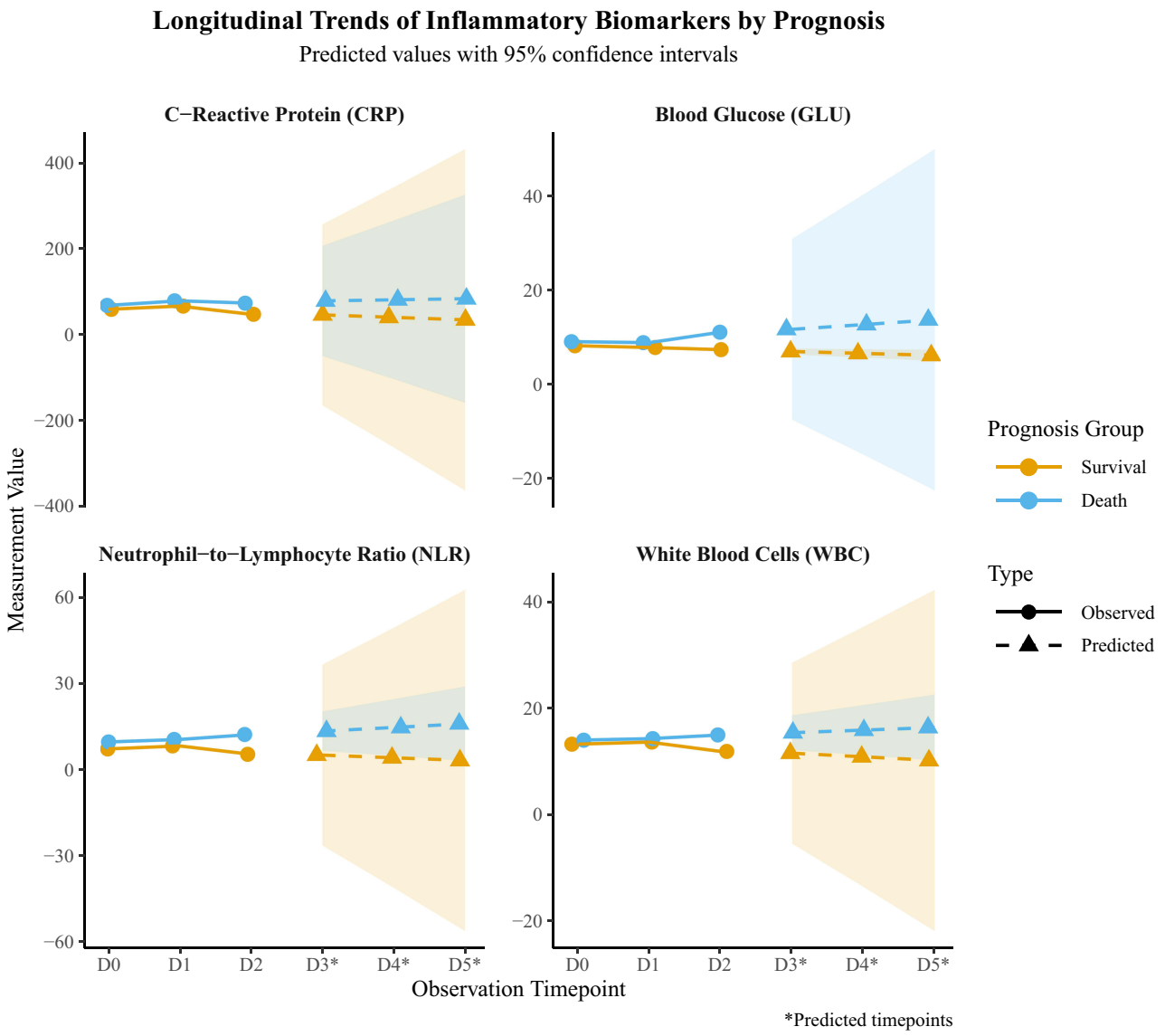

Figure 5 Longitudinal Trends of CRP, NLR, and GLU Across Prognosis Groups.
Notes: This figure demonstrates observed and predicted biomarker trajectories for survival and death groups. Solid lines represent observed data; dashed lines represent ARIMA-predicted trends. The death group exhibits worsening biomarker trends over time, emphasizing their prognostic value.
Abbreviations: WBC, White Blood Cell Count; CRP, C-Reactive Protein; NLR, Neutrophil-to-Lymphocyte Ratio; GLU, Blood Glucose Level; ARIMA, Autoregressive Integrated Moving Average; T0, Admission; T1/T2, Observed Time Points; T3*/T4*/T5*, Predicted Time Points.

parameters (p=1, d=1, q=0), while GLU required (p=2, d=1, q=1), reflecting a more complex temporal structure. Low AIC and BIC values confirmed that the models provided reliable predictions for future time points.

Cross-Time Series and Lag Analysis Between Glucose and Inflammatory Markers

This study examined the temporal interactions between glucose metabolism (GLU) and systemic inflammation (CRP, NLR, WBC) in elderly CAP patients using cross-correlation function (CCF) analysis. Significant temporal relationships emerged across different lags, highlighting the dynamic interplay between glucose regulation and inflammation (Figure 6).

At lag 0, a positive correlation between GLU and CRP indicates that acute hyperglycemia coincides with heightened systemic inflammation. Notably, the cross-correlation curves for CRP and NLR were highly similar, likely reflecting their

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Table 2 ARIMA Model Parameters and Fit for Biomarkers

Biomarker	ARIMA Parameters (*p, d, q*)	AIC	BIC
WBC	(1, 0, 1)	275.4	281.0
CRP	(1, 1, 0)	320.5	325.1
NLR	(2, 1, 1)	290.2	297.8
Glu	(2, 1, 1)	310.8	318.5

Notes: Lower AIC and BIC values indicate better model fit. ARIMA parameters include: *p* (autoregressive term), *d* (differencing term), and *q* (moving average term).
Abbreviations: CRP, C-reactive protein; NLR, Neutrophil-to-Lymphocyte Ratio; WBC, White Blood Cell count; Glu, Blood Glucose level; ARIMA, Autoregressive Integrated Moving Average; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

strong biological association as inflammatory markers. A delayed positive correlation at lag −1 between GLU and NLR suggests that elevated glucose levels may precede and contribute to subsequent increases in neutrophil-mediated inflammation. In contrast, the negative correlation at lag −1 between GLU and WBC suggests that early glucose

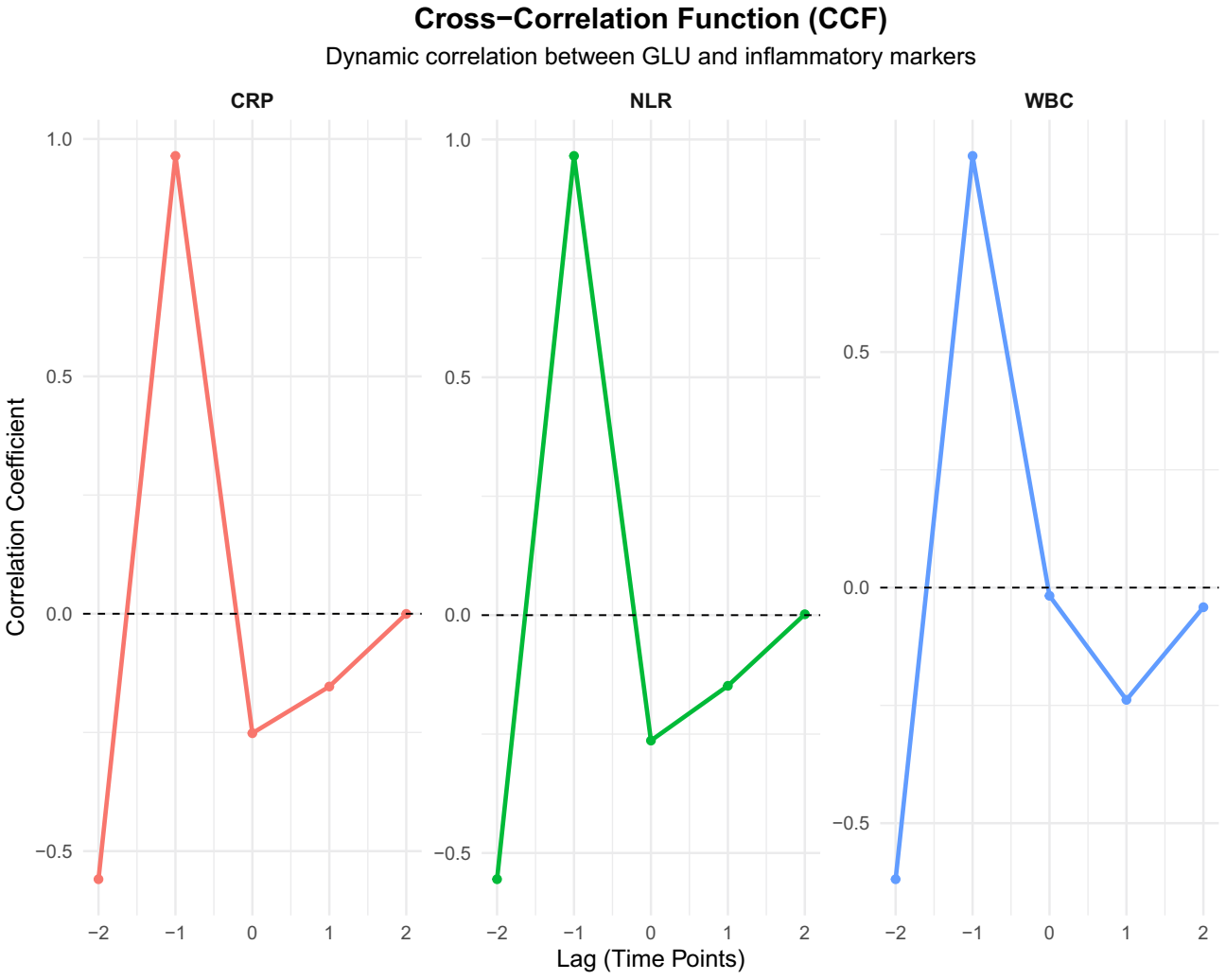


Figure 6 Cross-Time Series and Lag Analysis between Glucose-Inflammation Interactions.
Notes: Positive correlations at lag 0 reflect the simultaneous elevation of glucose and inflammation, while lag +1/−1 indicates delayed effects.
Abbreviations: GLU, Blood Glucose Level; CRP, C-Reactive Protein; NLR, Neutrophil-to-Lymphocyte Ratio; WBC, White Blood Cell Count; CCF, Cross-Correlation Function.

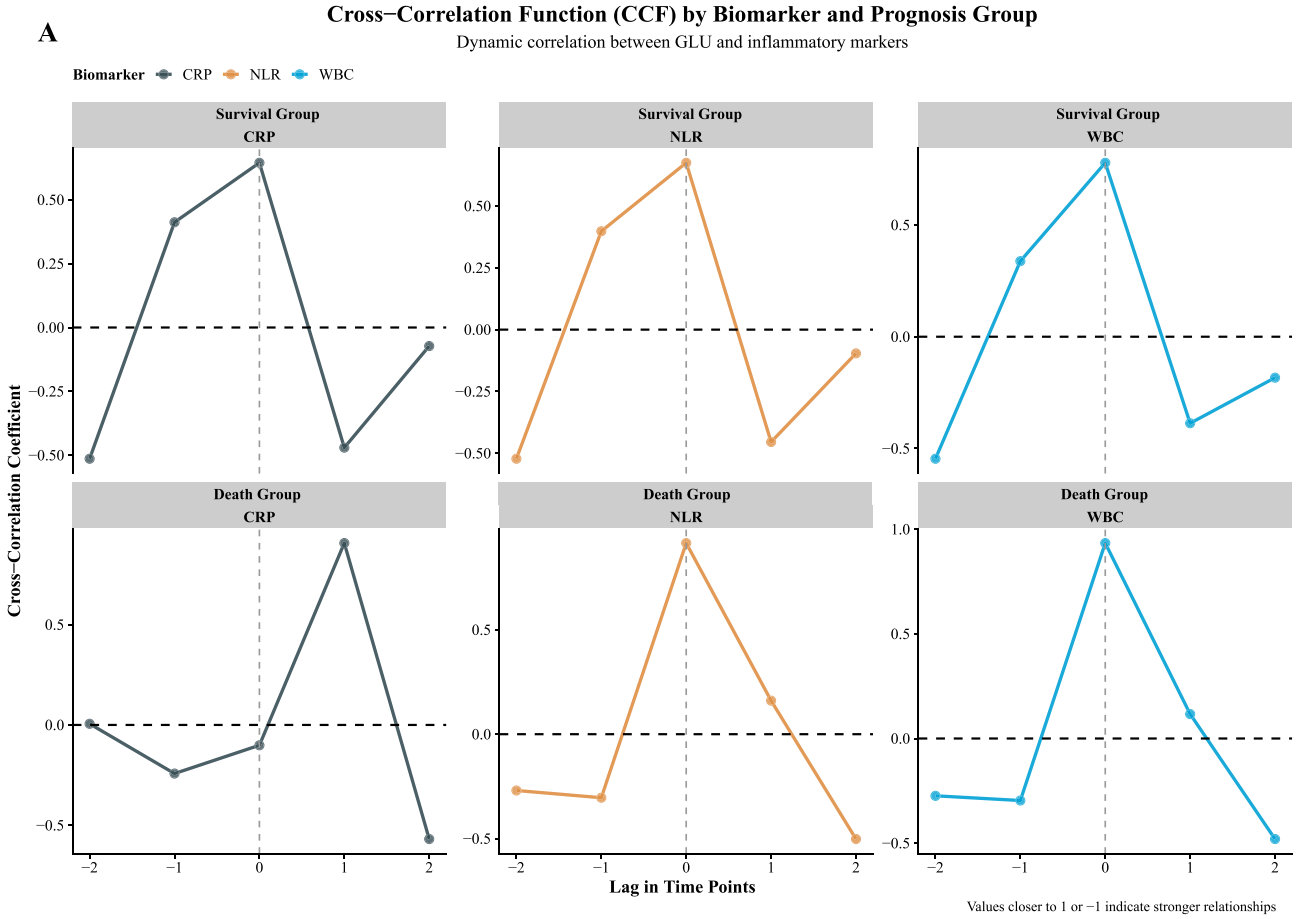
fluctuations inversely affect leukocyte dynamics prior to peak inflammatory responses. These findings emphasize the bidirectional relationship between glucose dysregulation and inflammation, positioning hyperglycemia as both a consequence and a driver of systemic inflammation in CAP.

Temporal Dynamics Across Prognosis Groups

Stratification by prognosis (survivors vs non-survivors) revealed marked differences in glucose–inflammation dynamics (Figure 7A). Among survivors, CRP and glucose exhibited immediate coupling, with the strongest synchrony at lag 0 (peak cross-correlation) and notable positive correlations at lag –1. This immediate synchrony shifted to a negative correlation at lag +1, reflecting prompt feedback regulation. In contrast, non-survivors displayed delayed CRP dynamics: maximal correlation emerged at lag +1 following an initial negative correlation at lag –1, indicating a loss of immediate coupling between glucose and inflammation.

For both NLR and WBC, synchrony at lag 0 was observed in both groups. However, survivors demonstrated physiologic regulatory patterns: positive antecedent correlations were followed by negative correlations at lag +1, indicative of effective feedback inhibition. In contrast, non-survivors showed a pathological phase inversion, with negative antecedent correlations switching to positive values at lag +1, reflecting disrupted regulatory mechanisms.

These patterns suggest compromised homeostatic control in non-survivors, with delayed and inverted immunometabolic responses indicating failure in coordinated counterregulation. Such temporal dyscoordination may serve as an early warning of biological system failure in critical illness and could potentially inform prognostic assessment and targeted interventions.



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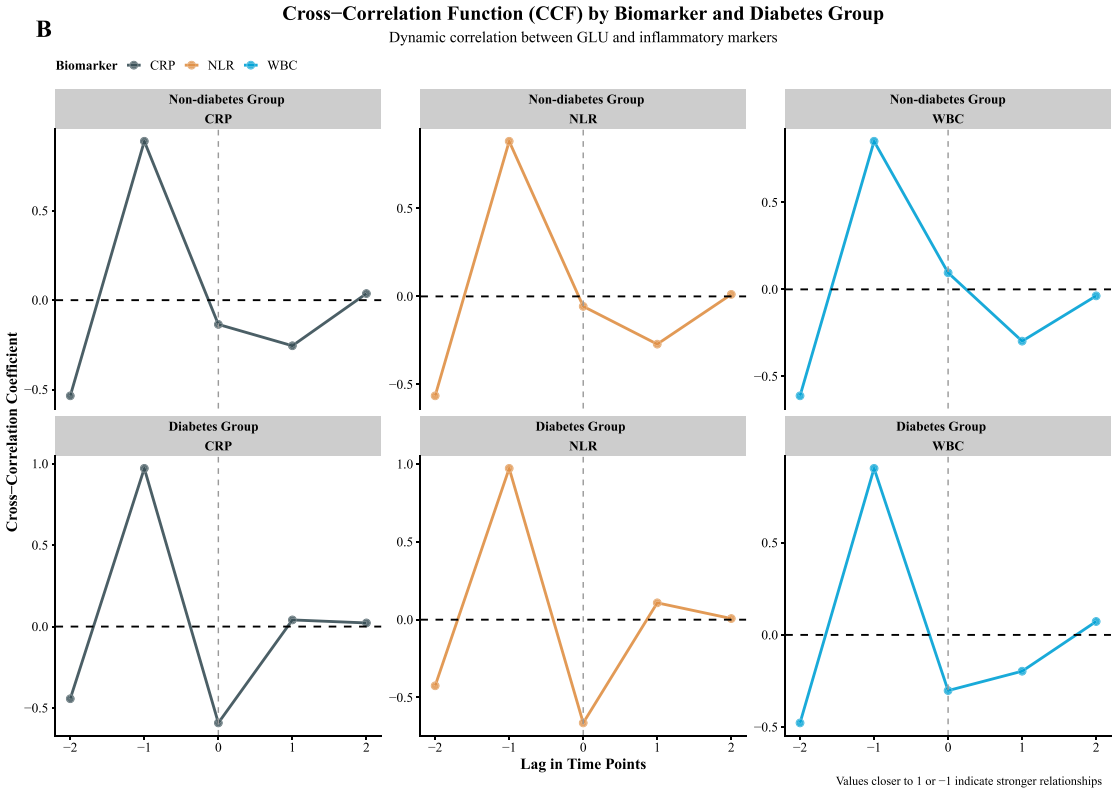

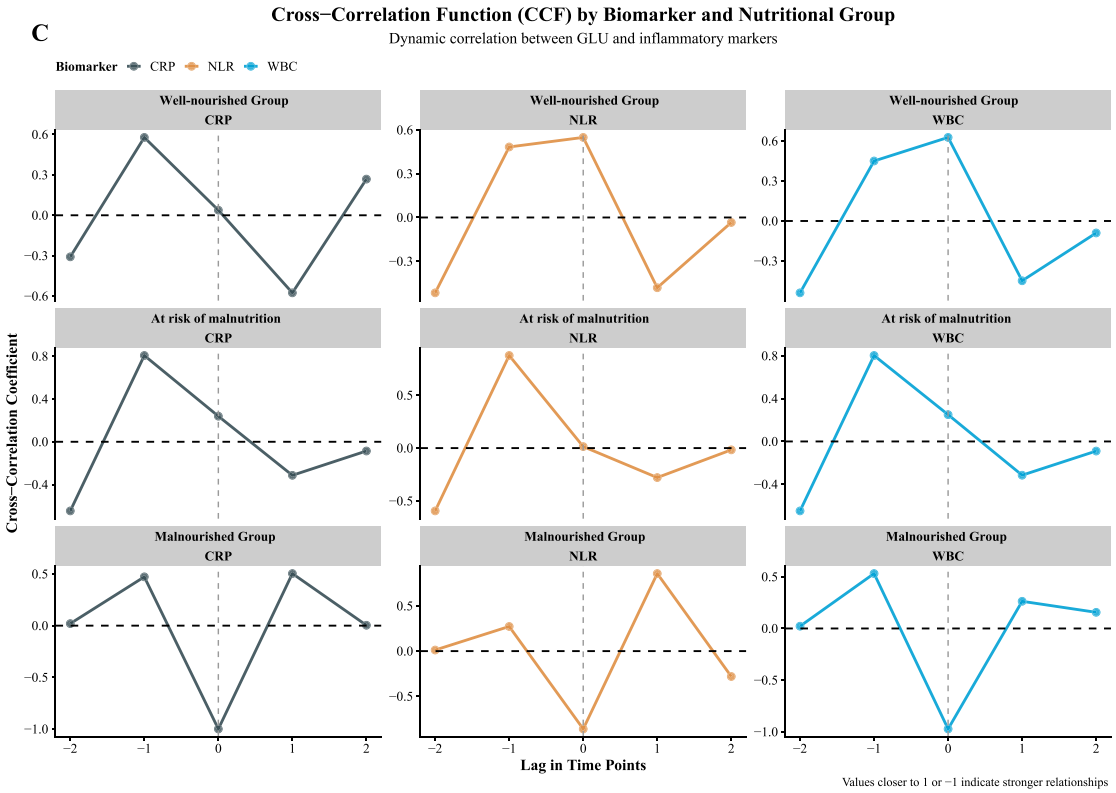

Figure 7 Continued.

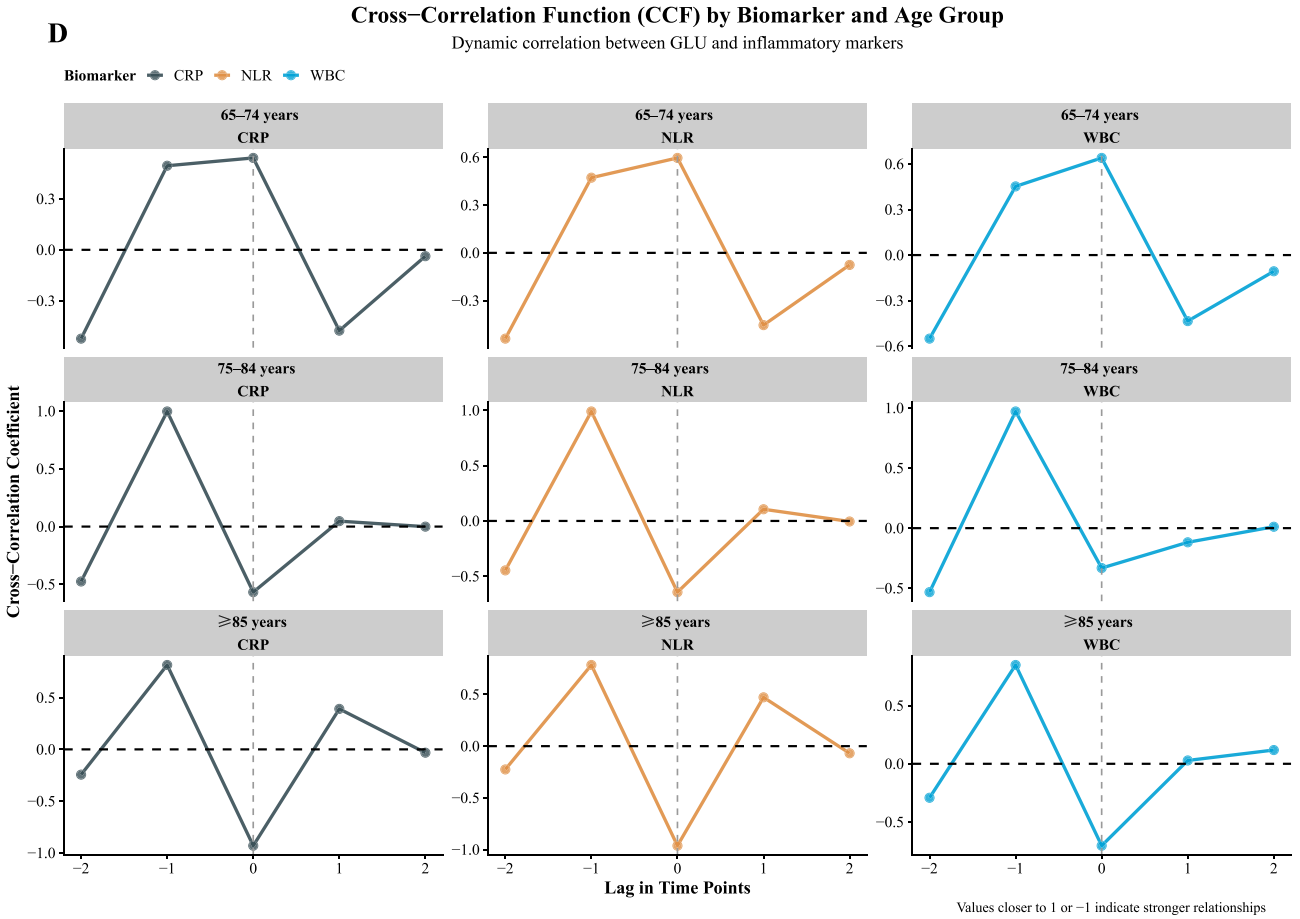

Figure 7 Cross-Time Series and Lag Analyses by Subgroups (Prognosis, Diabetes, Nutritional Status, Age). Interpretation of Lag: Lag 0: Indicates immediate correlations between GLU and inflammatory markers, suggesting a direct relationship. Lag +1: Delayed correlations, where glucose dysregulation potentially precedes and influences systemic inflammation. Lag −1: Fluctuations in glucose levels influence inflammatory markers prior to the peak inflammatory response.

Notes: (**A**) Cross-correlation by prognosis (survival vs death): Patients in the death group exhibited delayed CRP-glucose coupling—peaking at lag +1—and a reversal in regulatory dynamics for NLR and WBC (initial negative correlations followed by subsequent positive ones), contrasting the patterns observed in survivors. This suggests impaired homeostatic regulation and dysregulated immunometabolic responses in non-survivors. (**B**) Cross-correlation by diabetes status: Both diabetic and non-diabetic patients showed strong positive correlations between glucose and inflammatory markers at lag –1, indicating that rises in inflammation typically preceded changes in glucose, with this pattern most marked in the diabetic group. (**C**) Cross-correlation by nutritional status: Progressive disruption in glucose-inflammation coupling was evident with worsening nutritional status: diminished antecedent (lag –1) correlations, strong inverse contemporaneous (lag 0) associations, and a reversal to positive correlations at lag +1. (**D**) Cross-correlation by age group: Increasing age was associated with progressive disruption and phase reversal in the temporal dynamics between glucose and inflammation, with the most pronounced dysregulation in patients aged ≥85 years.

Abbreviations: CAP, Community-Acquired Pneumonia; CRP, C-Reactive Protein; NLR, Neutrophil-to-Lymphocyte Ratio; WBC, White Blood Cell Count; GLU, Blood Glucose Level; CCF, Cross-Correlation Function.

Temporal Dynamics Across Diabetes Groups

Analysis by diabetes status (Figure 7B) further highlighted differences in glucose–inflammation coupling. In both diabetic and non-diabetic patients, glucose and inflammatory markers (CRP, NLR, WBC) showed robust positive cross-correlations at lag –1, with stronger coefficients in the diabetes group. At lag 0, diabetic patients demonstrated moderate to strong negative correlations with CRP and NLR and a weaker negative association with WBC. In contrast, the non-diabetes group exhibited weak or near-zero contemporaneous correlations. At lag +1, correlations in the diabetes group were generally near zero or weakly positive, whereas the non-diabetes group showed modest negative values across all markers. These findings indicate that, particularly in diabetes, rises in inflammation tend to precede changes in glucose, underscoring distinct temporal patterns according to metabolic status.

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Temporal Dynamics Across Nutritional Status Groups

Subgroup analyses by nutritional status (Figure 7C) showed progressively disrupted temporal dynamics between glucose and inflammatory markers with worsening nutrition. Well-nourished patients had moderate positive lag –1 correlations, suggesting glucose elevations tended to precede increases in inflammation. Contemporaneous (lag 0) correlations were weak for CRP and moderate for NLR and WBC; lag +1 values were moderately negative, indicating a subsequent decline in inflammation following glucose changes.

In patients at risk of malnutrition, lag –1 correlations increased, but lag 0 associations weakened and lag +1 correlations remained weakly to moderately negative. Among the malnourished, lag –1 cross-correlations declined, while strong negative contemporaneous correlations emerged; notably, lag +1 correlations became positive, suggesting delayed and possibly dysregulated inflammatory responses to glucose fluctuations.

These results demonstrate a progressive breakdown of glucose–inflammation coupling as nutritional status deteriorates in elderly CAP patients, with malnutrition associated with diminished early correlations, concurrent inverse associations, and reversal to delayed positive correlations. This underscores the clinical relevance of timely nutritional and glycemic interventions to address metabolic-inflammatory dysregulation in this vulnerable population.

Temporal Dynamics Across Age Groups

Age-stratified analysis (Figure 7D) revealed distinct alterations in temporal glucose–inflammation relationships among elderly CAP patients. In the 65–74-year group, a typical physiological pattern was observed: moderate positive lag –1 correlations, peak contemporaneous synchrony, followed by negative lag +1 correlations, reflecting timely feedback regulation. In the 75–84-year group, antecedent (lag –1) correlations were markedly increased, while contemporaneous (lag 0) values became negative and lag +1 associations were weak or absent, indicating growing temporal disorganization. For patients aged ≥85 years, a highly dysregulated pattern emerged: lag –1 correlations remained strongly positive, lag 0 values became strongly negative, and lag +1 correlations returned to positive or near-zero levels. These findings indicate that with advancing age, the temporal coupling between glucose and inflammation shifts from a well-regulated, physiological pattern to pronounced disruption and phase reversal, underscoring the importance of accounting for age-related changes when managing metabolic and inflammatory responses in elderly patients with CAP.

Discussion

This study investigated the temporal dynamics between glucose metabolism (GLU) and inflammatory biomarkers (CRP, NLR) in older adults with CAP, revealing significant patterns of biomarker fluctuations and subgroup-specific characteristics. CCF analysis identified lagged relationships, with fluctuations in blood glucose consistently preceding inflammatory responses. These findings suggest a potential upstream role of hyperglycemia in driving systemic inflammation, particularly in vulnerable subgroups such as diabetic patients, malnourished individuals, and those aged ≥85 years. By elucidating the metabolic-inflammatory dysregulation associated with CAP, this study provides mechanistic insights and identifies potential strategies for tailoring interventions to high-risk populations.

Temporal Interplay Between Glucose Metabolism and Inflammation

Our findings consistently demonstrate that glucose fluctuations preceded elevations in inflammatory markers, particularly among patients with fatal outcomes. Notably, changes in NLR and WBC exhibited a lag of 1–2 days following glucose surges, indicating that metabolic dysregulation may act as a precursor to systemic inflammation. These results corroborate previous studies suggesting hyperglycemia activates key inflammatory pathways, such as NF-κB signaling, oxidative stress, and mitochondrial dysfunction, which in turn amplify cytokine release and immune dysregulation.[25,26]

The bidirectional relationship between metabolic and inflammatory dysfunction has been well-documented, with hyperglycemia not only exacerbating inflammation but also contributing to insulin resistance and increased hepatic glucose production, thereby perpetuating a self-reinforcing cycle. Prior research, such as the work of Marik et al and Lou et al, identified hyperglycemia as a predictor of poor outcomes in critically ill patients.[27,28] Our study adds a temporal dimension to this understanding, showing a delayed yet distinct sequence linking metabolic dysregulation to subsequent inflammatory responses. These insights underscore the importance of timing in therapeutic interventions, suggesting that

prompt and precise management of hyperglycemia could help mitigate systemic inflammation and improve outcomes in CAP.

Interpretation of Positive and Negative Cross-Correlation Coefficients

The finding of both positive and negative cross-correlation coefficients across various lags offers valuable insight into the temporal interplay between glucose metabolism and systemic inflammation in elderly CAP patients. Positive cross-correlation values indicate that elevations in glucose levels coincide with concurrent increases in inflammatory biomarkers, reflecting synchronous physiological processes that may be jointly driven by shared upstream factors, such as physiological stress or acute infection.

In contrast, negative cross-correlation values denote intervals when rises in glucose are associated with subsequent declines in inflammatory markers, or vice versa. These inverse patterns suggest the presence of antagonistic or feedback mechanisms, where fluctuations in one system may initiate compensatory responses in the other. For instance, the negative cross-correlation at lag +1 observed in survivors may reflect intact physiological feedback; following peaks in inflammation, homeostatic mechanisms act to normalize glycemic levels. Conversely, among non-survivors and those with malnutrition or advanced age, the absence, reversal, or delay of these negative correlations indicates disruption or loss of typical feedback control, which may be associated with a transition towards metabolic or immune dysregulation.

Collectively, these temporal cross-correlation patterns do more than demonstrate statistical associations; they reveal underlying pathophysiological dynamics—capturing synchrony, co-activation, and the robustness of adaptive feedback, as well as signaling when regulatory mechanisms deteriorate, particularly in high-risk subgroups.

Group-specific analyses further illustrate how the pattern, magnitude, and direction of cross-correlation coefficients reflect distinct states of physiological regulation. In well-compensated patients—such as survivors, those with better nutrition, or younger elderly—a progression from initial synchrony (evident as positive correlations at lag 0 or –1) to subsequent negative correlations (lag +1) is consistent with efficient feedback inhibition, characteristic of resilient biological systems. In contrast, among patients with poor prognosis, malnutrition, or advanced age, we observed persistent or reversed positive values, or attenuated negative correlations, indicating impaired or delayed regulatory responses.

These divergent temporal signatures provide a functional perspective on disease dynamics. They may help identify individuals at heightened risk of clinical deterioration and suggest opportunities for more precisely timed therapeutic interventions aimed at restoring effective homeostatic regulation.

Subgroup-Specific Insights

Our analysis revealed that diabetic patients exhibited a more pronounced and prolonged lag effect in the relationship between glucose fluctuations and inflammatory markers, reflecting a delayed but amplified inflammatory response. This finding suggests that chronic hyperglycemia in diabetic patients induces long-term metabolic adaptations—such as insulin resistance and oxidative stress—that exacerbate the inflammatory cascade. Conversely, non-diabetic patients demonstrated a more immediate inflammatory response, likely due to the absence of pre-existing metabolic adaptations. These results build on prior studies, such as Brunner et al,[29] which focused primarily on hyperglycemia's prognostic role in diabetic populations, and emphasize the nuanced interplay between metabolic dysfunction and immune dysregulation across different glycemic states. The observed differences highlight the need for tailored glucose management strategies, addressing hyperglycemia-induced inflammation in diabetic patients while proactively mitigating metabolic fragility in non-diabetic patients.

While earlier studies explored the pro-inflammatory effects of prolonged glucose exposure and its role in immune exhaustion,[30] our findings provide temporal precision, showing that glucose dysregulation serves as an upstream driver of immune activation rather than merely a concurrent phenomenon. This temporal specificity is critical for guiding therapeutic strategies, such as the application of tight glycemic control, enabling interventions at the earliest stages of inflammation to prevent organ damage and improve outcomes. Moreover, while previous research has often focused on single inflammatory markers or isolated glucose measurements, our study emphasizes the dynamic interplay among multiple biomarkers, including NLR, WBC, and glucose. For instance, Huang et al identified neutrophil-to-lymphocyte

ratio as a stand-alone predictor of mortality but did not investigate its interaction with metabolic metrics.[31] By integrating glucose dynamics with inflammatory markers, our study underscores the importance of a systems-based approach to understanding CAP progression, where metabolic and immune dysregulation are not treated in isolation but as interconnected processes.[32]

Malnourished patients exhibited the strongest lag effects between glucose fluctuations and inflammatory biomarkers, indicating significant metabolic-inflammatory dysregulation. Protein-energy malnutrition, mitochondrial dysfunction, and impaired antioxidant defenses likely exacerbate the inflammatory response in this subgroup. Chronic nutritional deficiencies increase vulnerability to oxidative stress and impair immune regulation, intensifying hyperglycemia-induced inflammation. These findings are consistent with prior studies linking malnutrition to poor clinical outcomes and prolonged systemic inflammation.[33] Our study extends this knowledge by quantifying the sequential metabolic-inflammatory interactions, demonstrating how prolonged lag effects delay recovery and worsen prognosis for malnourished patients. Clinically, these findings underscore the importance of early nutritional interventions—such as high-protein diets, caloric supplementation, and micronutrient support—combined with timely glycemic stabilization to address metabolic fragility and better regulate inflammation.

Aged patients (≥85 years) exhibited the longest and most pronounced lag effects between glucose fluctuations and inflammatory biomarkers, reflecting heightened susceptibility to delayed metabolic and immune responses. Advanced age is associated with immune senescence, reduced metabolic flexibility, and impaired mitochondrial function, all of which contribute to prolonged systemic inflammation and delayed resolution of hyperglycemia-induced immune activation.[34] Compared to younger elderly cohorts (65–74 years and 75–84 years), patients aged ≥85 years demonstrated significantly delayed inflammatory marker normalization, further supporting the concept of "inflammaging". This persistent low-grade inflammation amplifies acute responses to metabolic stress, such as hyperglycemia. These findings highlight the need for age-specific interventions tailored to mitigating prolonged inflammatory spillover in this vulnerable population through refined glycemic management and targeted anti-inflammatory strategies.

Methodological Strengths and Innovations

The methodological strength of this study lies in the application of CCF analysis, a technique rarely employed to explore time-delayed relationships between glucose metabolism and inflammatory markers in elderly CAP patients. Unlike conventional regression models, which assume static relationships between variables, the use of CCF provides a unique ability to capture temporal directionality, offering insight into the sequential interplay between metabolic and inflammatory dysregulation. This approach establishes a foundation for the development of predictive models that can inform real-time clinical decision-making and targeted therapeutic interventions.

The selection of dynamic statistical methods was specifically aimed at capturing the time-dependent nature of CAP pathophysiology. Alongside CCF, ARIMA modeling was employed to predict future biomarker trends, enabling early detection of dysregulated patterns and facilitating personalized management strategies. Together, these methodological innovations offer a comprehensive framework for understanding and treating the complex metabolic-inflammatory interactions underpinning CAP progression in older adults.

In conclusion, these findings point to significant temporal and subgroup-dependent effects of glucose metabolism on inflammation in elderly CAP patients, with potential implications for early detection and tailored management. Compared to previous studies, this work's combination of methodological innovation and subgroup-specific analysis underscores its relevance in advancing personalized medicine for older adults.

Mechanistic and Clinical Implications

Our findings offer critical mechanistic insights into the temporal dynamics of glucose-inflammation interactions and their clinical relevance. Hyperglycemia appears to function as an upstream driver of inflammation by activating NF-κB signaling, NLRP3 inflammasomes, and inducing oxidative stress, leading to cytokine overproduction.[34,35] Conversely, systemic inflammation exacerbates glucose dysregulation by promoting insulin resistance and dysregulated hepatic glucose production, perpetuating a vicious cycle of metabolic-inflammatory dysfunction.[36,37]

The distinct lag effects observed in high-risk subgroups—diabetic patients, malnourished individuals, and those aged ≥85 years—highlight unique pathophysiological vulnerabilities that necessitate tailored management strategies. Early and dynamic biomarker monitoring could enable clinicians to identify critical intervention windows and personalize treatment approaches.

Our findings further advocate for integrating predictive modeling techniques, such as ARIMA, into clinical workflows to forecast worsening biomarker trajectories. These models can enhance the timing of interventions, optimizing glycemic control, nutritional therapies, and anti-inflammatory treatments to preemptively address disease progression.

Clinical Relevance and Practical Applications

This study carries significant implications for improving personalized care in older adults with CAP. The identification of temporal dynamics between glucose fluctuations and inflammation highlights the importance of continuous biomarker monitoring to enhance risk stratification and guide targeted interventions.

Glycemic Control Interventions

The observed time-lagged relationship between hyperglycemia and subsequent inflammatory responses underscores the need for proactive glucose management. Early and precise stabilization of blood glucose, potentially through insulin therapy, could mitigate downstream inflammatory cascades. Previous studies demonstrate improved outcomes in critically ill patients following tight glycemic control. However, achieving this balance in elderly CAP patients requires careful individualization to minimize the risks of hypoglycemia while effectively reducing inflammation-driven complications. Further research is needed to determine optimal glycemic targets and individualized approaches specific to this vulnerable population.

Dynamic Monitoring of CRP and NLR

Dynamic assessments of inflammatory biomarkers, such as CRP and NLR, represent valuable tools for tracking disease progression and tailoring interventions. Persistently elevated CRP levels, despite glycemic control, may signal the need for adjunctive anti-inflammatory therapies such as corticosteroids, aligned with biomarker trajectories. Likewise, monitoring NLR—a robust marker of systemic inflammation—can aid in predicting clinical deterioration and guiding timely escalation of care. These findings support the integration of biomarker trends into treatment strategies to optimize outcomes for elderly CAP patients.

Nutritional Support Strategies

The exaggerated biomarker fluctuations and prolonged lag effects observed in malnourished patients emphasize the critical role of nutritional status in modulating metabolic and inflammatory processes. Early, targeted nutritional interventions—providing adequate protein, essential amino acids, and micronutrient-rich supplements—may restore metabolic balance and reduce inflammation-related morbidity. Randomized controlled trials are necessary to validate these strategies and establish evidence-based guidelines for managing malnutrition in elderly CAP patients.

While prior studies have established that elevated levels of CRP, NLR, and blood glucose are associated with poor outcomes in CAP, this study expands on these findings by uncovering the temporal patterns and lag effects of these biomarkers. Notably, the observation that glucose fluctuations precede changes in inflammatory markers provides new insights into the sequential interaction between metabolic dysregulation and inflammation in elderly CAP patients. Additionally, subgroup analyses further highlight the heterogeneity in CAP presentations, underscoring the need for stratified management strategies. For example, the greater prognostic value of CRP and NLR in malnourished patients emphasizes the critical role of addressing nutritional deficits as a key component of CAP care. Similarly, the pronounced effect of glucose fluctuations in non-diabetic patients reinforces the importance of tailoring metabolic interventions to the specific glycemic state of individual patients.

This study introduces a dynamic perspective on the prognostic utility of metabolic and inflammatory biomarkers in elderly CAP patients, offering practical implications for clinical care. First, continuous monitoring of biomarkers such as CRP, NLR, and glucose can provide early warning signs of disease progression, enabling timely interventions to improve clinical outcomes. Second, identifying subgroup-specific differences in biomarker dynamics supports the development of

personalized care approaches. For instance, malnourished patients may benefit from targeted nutritional interventions, while non-diabetic patients with hyperglycemia may require more aggressive glucose control measures. Finally, the integration of predictive models, such as ARIMA, to forecast biomarker trajectories offers a valuable tool for clinical decision-making in high-risk populations. By leveraging these models, clinicians can more effectively identify critical intervention points, optimizing treatment strategies and improving care for older adults with CAP.

Limitations and Future Directions

Despite its strengths, this study has certain limitations. The retrospective design introduces potential selection bias, and the single-center setting may restrict the generalizability of the findings. Future studies involving multi-center cohorts with more diverse populations are essential to validate these results. Although CRP and NLR are widely recognized as indicators of systemic inflammation, the lack of direct cytokine measurements limits our ability to definitively characterize the inflammatory response in each group. Including a broader panel—such as IL-6, procalcitonin, and lactate—would provide a more comprehensive understanding of CAP pathophysiology.

It should also be noted that some blood glucose measurements in our cohort were obtained under non-fasting (random) conditions, while acute illness itself may have precipitated stress-induced hyperglycemia. Both factors likely contributed to the relatively high GLU values observed, and could complicate the interpretation of glycemic status as well as its association with patient outcomes. Additionally, the relatively short observation period constrains the robustness of the ARIMA models for predicting long-term trends in biomarker dynamics.

Future research should address the following: (1) Evaluating the impact of early glycemic control and nutritional interventions on biomarker dynamics and clinical outcomes. (2) Conducting longitudinal, multi-center studies to confirm the observed biomarker lag effects and subgroup-specific differences. (3) Developing advanced AI-driven prognostic models that incorporate multi-biomarker panels to guide personalized management strategies for elderly CAP patients.

Conclusion

This study provides novel insights into the temporal dynamics between glucose metabolism and inflammation in older adults with CAP. By identifying significant lag effects and subgroup-specific vulnerabilities, it highlights the critical roles of continuous biomarker monitoring, personalized glycemic regulation, and timely nutritional interventions. These findings deepen our understanding of the interplay between metabolic and inflammatory dysregulation and lay the groundwork for advancing individualized care in high-risk elderly CAP populations.

Data Sharing Statement

The datasets generated during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

Patient data confidentiality was strictly protected throughout this study. All patient records were anonymized and de-identified before analysis. Only the research team had access to the data, which were stored securely. This study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Second People's Hospital of Lianyungang (approval number 2022K040), which waived the requirement for informed consent due to the retrospective, non-interventional, and non-intrusive nature of the study. The data were used solely for the purposes of this research and were handled with strict confidentiality.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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