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ARTICLE

Diagnostic Utility of Combined Serum Procalcitonin and C-Reactive Proteins in Neonatal Sepsis

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Abstract

Aims/Background Early diagnosis of neonatal sepsis is hindered by nonspecific clinical signs and suboptimal biomarkers. Therefore, this study aimed to evaluate the diagnostic accuracy of serum procalcitonin (PCT) and C-reactive protein (CRP), both individually and in combination, and assess the robustness and clinical utility of a combined predictive model.

Methods This single-center retrospective cohort (2022–2025, Longyan First Hospital Affiliated to Fujian Medical University, China) included 293 neonates (161 with sepsis and 132 controls). Univariate logistic regression was applied to compare the clinical and laboratory parameters between the sepsis and control groups. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) curves, contingency tables, and the DeLong tests. A logistic regression–based combined prediction model was developed using a 7:3 stratified random split into training and validation sets. Model robustness was assessed via calibration plots, decision curve analysis (DCA), and visualized as a nomogram. Subgroup and culture-confirmed-only sensitivity analyses further assessed the consistency of the combined predictive model.

Results Sepsis cases exhibited significantly higher PCT, CRP, and white blood cell (WBC), and lower hemoglobin (Hb) and platelet (PLT) (all $p < 0.001$). Univariate logistic regression confirmed PCT [odds ratio (OR) = 3.32, 95% confidence interval (CI): 2.23–4.93, $p < 0.001$] and CRP (OR = 1.03, 95% CI: 1.01–1.05, $p = 0.003$) as significant predictors of neonatal sepsis. The combined PCT-CRP model provided better diagnostic performance, achieving a significantly greater area under the curve (AUC) of 0.94 (95% CI 0.92–0.97) than either marker alone (0.88 for PCT, 0.87 for CRP) as shown by DeLong test ($p < 0.001$). Furthermore, the model maintained higher sensitivity (82.61%) while significantly improving specificity (93.18%) and overall diagnostic accuracy (87.36%). The nomogram, validated in both sets, exhibited good calibration and net clinical benefit in DCA. Subgroup analysis confirmed consistent predictive performance across gestational age, delivery mode, and sex, with CRP more pronounced in preterm infants. Sensitivity analyses using culture-confirmed sepsis validated model robustness (AUC = 0.94).

Conclusion PCT and CRP are key diagnostic biomarkers for neonatal sepsis. Their integration as a combined predictive model significantly enhances diagnostic performance and clinical applicability, providing a practical framework for early sepsis identification and potential for clinical implementation.

Key words: sepsis; neonate; procalcitonin; C-reactive protein; ROC curve; biomarkers

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Introduction

Neonatal sepsis remains a significant global health challenge. Despite a decline in overall incidence over recent decades, millions of newborns still get severe infections each year, resulting in high mortality and long-term morbidity, particularly in

low- and middle-income regions of the world (Bakhuizen et al, 2014; Fleischmann et al, 2021; Gan et al, 2022). It often presents with nonspecific symptoms, including respiratory distress, unstable body temperature, or feeding difficulties, which overlap considerably with non-infectious conditions and complicate early clinical differentiation (Eichberger et al, 2022). Blood culture remains a preferred diagnostic approach; however, its clinical utility in early decision-making using this approach is limited by small sample volumes obtained from neonates and the longer time required for results (Cantey and Prusakov, 2022; Eichberger et al, 2022). Consequently, clinicians frequently administer empirical antibiotic therapy, typically ampicillin and gentamicin, which contributes to considerable antimicrobial overuse (Obiero et al, 2015). Hence, the prompt and accurate identification of neonates with sepsis, before infection is microbiologically confirmed, is critical for guiding appropriate treatment while reducing unnecessary exposure to antimicrobial drugs.

Serum biomarkers, including procalcitonin (PCT) and C-reactive protein (CRP), due to their rapid responsiveness and usefulness for dynamic monitoring, have gained considerable attention in recent years. PCT, a highly sensitive predictor of systemic bacterial infection, rises within 2–4 h of onset, achieves its peak around 12 h, and declines to baseline within 2–3 days, making it crucial for early differentiation of bacterial infections (Whicher et al, 2001). In contrast, CRP is an acute-phase protein synthesized by the liver in response to inflammation which respond more slowly but has long been known for its diagnostic reliability (Boscarino et al, 2023). A meta-analysis has reported that PCT offers high sensitivity (Se) (up to 85%) but only moderate specificity (Sp) in neonatal sepsis (Pontrelli et al, 2017), whereas CRP shows more consistent diagnostic performance, albeit with lower Se of approximately 71% (Anugu and Khan, 2021). Evidence indicates that combining these markers improves diagnostic performance, with reported combined area under the curve (AUC) values approaching 0.96, compared with 0.91 for PCT alone and 0.85 for CRP (Ruan et al, 2018). Despite these observations, a comprehensive evaluation of their diagnostic performance in a relatively large neonatal cohort, particularly under real-world clinical settings, remains limited.

In clinical practice, logistic regression models are increasingly employed to incorporate biomarkers into predictive frameworks, often visualized as nomograms and validated using decision curve analysis (DCA) to determine their net clinical benefit. Such models have been applied to neonatal populations for estimating sepsis risk, demonstrating promising predictive performance (Wu et al, 2024).

In this study, we performed a single-center retrospective cohort analysis of neonates who were hospitalized between 2022 and 2025 to systematically compare the diagnostic performance of PCT and CRP as well as to evaluate their combined utility. The distinct strength and novelty of this study lie in the inclusion of a relatively large neonatal cohort to systematically compare their combined diagnostic performance, with model robustness and clinical relevance ensured through internal validation, calibration, and DCA. Moreover, a nomogram was developed to enhance clinical applicability, while subgroup and sensitivity analyses were conducted to examine the consistency of results across different clinical strata and pathogen-positive cases.

Methods

Study Design

This single-center retrospective cohort study was conducted at Longyan First Hospital Affiliated to Fujian Medical University between January 2022 and July 2025.

Study Population and Grouping

The study included hospitalized neonates with a gestational age (GA) of ≥32 weeks who had available baseline measurements of PCT and CRP.

Inclusion criteria for patient selection were as follows: (1) Patients meeting the clinical diagnostic criteria for neonatal sepsis, defined by compatible clinical manifestations and at least one of the following laboratory indicators (Neonatology Group of Pediatrics Branch of Chinese Medical Association and Association, 2019): leukopenia ($<5 \times 10^9$/L) or leukocytosis ($>25 \times 10^9$/L); elevated CRP (>4 mg/L at birth or >10 mg/L at 12–60 h after birth); PCT rising within the first 2 days of life followed by a decline after day 3; or an immature-to-total neutrophil ratio (I/T) ≥0.16. (2) Neonates were classified as culture-proven sepsis if blood culture was positive for a bacterial pathogen, or as clinical sepsis if blood culture was negative but both clinical and laboratory criteria were fulfilled. (3) Availability of PCT and CRP measurements.

Exclusion criteria included (1) major congenital malformations or traumatic diseases, (2) documented antibiotic exposure before admission, including maternal intrapartum antibiotic prophylaxis or neonatal pre-admission therapy, (3) known immunodeficiency, severe malnutrition, or significant hepatic or renal impairment, (4) maternal infections during pregnancy (e.g., chorioamnionitis, intrapartum fever requiring antimicrobial therapy), (5) administration of intravenous immunoglobulin or blood transfusion likely to affect inflammatory or immune markers, and (6) early death, inter-hospital transfer, or incomplete records precluding reliable assessment of clinical outcomes.

However, inclusion criteria for the control group were as follows: (1) no evidence of maternal infection during pregnancy; (2) absence of infection-related symptoms or therapeutic interventions within 72 h after birth; and (3) complete availability of relevant clinical and laboratory data. Furthermore, those with (1) maternal gestational diabetes or hypertensive disorders, (2) exposure to phototherapy (for jaundice) or parenteral nutrition, and (3) early death or loss to follow-up that prevented confirmation of outcome status were not included in the control group.

A total of 293 neonates met the eligibility criteria and were included in the final analysis: 161 with sepsis (either culture-confirmed or clinical) and 132 non-septic controls. The overall study design and patient selection process are illustrated in Fig. 1. Culture-confirmed cases were defined as those identified by isolation of pathogens, including *Escherichia coli*, group B *Streptococcus* (GBS), coagulase-negative *Staphylococcus* (CONS), *Acinetobacter baumannii*, *Streptococcus gallolyticus*, *Pseudomonas aeruginosa*, or *Klebsiella pneumoniae*.

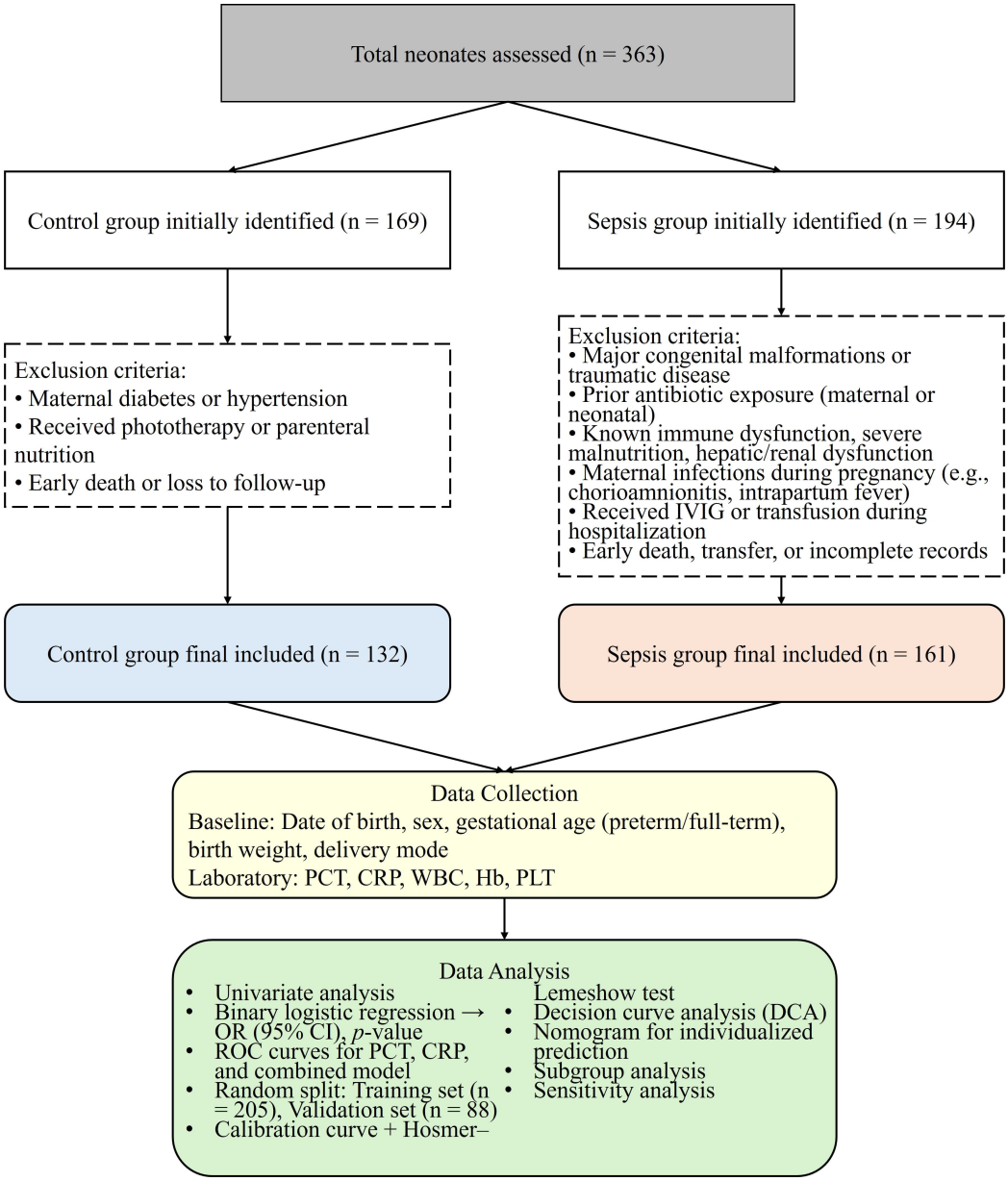

Fig. 1. A flowchart of patient selection and study design. IVIG, intravenous immunoglobulin; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; ROC, receiver operating characteristic; OR, odds ratio; CI, confidence interval.

Data Collection

Structured data were extracted from the hospital's electronic medical record and laboratory information system (LIS), and manually verified for accuracy. Baseline variables included date of birth, sex, delivery mode (cesarean or vaginal), GA (in weeks), GA category (preterm <37 weeks; term ≥ 37 weeks), and birth weight (kg). Laboratory parameters included PCT (ng/mL), CRP (mg/L), white blood cell (WBC, $\times 10^9$/L) count, hemoglobin (Hb) (g/L), and platelet (PLT) count ($\times 10^9$/L). Both raw and $\log_{10}$-transformed values were retained for analysis. The interval between birth and blood sampling (in hours since) was recorded and included as a covariate in the regression analysis.

In the sepsis cohort, blood samples were collected during the first clinical assessment for suspected cases, typically coinciding with the onset of infection-related symptoms and blood culture collection. For the control group, the initial routine blood test performed upon hospital admission was used. All analyses were based on the first available measurement, which was incorporated as a covariate to reduce potential bias. For diagnostic evaluation, the reference outcome was defined as sepsis (1 = culture-confirmed or clinical sepsis, 0 = no sepsis).

Specimen Collection and Laboratory Assays

Venous blood samples (1–2 mL) were collected as part of routine clinical assessment. Approximately 1.0 mL of the collected specimen was used for blood culture, while the remaining sample was used for hematological and biochemical analyses. Complete blood counts (CBCs) were performed on ethylene diamine tetraacetic acid K2 (EDTA-K2)-anticoagulated samples using an XN-1000 automated hematology analyzer (Sysmex Corporation, Kobe, Japan). Serum CRP and PCT levels were determined following standard laboratory protocols: CRP was assessed by immunoturbidimetry using the AU5800 chemistry analyzer (Beckman Coulter, Brea, CA, USA), and PCT was measured through electrochemiluminescence immunoassay or chemiluminescence immunoassay (ECLIA/CLIA) (Cobas e601 analyzer, Roche Diagnostics, Mannheim, Germany), with a validated analytical range of 0.02–100 ng/mL. Quality assurance was maintained through routine internal control and participation in external quality assessment programs.

Blood cultures were processed using automated culture systems following the manufacturer's instructions. Positive cultures underwent gram staining, species identification by Matrix-Assisted Laser Desorption/Ionization–Time of Flight (M ALDI-TOF) or conventional biochemical methods, and antimicrobial susceptibility testing. All laboratory data were retrospectively retrieved from the hospital LIS.

Statistical Analysis

GraphPad Prism (version 10.0, GraphPad Software, San Diego, CA, USA) was used for plotting receiver operating characteristic (ROC) curves, R (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria) was employed for AUC comparison, modeling, and validation. All statistical tests were two-sided, with a significance threshold set at $\alpha = 0.05$.

Data normality was assessed using the Shapiro–Wilk test. Outliers were examined through boxplots and interquartile-range methods, and extreme values were retained only after verification against corresponding clinical records. Missing data accounted for $<5\%$ of the total dataset; therefore, complete-case analysis was performed, with exclusions applied if critical exposures or outcomes were missing. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median (interquartile range) and compared using Student's t test or Mann-Whitney U test, as appropriate. Categorical variables were expressed as counts and percentages (%), and compared using the χ^2 or Fisher's exact tests, depending on data distribution.

Binary logistic regression was performed using SPSS 27.0 (IBM Corporation, Armonk, NY, USA). Initially, univariable logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) and corresponding *p*-values. Diagnostic performance was evaluated by plotting ROC curves for PCT, CRP, and the combined model across the entire study cohort. The AUC (95% CI) was calculated to determine discriminative ability. Optimal cut-off values were derived using the Youden index (J = Se + Sp – 1), and diagnostic metrics, including Se, Sp, accuracy (Acc), positive predictive value (PPV), and negative predictive value (NPV), were reported. Pairwise comparisons of AUCs were conducted using the DeLong test, with Z-statistics and *p*-values presented; multiple comparisons were performed using the Holm correction approach.

A multivariable logistic regression model incorporating PCT and CRP was constructed to assess their combined predictive performance. The dataset was randomly divided into training and validation datasets using stratified sampling (7:3) ratio to maintain proportional presentation of sepsis and control groups. Model calibration was assessed using calibration curves and the Hosmer–Lemeshow tests. DCA was performed within a clinically plausible probability range (0–0.8) to evaluate net benefit compared with "treat all" and "treat none" strategies. A nomogram was constructed from the regression coefficients of the training dataset to support individualized risk prediction.

Subgroup analyses were conducted using logistic regression to evaluate the effect of PCT (per 1 ng/mL increase), CRP (per 10 mg/L increase), and the combined model (positive prediction at $\geq$threshold probability) across strata defined by delivery mode (cesarean vs. vaginal), GA (preterm vs. term), and sex. Interaction *p*-values were calculated using Wald or likelihood-ratio tests.

For sensitivity analysis, sepsis was redefined as culture-confirmed infection, with the control group unchanged. Optimal cut-off values were recalculated using the Youden index, and diagnostic metrics (Se, Sp, Acc, PPV, NPV, AUC) were re-estimated and compared with the primary analysis to assess model robustness.

Results

Comparison of Baseline Characteristics and Laboratory Parameters Between the Two Groups

This study enrolled 293 neonates, including 132 controls and 161 with sepsis. There were no significant differences between the two groups in GA, preterm, birth weight, sex distribution, or delivery mode ($p > 0.05$), indicating comparable baseline demographics (Table 1).

However, inflammatory and hematologic parameters differed substantially between groups. Compared with controls, neonates with sepsis showed significantly higher levels of PCT [8.45 (5.05–11.05) vs. 1.67 (0.83–2.41) ng/mL, $p < 0.001$], CRP [110.50 (76.30–145.80) vs. 32.20 (17.55–73.38) mg/L, $p < 0.001$], and WBC [16.30 (10.20–22.50) vs. 11.30 (9.10–13.03) $\times 10^9$/L, $p < 0.001$]. Conversely, Hb [139.90 (130.70–150.70) vs. 158.85 (149.47–170.33) g/L, $p < 0.001$] and PLT counts [168.00 (124.00–204.00) vs. 242.00 (203.75–298.25) $\times 10^9$/L, $p < 0.001$]

Table 1. Comparison of baseline characteristics and laboratory parameters between the two groups.

Variables	Control (n = 132)	Neonatal sepsis (n = 161)	Statistic	*p*-value
Gestational weeks, M (Q_1, Q_3)	36.55 (33.10, 38.10)	36.50 (34.80, 37.40)	Z = –1.47	0.140
Preterm, n (%)			χ^2 = 0.35	0.552
Yes (<37 weeks)	36 (27.27)	39 (24.22)		
No (≥37 weeks)	96 (72.73)	122 (75.78)		
Birth weight (kg), M (Q_1, Q_3)	2.32 (2.14, 2.92)	2.45 (2.14, 2.88)	Z = –0.79	0.431
Sex, n (%)			χ^2 = 1.40	0.238
Female	69 (52.27)	73 (45.34)		
Male	63 (47.73)	88 (54.66)		
Delivery mode, n (%)			χ^2 = 0.01	0.907
Cesarean	55 (41.67)	66 (40.99)		
Vaginal	77 (58.33)	95 (59.01)		
PCT (ng/mL), M (Q_1, Q_3)	1.67 (0.83, 2.41)	8.45 (5.05, 11.05)	Z = –11.44	<0.001
CRP (mg/L), M (Q_1, Q_3)	32.20 (17.55, 73.38)	110.50 (76.30, 145.80)	Z = –11.00	<0.001
WBC ($\times 10^9$/L), M (Q_1, Q_3)	11.30 (9.10, 13.03)	16.30 (10.20, 22.50)	Z = –5.79	<0.001
Hb (g/L), M (Q_1, Q_3)	158.85 (149.47, 170.33)	139.90 (130.70, 150.70)	Z = –10.48	<0.001
PLT ($\times 10^9$/L), M (Q_1, Q_3)	242.00 (203.75, 298.25)	168.00 (124.00, 204.00)	Z = –10.80	<0.001

Z, Mann-Whitney U test; M, median; Q_1, 1st Quartile; Q_3, 3rd Quartile.

were significantly lower in the sepsis group, reflecting pronounced inflammatory activation and hematologic alterations (Table 1).

Univariate Logistic Regression Analysis

In univariate logistic regression analysis, PCT (OR = 3.32, 95% CI: 2.23–4.93, $p < 0.001$) and CRP (OR = 1.03, 95% CI: 1.01–1.05, $p = 0.003$) were significantly associated with an increased risk of neonatal sepsis. PLT count showed a significant inverse association with neonatal sepsis (OR = 0.99, 95% CI: 0.98–1.00, $p = 0.012$), whereas WBC was positively associated with sepsis risk (OR = 1.13, 95% CI: 1.00–1.28, $p = 0.046$). In contrast, Hb level exhibited a negative but non-significant trend (OR = 0.97, 95% CI: 0.93–1.01, $p = 0.134$) (Table 2).

Diagnostic Performance of PCT, CRP, and the Combined Prediction Model

To evaluate the diagnostic performance of PCT and CRP, we compared the sensitivity, specificity, and ROC curves for each individual marker and for their combined model. Using single-marker analysis, PCT identified 138 of 161 septic neonates (sensitivity 85.71%) and accurately classified 105 of 132 controls (specificity 79.55%) (Tables 3,4). CRP showed higher sensitivity, detecting 146 positive cases (sensitivity 90.68%), but had lower specificity (71.97%), indicating enhanced detection capability but limited precision relative to PCT (Tables 3,4).

When combined, the model yielded 133 positive and 123 negative classifications, with a sensitivity of 82.61% (slightly lower than individual markers) but substantially improved specificity (93.18%) and overall diagnostic Acc (87.36%). The PPV and NPV were 93.66% and 81.46%, respectively (Tables 3,4). ROC curve

Table 2. Univariate logistic regression analysis of risk factors for neonatal sepsis.

Variables	β	SE	Wald	p-value	OR (95% CI)
Sex					
Female					1.00 (Reference)
Male	–0.02	0.28	0.005	0.944	0.98 (0.56–1.71)
Preterm					
No (≥37 weeks)					1.00 (Reference)
Yes (<37 weeks)	–0.29	0.28	1.07	0.300	0.75 (0.43–1.31)
Delivery mode					
Vaginal					1.00 (Reference)
Cesarean	0.15	0.27	0.31	0.578	1.16 (0.67–2.02)
GA (weeks)	0.13	0.08	2.64	0.104	1.14 (0.98–1.33)
Birth weight (kg)	–0.05	0.24	0.04	0.836	0.95 (0.59–1.52)
PCT (ng/mL)	1.20	0.20	36.00	<0.001	3.32 (2.23–4.93)
CRP (mg/L)	0.03	0.01	9.00	0.003	1.03 (1.01–1.05)
PLT ($\times 10^9$/L)	–0.01	0.004	6.25	0.012	0.99 (0.98–1.00)
WBC ($\times 10^9$/L)	0.12	0.06	4.00	0.046	1.13 (1.00–1.28)
Hb (g/L)	–0.03	0.02	2.25	0.134	0.97 (0.93–1.01)

GA, gestational age; β, regression coefficien; SE, standard error.

analysis corroborated these findings (Fig. 2): the AUC for PCT was 0.88 (95% CI: 0.85–0.92), for CRP 0.87 (95% CI: 0.84–0.91), and for the combined model 0.94 (95% CI: 0.92–0.97). Pairwise comparison using the DeLong test showed no significant difference between PCT and CRP ($Z = 0.42$, $p = 0.67$), whereas the combined model outperformed both PCT ($Z = 3.85$, $p < 0.001$) and CRP ($Z = 4.12$, $p < 0.001$).

Validation and Visualization of the Combined Model

The model's performance was further evaluated in both the training (n = 205) and validation sets (n = 88) (Table 5). No statistically significant differences were observed between the two cohorts with respect to GA, preterm birth rate, birth weight, sex, delivery mode, or laboratory indices (PCT, CRP, WBC, Hb, PLT) ($p > 0.05$), indicating balanced baseline characteristics. Calibration curves for the training (Fig. 3A) and validation datasets (Fig. 3B) demonstrated close agreement between predicted probabilities and observed outcomes, with Hosmer–Lemeshow p-values of 0.502 and 0.355, respectively, indicating good model calibration across datasets.

DCA revealed that across a broad range of threshold probabilities, the combined model provided greater net clinical benefit than either "treat-all" or "treat-none" strategies in both the training (Fig. 3C) and validation cohorts (Fig. 3D), highlighting its superior clinical applicability. Furthermore, a nomogram incorporating PCT and CRP was constructed (Fig. 3E) to visually represent each marker's contribution to sepsis risk prediction, enabling individualized risk estimation. Individual risk can be estimated by summing cumulative scores, offering clinicians

Table 3. A 2 × 2 contingency table for PCT, CRP, and their combined detection.

Test	Gold standard	Positive	Negative	Total
PCT	Positive	138	27	165
	Negative	23	105	128
	Total	161	132	
CRP	Positive	146	37	183
	Negative	15	95	110
	Total	161	132	
Combined detection	Positive	133	9	142
	Negative	28	123	151
	Total	161	132	

Table 4. Diagnostic performance of PCT, CRP, and their combined detection.

Indicator	AUC	Youden Index	Cut-off	*p*-value	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
PCT	0.88 (0.85–0.92)	0.65	2.52 ng/mL	<0.001	85.71	79.55	82.94	83.64	82.03
CRP	0.87 (0.84–0.91)	0.63	45.45 mg/L	<0.001	90.68	71.97	82.25	79.78	86.36
Combined detection	0.94 (0.92–0.97)	0.76	0.67	<0.001	82.61	93.18	87.36	93.66	81.46

PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

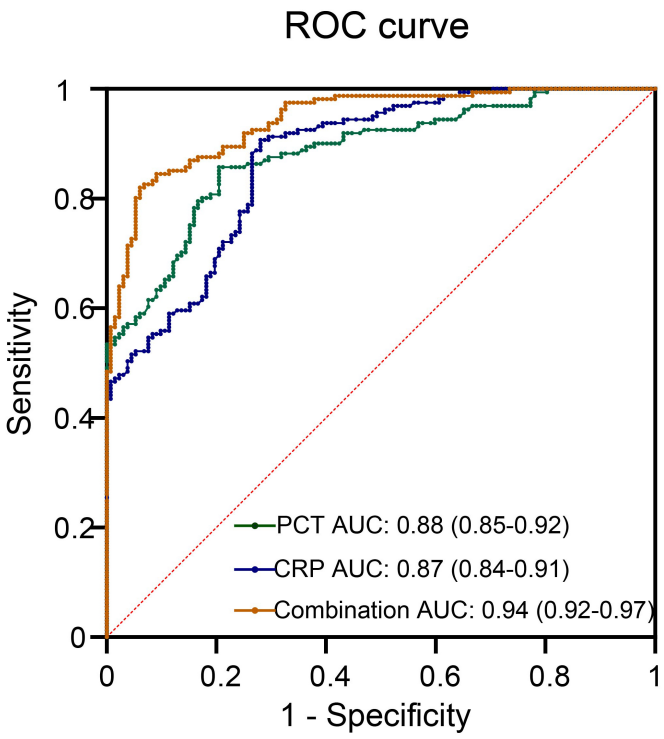

Fig. 2. ROC curves comparing diagnostic performance of PCT, CRP, and their combined detection.

Table 5. Comparison of baseline characteristics and laboratory parameters between the training and validation cohorts.

Variables	Train (n = 205)	Validation (n = 88)	Statistic	*p*-value
Gestational weeks, M (Q_1, Q_3)	36.50 (34.80, 37.80)	36.55 (34.35, 37.73)	Z = –0.50	0.615
Preterm, n (%)			χ^2 = 0.02	0.878
Preterm	53 (25.85)	22 (25.00)		
Term	152 (74.15)	66 (75.00)		
Birth weight (kg), M (Q_1, Q_3)	2.38 (2.14, 2.83)	2.48 (2.14, 3.02)	Z = –1.36	0.174
Sex, n (%)			χ^2 = 0.87	0.352
Female	103 (50.24)	39 (44.32)		
Male	102 (49.76)	49 (55.68)		
Delivery mode, n (%)			χ^2 = 0.75	0.387
Cesarean	88 (42.93)	33 (37.50)		
Vaginal	117 (57.07)	55 (62.50)		
PCT (ng/mL), M (Q_1, Q_3)	4.18 (1.51, 8.88)	5.63 (1.70, 8.86)	Z = –0.82	0.414
CRP (mg/L), M (Q_1, Q_3)	76.90 (34.90, 116.30)	77.75 (30.92, 116.08)	Z = –0.08	0.937
WBC ($\times 10^9$/L), M (Q_1, Q_3)	12.80 (10.00, 17.10)	11.60 (8.88, 15.07)	Z = –1.55	0.121
Hb (g/L), M (Q_1, Q_3)	148.80 (135.90, 158.60)	150.15 (139.97, 158.90)	Z = –0.53	0.598
PLT ($\times 10^9$/L), M (Q_1, Q_3)	200.00 (152.00, 241.00)	201.50 (154.25, 241.50)	Z = –0.62	0.535

a practical tool for personalized risk assessment and facilitating clinical decision-making.

Subgroup Analysis

To evaluate the influence of clinical characteristics on model performance, stratified subgroup analyses were conducted (Fig. 4). For PCT (Fig. 4A), the risk-prediction effect remained consistent across delivery mode, GA, and sex subgroups, with ORs significantly greater than 1 ($p < 0.001$). Interaction tests yielded non-significant outcomes ($p > 0.05$), indicating minimal heterogeneity among subgroups.

For CRP (Fig. 4B), predictive effects were significant in all subgroups ($p < 0.001$). Notably, within the GA subgroup, preterm neonates exhibited a slightly higher risk (OR = 1.07, 95% CI: 1.04–1.10) with a significant interaction ($p = 0.012$), suggesting that GA may modulate the predictive performance of CRP. However, no significant interactions were observed for delivery mode or sex.

In the combined PCT-CRP model (Fig. 4C), strong predictive effects were observed across all subgroups (all OR >5.0, $p < 0.001$), with no significant interaction ($p > 0.05$). These observations confirm that the model provides stable and broadly applicable risk estimation regardless of GA, delivery mode or sex.

Sensitivity Analysis

In a sensitivity analysis restricted to pathogen culture-confirmed positive cases, the overall diagnostic performance for PCT, CRP, and their combined model remained consistent with the findings of the primary analysis based on the composite standard (Table 6). Individually, PCT achieved a sensitivity of 86.00%, a specificity of 79.50%, and an AUC of 0.88 (95% CI: 0.84–0.93). CRP showed slightly higher

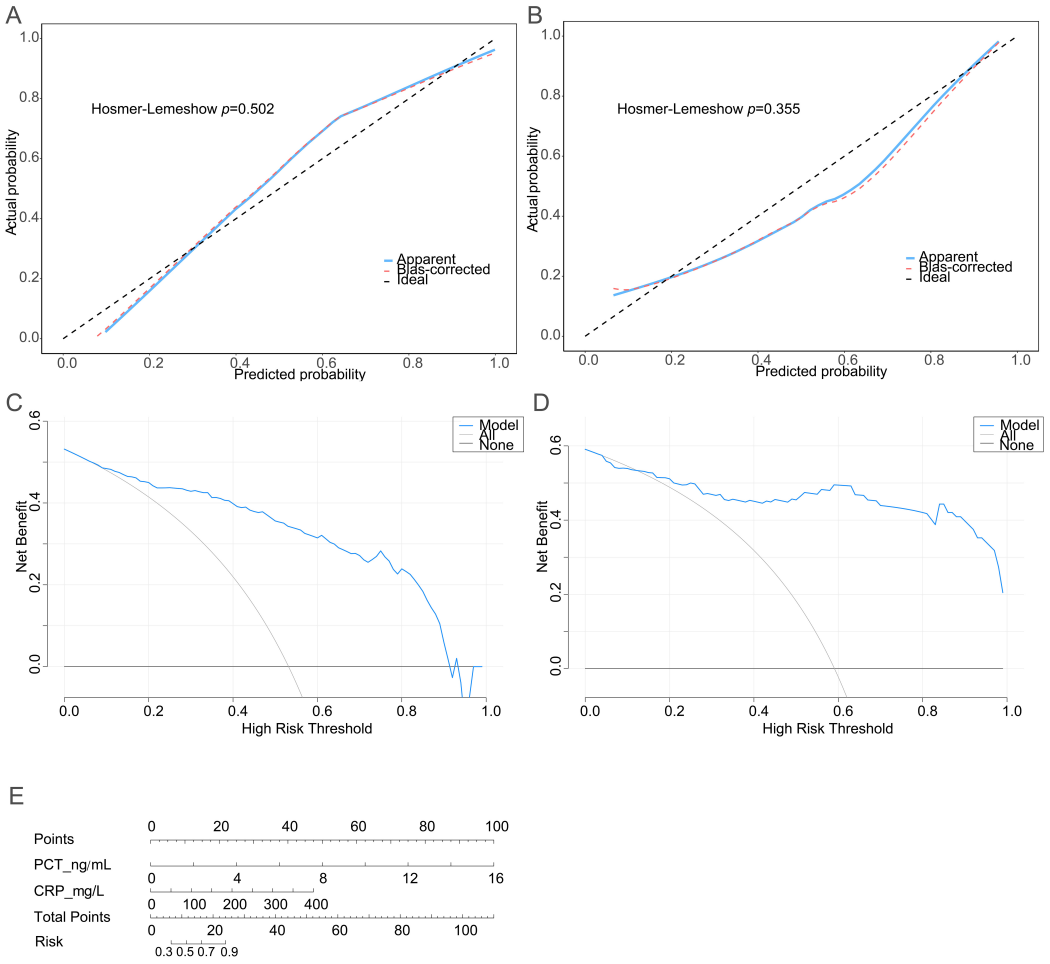

Fig. 3. Internal validation and visualization of the combined prediction model. (A) Training set calibration curve (Hosmer–Lemeshow $p = 0.502$). (B) Validation set calibration curve ($p = 0.355$). (C) DCA for training cohort. (D) DCA for validation cohort. (E) Nomogram for individualized sepsis risk prediction by incorporating PCT and CRP.

sensitivity (89.20%) but reduced specificity (73.50%), yielding an equivalent AUC of 0.88 (95% CI: 0.84–0.92).

The combined model maintained high Se (87.10%) and NPV (90.30%) while significantly improving Sp (84.80%) and overall diagnostic Acc (85.80%), with an AUC of 0.94 (95% CI: 0.91–0.97), surpassing single markers. These results validate the robustness of the primary findings, reinforcing the diagnostic reliability of the combined PCT-CRP detection model in neonates with microbiologically confirmed sepsis.

Discussion

In this study, serum PCT and CRP levels were substantially elevated in neonates with sepsis, and both biomarkers independently predicted sepsis in univariate logistic regression (PCT OR = 3.32; CRP OR = 1.03). When evaluated individually, PCT exhibited a sensitivity of 85.71% and a specificity of 79.55%, whereas CRP achieved higher Se (90.68%) but lower Sp (71.97%). The combined detec-

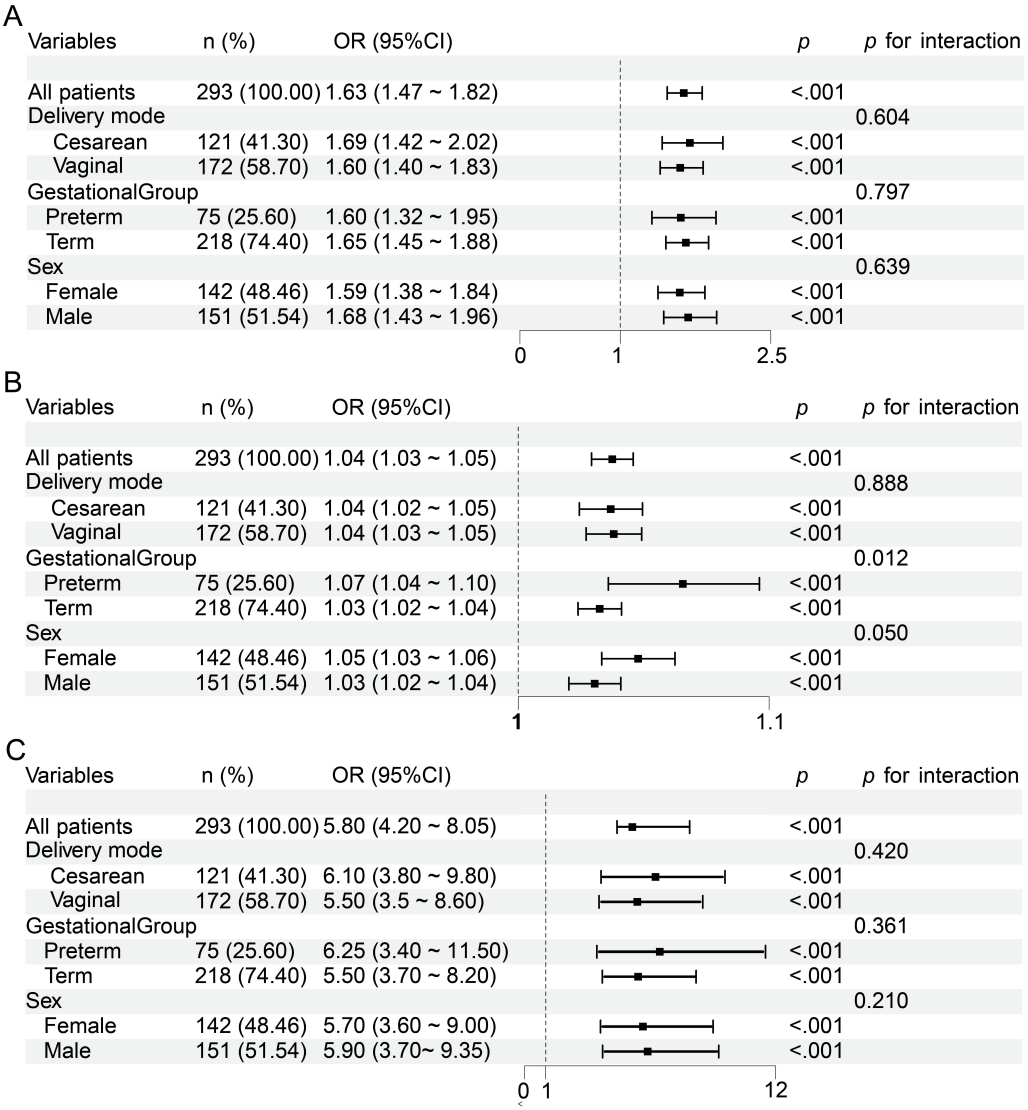

Fig. 4. Forest plots illustrate the risk-prediction effects of PCT, CRP, and their combined detection across clinical subgroups. (A) PCT. (B) CRP. (C) Combined detection.

tion significantly improved diagnostic performance, yielding 93.18% Sp, 87.36% overall Acc, and positive and NPVs of 93.66% and 81.44%, respectively. ROC curve analysis demonstrated AUCs of 0.88 and 0.87 for PCT and CRP, respectively, rising to 0.94 for the combined model, which clearly outperformed either marker alone. Overall, these findings indicate that PCT and CRP are effective diagnostic biomarkers of neonatal sepsis, with the combined use enhancing diagnostic precision through improved sensitivity and specificity.

PCT and CRP differ significantly in their biological roles and temporal dynamics, which influence their diagnostic performance. PCT, the precursor of calcitonin, is normally secreted at minimal levels by thyroid C cells under normal conditions. However, during infection, its production is rapidly upregulated in various tissues (Wang and Yu, 2020), resulting in a sharp increase in serum levels within 2–4 h, peaking at 6–12 h, and then gradually declining (Cantey and Lee, 2021; Celik et

Table 6. Diagnostic performance of PCT, CRP, and their combined detection in culture-confirmed positive sepsis cases.

Indicator	AUC	Youden Index	Cut-off	*p*-value	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
PCT	0.88 (0.84–0.93)	0.66	2.51 ng/mL	<0.001	86.00	79.50	82.20	74.80	89.00
CRP	0.88 (0.84–0.92)	0.62	50.00 mg/L	<0.001	89.20	73.50	80.00	70.30	90.70
Combined detection	0.94 (0.91–0.97)	0.72	0.56	<0.001	87.10	84.80	85.80	80.20	90.30

al, 2022). This rapid kinetics explain PCT's high sensitivity as an early marker of systemic inflammation.

In contrast, CRP is an acute-phase protein synthesized by the liver in response to proinflammatory cytokines, such as interleukin-6 (IL-6). As its secretion depends on upstream signaling, CRP levels increase more slowly, typically begin to rise 8–12 h after infection and peak at 24–48 h (Cantey and Lee, 2021; Hofer et al, 2012; Pepys and Hirschfield, 2003), making CRP more effective for monitoring the mid-to-late-phase inflammatory response.

In our study, both PCT and CRP were significantly elevated among septic neonates, reflecting a pronounced systemic inflammatory state. Research evidence has shown that single-point measurements of CRP or PCT can be influenced by non-infectious factors, including fetal distress or delivery-related stress, limiting their diagnostic reliability when used alone (Eichberger et al, 2022). Therefore, combining these biomarkers with clinical assessment, additional laboratory indicators, or serial monitoring is recommended to improve diagnostic accuracy. Our findings support this perspective: although CRP increases later than PCT, their combined evaluation compensates for temporal differences and enhances overall diagnostic performance among septic neonates.

A meta-analysis reported that PCT had higher sensitivity than CRP in sepsis diagnosis (0.85 vs. 0.71), while their combined PCT-CRP detection model further enhanced diagnostic accuracy, achieving a sensitivity of 0.91 and an AUC of approximately 0.96 (Ruan et al, 2018). The findings further suggested optimal diagnostic thresholds of 0.5–2.0 ng/mL for PCT and >10 mg/L for CRP to yield an appropriate balance between sensitivity and specificity. In our study, CRP demonstrated even higher sensitivity (90.68%) than that reported in this meta-analysis, which may be due to differences in sampling time, infection definitions, and threshold values. Similarly, another study observed that a PCT threshold of 2.5 ng/mL showed excellent diagnostic performance, with 90.9% sensitivity and 94.4% specificity, exceeding CRP detected at 21 mg/L (63.6% sensitivity, 93.3% specificity) (Ngo and Nguyen, 2020). These results suggest that using higher PCT cut-offs may optimize diagnostic performance and reduce false-positive findings in neonatal sepsis.

Neonates exhibit unique physiological characteristics, as both CRP and PCT undergo postnatal physiological elevation, a phenomenon often referred to as "physiological inflammatory response", necessitating biomarker interpretation in the con-

text of age-specific baseline levels and the timing of symptom onset (Cao et al, 2024; Srinivasan et al, 2023). This pattern was evident in our subgroup analyses, where CRP levels varied by GA, with preterm infants generally exhibiting lower baseline CRP levels than term infants. Additionally, several non-infectious perinatal factors, such as meconium aspiration and surfactant therapy, can further elevate CRP levels, highlighting the significance of GA-specific interpretation (Hofer et al, 2011; Strunk et al, 2012). In our dataset, CRP showed a stronger association with sepsis in preterm neonates, suggesting that GA may affect its diagnostic performance. Although both PCT and CRP levels increase in response to infection-driven inflammation, PCT shows more rapid and specific response, whereas CRP is more easily affected by non-infectious stimuli. Therefore, their combined assessment provides a more comprehensive reflection of the underlying biological changes in neonatal sepsis, improving both early detection and dynamic monitoring (Hisamuddin et al, 2015; Park et al, 2014).

Subgroup analyses demonstrated that the predictive performance of PCT and CRP remained generally stable across different clinical strata, except that CRP exhibited a slightly greater rise in risk per unit among preterm neonates. The interaction between the two biomarkers was modest, indicating that the combined PCT-CRP model retains greater applicability across diverse neonatal subgroups. Overall, although previous national and international studies have reported some variation in specific findings, most consistently recognize PCT and CRP as effective early biomarkers of infection. Notably, CRP has been observed to outperform PCT in particular contexts, for instance, Shravya et al (2025) reported a higher AUC (0.811) for CRP in neonatal intensive care unit (NICU) patients, likely due to differences in study populations or assay methodology. In the present study, the AUCs for PCT and CRP were 0.88 and 0.87, respectively, which are within a higher range reported previously. These observations support the complementary diagnostic significance of combining both biomarkers to minimize the individual limitations of single-marker assessment.

The model exhibited robust calibration in both the training and validation cohorts, indicating close agreement between predicted probabilities and observed outcomes. DCA further demonstrated that, across a wide range of threshold probabilities, the combined PCT–CRP model provided a greater net clinical benefit than either the “treat-all” or “treat-none” strategies. By integrating PCT and CRP into a combined predictive model, clinicians can achieve a more optimal balance between sensitivity and specificity, thereby reducing unnecessary antibiotic exposure while maintaining early identification of high-risk neonates. Notably, the high specificity (93.18%) and PPV of the model highlight its ability to effectively exclude uninfected neonates, thereby avoiding overtreatment. In summary, integrating these two readily available biomarkers enhances diagnostic accuracy and clinical feasibility, providing a valuable tool for rapid clinical assessment of sepsis risk.

Despite promising outcomes, several limitations should be acknowledged in this study. First, this was a single-center retrospective study with a limited sample size, which may introduce selection bias. Second, lacking external validation in independent cohorts limits the generalizability of the model, warranting multicen-

ter studies to validate its robustness. Third, early-onset and late-onset sepsis were not analyzed separately, although these two differ in their pathophysiology and may require optimal diagnostic thresholds. Fourth, additional potential biomarkers, such as presepsin or inflammatory cytokines, were not incorporated into the present model. Maternal intrapartum antibiotic exposure may affect neonatal blood culture results and the levels of inflammatory markers. Although efforts were made to reduce this bias by collecting index samples before neonatal antibiotic administration and performing sensitivity analyses restricted to culture-confirmed sepsis, residual confounding cannot be entirely excluded. Future studies should aim to validate these observations in larger, prospective, multicenter cohorts, refine threshold settings, and incorporate a broader range of biomarkers, further enhancing the reliability and clinical applicability of the model.

Conclusion

This study demonstrates that combined serum PCT and CRP measurement provides significant diagnostic value for neonatal sepsis. Each biomarker independently reflects the inflammatory response, while their joint analysis substantially improves specificity and overall diagnostic accuracy. The resulting predictive model exhibits robust diagnostic performance and potential clinical utility, offering a practical approach for early sepsis identification and antibiotic decision-making. Further larger, prospective studies are warranted to validate and optimize the model for integration into routine clinical care.

Key Points

- Neonatal sepsis remains a major clinical challenge, emphasizing the significance of early and accurate diagnosis in improving clinical outcomes.
- PCT and CRP demonstrated significant diagnostic value, with PCT showing higher specificity and CRP showing higher sensitivity.
- Combined detection of PCT and CRP yielded superior diagnostic performance, achieving higher AUC, specificity, and overall accuracy compared to either marker alone.
- The logistic regression–based combined predictive model exhibited good calibration and clinical utility, supported by DCA and nomogram visualization.
- Subgroup and sensitivity analyses confirmed the robustness and broader applicability of the combined predictive model across different clinical contexts.

Abbreviations

PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; EDTA-K2, ethylene diamine tetraacetic acid K2; CBC, complete blood count; ECLIA, electrochemiluminescence immunoassay; CLIA,

chemiluminescence immunoassay; MALDI-TOF, Matrix-Assisted Laser Desorption/Ionization–Time of Flight; LIS, laboratory information system; ROC, receiver operating characteristic; AUC, area under the curve; Se, sensitivity; Sp, specificity; Acc, accuracy; PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio; CI, confidence interval; DCA, decision curve analysis; GA, gestational age; IL-6, interleukin-6; NICU, neonatal intensive care unit.

Availability of Data and Materials

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

Author Contributions

QBC performed data analysis and drafted the manuscript. JDC contributed to data acquisition and analysis. RHZ was involved in study design. All authors revised it critically for important intellectual content. All authors have made significant contributions to the work, approved the final version, and agreed to be accountable for its integrity.

Ethics Approval and Consent to Participate

The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Longyan First Hospital Affiliated to Fujian Medical University (Approval Number: LYREC2025-k179-01). As this study was based on retrospective and existing medical records and routine laboratory test results, no prospective interventions or additional procedures were involved. All data were anonymized to ensure confidentiality, and no extra biological samples were collected. Ethical approval was obtained, and the requirement for written informed consent was waived.

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Conflict of Interest

The authors declare no conflict of interest.

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