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C-reactive protein to platelet ratio as an early biomarker in differentiating neonatal late-onset sepsis in neonates with pneumonia

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Neonates with pneumonia (NWP) may experience unidentified life-threatening sepsis, yet distinguishing NWP from neonates with sepsis (NWS) based solely on clinical presentation remains challenging. This study aimed to evaluate the diagnostic utility of the C-reactive protein to platelet ratio (CPR) in distinguishing neonatal late-onset sepsis (LOS) among NWPs. From February 2016 to March 2022, a total of 1385 NWPs aged over 3 days were included. Of these, 174 neonates with confirmed positive blood cultures were categorized into the sepsis cohort, while the remainder formed the pneumonia cohort. All clinical data were retrospectively extracted from electronic medical records. CPR was calculated as the ratio of C-reactive protein levels to platelet count. Independent risk factors (IRFs) for neonatal LOS were identified through multivariate logistic regression. The diagnostic performance of CPR in identifying LOS among NWPs was analyzed using receiver operating characteristic (ROC) curve metrics. Statistical analyses were conducted using SPSS version 24.0 and MedCalc version 15.2.2. Neonates with NWS demonstrated significantly higher CPR compared to those with NWP alone. Further analysis revealed a notably increased incidence of sepsis among neonates exhibiting elevated CPR levels relative to those with lower values. Correlation analysis identified a direct association between CPR and elevated procalcitonin, creatinine, and urea nitrogen levels, as well as prolonged hospitalization. Multiple logistic regression analysis identified CPR as an IRF for late-onset NWS. ROC curve analysis demonstrated that CPR outperformed CRP and platelet count individually in diagnosing NWS, with a diagnostic sensitivity of 54% and specificity of 85%. CPR serves as an effective initial diagnostic marker with superior accuracy in distinguishing delayed NWS from NWP compared to CRP and platelet count alone.

Keywords C-reactive protein to platelet ratio, Neonate, Late-onset sepsis, Pneumonia

Abbreviations

NWP	Neonates with pneumonia
NWS	Neonates with sepsis
CPR	C-reactive protein to platelet ratio
LOS	Late-onset sepsis
IRFs	Independent risk factors
ROC	Receiver operating characteristic
CRP	C-reactive protein
PLTs	Platelets
SIRS	Systemic inflammatory response syndrome
SBP	Systolic blood pressure
DBP	Diastolic blood pressure

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ALT	Aminotransferase
AST	Aspartate aminotransferase
CREA	Creatinine
UREA	Urea nitrogen
PCT	Procalcitonin
WBC	White blood cells
AUC	Area under the receiver operating characteristic curve

Compared to adults, neonates are more susceptible to infections by pathogenic microbes, often resulting in respiratory illnesses or bloodstream infections due to their underdeveloped immune systems[1]. Neonates with sepsis (NWS) poses a substantial threat to infant health, ranking as the third leading cause of neonatal mortality globally and accounting for 13% of total neonatal deaths[2–4]. Additionally, cases of neonates with pneumonia (NWP) may involve undiagnosed sepsis, and the absence of timely interventions aligned with the Surviving Sepsis Campaign Physician's guidelines could impede the efficacy of standardized treatment plans[5]. Differentiating between NWP and NWS remains challenging, as both conditions frequently present overlapping clinical features[6]. Furthermore, while blood culture is the diagnostic gold standard for NWS, it is time-intensive and demonstrates low sensitivity[7]. This highlights the need for more efficient and reliable biomarkers to facilitate the early detection of sepsis in neonates.

An acute-phase reactant, C-reactive protein (CRP), undergoes significant elevation during inflammatory processes within the body[8]. Extensive research has demonstrated strong associations between CRP levels and systemic inflammation[9–11]. Recognized as one of the most studied and clinically relevant biomarkers, CRP plays a key role in the early detection of sepsis, serving as a reliable prognostic indicator and a determinant of adverse outcomes in septic patients[12,13]. Moreover, CRP exhibits superior screening accuracy for late-onset NWS compared to early-onset sepsis, further establishing its diagnostic utility[14]. Platelets (PLTs), essential cellular components in the bloodstream, are integrally involved in hemostatic disruption and immunoinflammatory processes during sepsis. Enriched with pro-inflammatory cytokines, PLTs release highly reactive particles and interact with endothelial cells, contributing to microthrombus formation and subsequent organ dysfunction[15–18]. Clinical evidence indicates a frequent correlation between sepsis and thrombocytopenia in both adult and neonatal populations[19–21]. The C-reactive protein to platelet ratio (CPR) has emerged as a novel indicator reflecting both inflammatory and coagulation states. However, its clinical applicability in differentiating neonatal late-onset sepsis (LOS) from NWP remains insufficiently defined. This study aims to evaluate the diagnostic potential of CPR in distinguishing sepsis from pneumonia in neonates.

Methodologies and materials

Study design and population

This retrospective single-center observational study, conducted at Henan Children's Hospital, China, from February 2016 to March 2022, focused on hospitalized NWPs aged 3–28 days admitted through the emergency department. Inclusion criteria were strictly applied, excluding neonates with hematological disorders, malignancies, major congenital anomalies, or incomplete data on body temperature, CRP levels, and PLT counts at admission. Premature neonates (gestational age < 37 weeks) were also excluded. The study adhered to the ethical principles outlined in the Declaration of Helsinki and received approval from the Hospital Ethics Review Board of Henan Children's Hospital (No. 2024-009). Data collection was retrospective, with strict anonymization protocols ensuring confidentiality. Due to the study's retrospective design, the requirement for informed consent was waived, as confirmed by the Hospital Ethics Review Board of Henan Children's Hospital (No. 2024-009).

Clinical definitions

The neonates included in this study all met the diagnostic criteria for neonatal pneumonia[22] and determined independently by two physicians based on patients' medical history, clinical manifestations, and laboratory findings. Key factors evaluated included high-risk conditions for NWP, prior contact with infected individuals, irregular body temperature, cough, respiratory distress, snoring, deviations in peripheral blood immune cells, and inflammatory markers. Additionally, chest X-rays were utilized to detect pulmonary infiltrates, a characteristic feature in NWP cases. Neonatal LOS was defined by the presence of a positive blood culture alongside systemic inflammatory response syndrome (SIRS), occurring beyond 72 h post-birth. SIRS diagnosis necessitated meeting at least two of four criteria, one of which was an abnormal temperature or leukocyte count: (1) temperature deviation (> 38.5 °C or < 36 °C), (2) leukocyte abnormalities, (3) tachycardia or bradycardia, and (4) irregular respiratory rate. The criteria were established following the International Pediatric Sepsis Consensus[23].

Data collection and laboratory evaluation

The study analyzed clinical and laboratory data extracted from patients' electronic medical records during hospitalization. Key parameters recorded included age, sex, body weight, body temperature, respiratory and heart rates, systolic blood pressure (SBP), diastolic blood pressure (DBP), length of hospital stay, and levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (CREA), urea nitrogen (UREA), procalcitonin (PCT), and CRP. Additional hematological measures included white blood cells (WBC) count, neutrophil count, lymphocyte count, and PLT count. ALT, AST, CREA, and UREA levels were quantified using standard clinical methods on a Beckman automatic biochemical analyzer (Beckman Coulter, Brea, CA, USA). PCT concentrations were determined via electrochemiluminescence on the Elecsys® BRAHMS PCT platform, with a detection range of 0.02–100 ng/mL (Roche Diagnostics, Rotkreuz, Switzerland). CRP levels were measured through a latex-enhanced immunoturbidimetric assay with a range of 0.08–320 mg/L (Ultrasensitive

CRP kit; Upper Bio-Tech, Shanghai, China). Hematological parameters, including neutrophils, lymphocytes, and PLTs, were evaluated using a Sysmex automated CBC analyzer (Sysmex Corporation, Japan). To address assay detection limits, PCT concentrations exceeding 100 ng/mL or below 0.02 ng/mL were assigned values of 101 ng/mL and 0.01 ng/mL, respectively, while CRP levels under 0.8 mg/L were recorded as 0.7 mg/L. The CPR was calculated as the ratio of CRP (mg/L) to PLT count ($\times 10^8$ cells/L).

Statistical analysis

Data with normal distributions were expressed as means ± standard deviations and analyzed using independent t-tests or one-way ANOVA, while non-normally distributed variables were presented as medians (interquartile range) and evaluated through the Mann–Whitney U test. Categorical data were described as frequencies and percentages and analyzed via chi-square tests. Spearman's correlation coefficient was applied to determine associations between CPR and other continuous variables. To evaluate CPR's potential as an early diagnostic marker for distinguishing sepsis from pneumonia, univariate and multivariate logistic regression models were constructed. Variables demonstrating statistical significance ($P < 0.05$) in univariate analyses were included in multivariate binary logistic regression. ROC curves were generated to evaluate CPR's diagnostic performance in identifying sepsis within NWP, with the area under the ROC curve (AUC) calculated and compared using the DeLong test. The optimal CPR cutoff point was determined based on Youden's index (sensitivity + specificity − 1)[24]. Statistical analyses were conducted with SPSS (Version 24.0, SPSS Inc., Chicago, IL, USA, URL: https://www.ibm.com/support/pages/downloading-ibm-spss-statistics-24) and MedCalc (Version 15.2.2, MedCalc Software, Mariakerke, Belgium, URL: https://www.medcalc.org). Statistical significance was defined as a two-tailed P value of < 0.05.

Results

Study population characteristics

The study included 1385 NWPs who met the defined inclusion criteria (Fig. 1). Of these, 174 neonates (12.6%) with positive blood cultures were diagnosed with sepsis and allocated to the sepsis cohort, while the remaining 1211 (87.4%) neonates without sepsis were assigned to the pneumonia cohort. Table 1 outlined the baseline characteristics of the participants. Compared with NWP alone, NWS demonstrated reduced gestational age, body weight, SBP, and DBP, alongside an increased frequency of mechanical ventilation ($P < 0.01$). Biochemical and CBC analyses indicated significantly higher levels of PCT, CRP, CREA, UREA, WBC, and neutrophil counts in NWS ($P < 0.05$), whereas lymphocyte and PLT counts were notably lower ($P < 0.001$). Additionally, CPR levels in NWS were significantly elevated compared with NWP alone ($P < 0.001$).

Association between CPR levels and the occurrence of NWS

Neonates were stratified into two cohorts based on the median CPR value. The high CPR cohort demonstrated greater age and elevated PCT levels compared to the low CPR cohort (Table 2). Analysis indicated a significantly

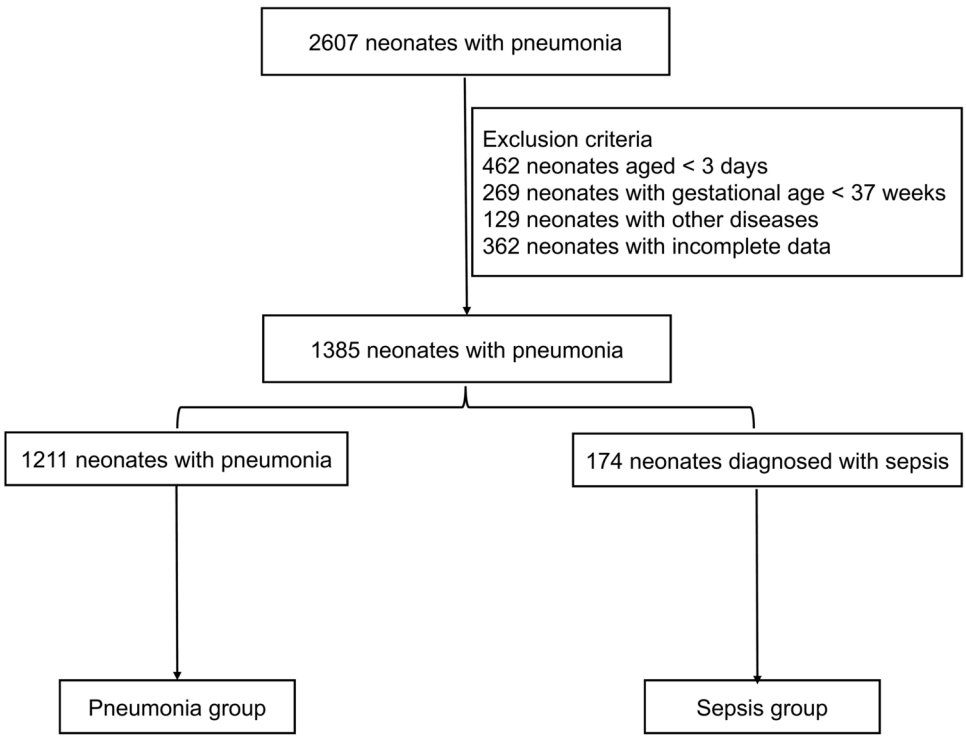

Fig. 1. Flow chart of the follow-up.

Variables	Pneumonia (n = 1211)	Sepsis (n = 174)	P
Age (days)	12.0 (7.0, 20.0)	12.0 (8.0, 16.0)	0.632
Gestational age (weeks)	39.3 ± 1.2	38.1 ± 1.0	**< 0.001**
Male, n (%)	717 (59.2%)	100 (57.5%)	0.663
Weight (kg)	3.3 ± 0.6	2.9 ± 0.9	**< 0.001**
Temperature (℃)	37.0 ± 0.5	37.1 ± 0.9	0.108
Respiratory (rate/min)	51.0 ± 10.6	51.6 ± 12.1	0.537
Respiratory rate > 60 rate/min, n (%)	206 (17.0%)	37 (21.3%)	0.168
Heart rate (bpm)	148.0 ± 16.0	150.9 ± 21.6	0.085
SBP (mm Hg)	77.1 ± 8.0	74.7 ± 10.9	**0.005**
DBP (mm Hg)	46.9 ± 7.8	44.5 ± 9.4	**0.001**
Biochemical parameters			
PCT (ng/ml)	0.11 (0.08, 0.16)	0.46 (0.14, 7.36)	**< 0.001**
CRP (mg/L)	0.7 (0.7, 0.7)	0.7 (0.7, 28.1)	**< 0.001**
ALT (U/L)	27.9 (21.3, 36.7)	25.2 (19.2, 38.0)	0.207
AST (U/L)	35.0 (27.6, 44.9)	34.8 (27.8, 48.2)	0.527
CREA	41.6 (32.3, 51.4)	47.1 (36.4, 73.1)	**< 0.001**
UREA	2.5 (1.6, 3.6)	3.7 (2.6, 5.4)	**< 0.001**
WBC (10^6 cells/L)	9.7 (7.8, 11.9)	10.6 (7.5, 14.9)	**0.016**
Neutrophils (10^6 cells/L)	3.8 (2.7, 5.4)	5.7 (3.3, 9.1)	**< 0.001**
Lymphocytes (10^6 cells/L)	4.3 (3.3, 5.5)	3.2 (1.9, 4.7)	**< 0.001**
PLT (10^9 cells/L)	330.1 (254.0, 410.0)	234.5 (98.0, 360.7)	**< 0.001**
CPR (mg/10^8 cells)	0.02 (0.02, 0.03)	0.07 (0.02, 2.01)	**< 0.001**
Mechanical ventilation, n (%)	304 (25.1%)	61 (35.1%)	**0.005**
Length of hospital stay (days)	9.0 (8.0, 12.0)	17.0 (13.0, 26.0)	**< 0.001**

Table 1. Basic characteristics of study subjects by groups. Significant values are in bold. *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PCT* procalcitonin, *CRP* C-reactive protein, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CREA* creatinine, *UREA* urea nitrogen, *WBC* White blood cells, *PLT* Platelet, *CPR* C-reactive protein to platelet ratio.

Variables	Low CPR group (≤ 0.024) (n = 694)	High CPR group (> 0.024) (n = 691)	P
Age (days)	13.0 (9.0, 21.0)	10.0 (6.0, 17.0)	**< 0.001**
Male, n (%)	392 (56.5%)	425 (61.5%)	0.057
PCT (mg/L)	0.10 (0.07, 0.14)	0.15 (0.09, 0.32)	**< 0.001**
Clinical data			
Pneumonia, n (%)	648 (93.4%)	563 (81.5%)	**< 0.001**
Sepsis, n (%)	46 (6.6%)	128 (18.5%)	**< 0.001**
Length of hospital stay (days)	9.0 (8.0, 12.0)	11.0 (8.0, 17.0)	**< 0.001**

Table 2. Clinical and demographic characteristics according to the median of CPR. Significant values are in bold. *PCT* procalcitonin, *CPR* C-reactive protein to platelet ratio.

higher incidence of sepsis in the high CPR cohort compared to the low CPR cohort (18.5% vs. 6.6%, $P < 0.001$), accompanied by a markedly lower incidence of pneumonia (81.5% vs. 93.4%, $P < 0.001$).

Association between CPR and clinical parameters

Spearman's correlation analysis identified significant associations between CPR and various clinical parameters, as shown in Table 3. CPR exhibited inverse correlations with age ($r = -0.204$, $P < 0.001$), body weight ($r = -0.151$, $P < 0.001$), SBP ($r = -0.133$, $P < 0.001$), DBP ($r = -0.083$, $P = 0.002$), and lymphocyte count ($r = -0.388$, $P < 0.001$). Positive correlations were observed with PCT ($r = 0.371$, $P < 0.001$), CREA ($r = 0.209$, $P < 0.001$), UREA ($r = 0.067$, $P = 0.013$), neutrophil count ($r = 0.135$, $P < 0.001$), and hospitalization duration ($r = 0.188$, $P < 0.001$). No significant correlations were detected between CPR and body temperature, heart rate, ALT, or AST levels.

Independence of CPR levels in identifying NWS

Variables with $P < 0.05$ identified in the univariate analysis included body temperature, heart rate, SBP, DBP, PCT, ALT, AST, CREA, UREA, neutrophil count, lymphocyte count, and mechanical ventilation. Following adjustments for these factors, multivariate analysis revealed that CPR remained an independent predictor of NWS

Variables	Overall population	
	r	P
Age (day)	−0.204	**<0.001**
Weight (kg)	−0.151	**<0.001**
Temperature (℃)	0.007	0.796
Respiratory (rate/min)	0.043	0.113
Heart rate (bpm)	−0.024	0.375
SBP	−0.133	**<0.001**
DBP	−0.083	**0.002**
PCT (ng/L)	0.371	**<0.001**
ALT (U/L)	−0.047	0.082
AST (U/L)	−0.003	0.898
CREA	0.209	**<0.001**
UREA	0.067	**0.013**
Neutrophils	0.135	**<0.001**
Lymphocytes	−0.388	**<0.001**
Length of hospital stay (days)	0.188	**<0.001**

Table 3. Correlations between CPR and clinical parameters. Significant values are in bold. *CPR* C-reactive protein to platelet ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PCT* procalcitonin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CREA* creatinine, *UREA* urea nitrogen.

Variables	Univariate		Multivariate*	
	OR (95% CI)	P	OR (95% CI)	P
Presence of sepsis				
CPR	2.194 (1.730–2.782)	**<0.001**	1.555 (1.237–1.954)	**<0.001**
CPR group				
Low CPR group	1		1	
High CPR group	3.203 (2.245–4.569)	**<0.001**	1.764 (1.166–2.669)	**0.007**

Table 4. Predictive value of CPR for sepsis in neonates with pneumonia. Significant values are in bold. *Adjusted for body temperature, heart rate, SBP, DBP, PCT, ALT, AST, CREA, UREA, neutrophils, lymphocytes and mechanical ventilation. *CPR* C-reactive protein ratio to platelet, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PCT* procalcitonin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CREA* creatinine, *UREA* urea nitrogen.

in NWP (odds ratio [OR] = 1.555, 95% confidence interval [CI] 1.237–1.954, P < 0.001; Table 4). Additionally, CPR tertiles demonstrated an independent association with an increased likelihood of NWS (OR = 1.764, 95% CI 1.166–2.669, P = 0.007).

Diagnostic value of CPR in NWS

ROC curve analysis was performed to assess the diagnostic efficacy of CPR in differentiating sepsis from pneumonia in neonates. Figure 2 illustrated that the AUC for CPR demonstrated strong diagnostic performance in identifying NWS (AUC = 0.73, 95% CI 0.68–0.78, P < 0.001), exceeding the performance of CRP (AUC = 0.68, 95% CI 0.63–0.73, P < 0.001) and PLT count (AUC = 0.67, 95% CI 0.62–0.72, P < 0.001) (P < 0.05). The optimal CPR threshold for predicting NWS was determined to be 0.054, providing 54% sensitivity and 85% specificity. Based on this threshold, neonates were stratified into two groups: CPR ≤ 0.054 and CPR > 0.054. Table 5 indicated that the CPR ≤ 0.054 cohort comprised 1027 (92.8%) NWP and 80 (7.2%) NWS cases, whereas the prevalence of NWS in the CPR > 0.054 cohort was significantly higher compared to the CPR ≤ 0.054 group (33.8% vs 7.2%, P < 0.001).

Discussion

Neonates are particularly vulnerable to infections due to the immaturity of their physiological systems, with various pathogens capable of inducing NWP[1] upon lung invasion. Without timely intervention, NWP may progress to NWS[25], characterized by systemic inflammation and multi-organ dysfunction, which significantly impairs neonatal health. NWS remains a leading cause of neonatal mortality and long-term disability, posing a critical global public health challenge[26]. According to the Global Sepsis Alliance, infection-related sepsis accounts for approximately 20% of neonatal deaths globally[27] with sepsis-associated mortality rising to 37.2% during the late neonatal period (7–27 days)[28]. Early detection of NWS is essential to enable timely intervention,

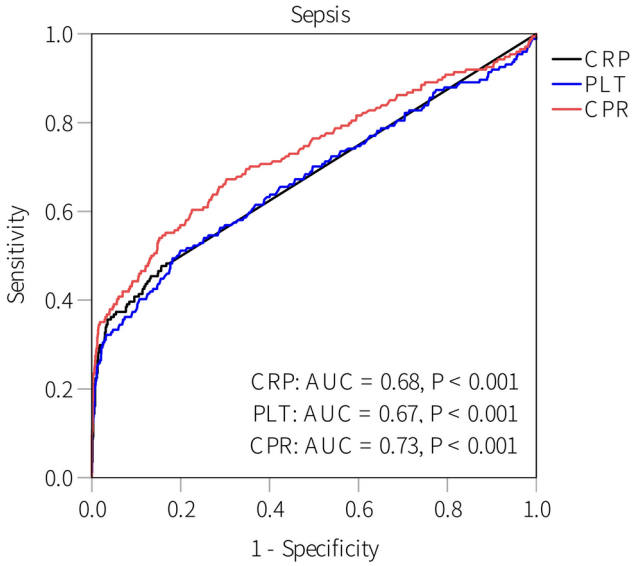

Fig. 2. ROC curve of the CRP, PLT count, and CPR in predicting neonatal sepsis.

effective treatment, prevention of severe complications, and reduction of mortality[5]. Blood culture, recognized as the diagnostic gold standard for NWS, is hindered by limitations such as prolonged processing times, low positivity rates due to small blood sample volumes, potential contamination, or prior antibiotic use before hospitalization[7,29,30]. In contrast, peripheral blood circulation markers offer a more accessible and cost-effective alternative for diagnosis.

From a pathophysiological standpoint, sepsis is characterized as a systemic hypermetabolic inflammatory condition, with inflammatory cells and cytokines playing a central role in its progression[31,32]. Among these

Variables	CPR ≤ 0.054 (n = 1107)	CPR > 0.054 (n = 278)	P
Control, n (%)	1027 (92.8%)	184 (66.2%)	**< 0.001**
Sepsis, n (%)	80 (7.2%)	94 (33.8%)	**< 0.001**

Table 5. Distribution of neonates with/without sepsis based on the optimal cutoff point of CPR. Significant values are in bold. *CPR* C-reactive protein to platelet ratio.

cytokines, CRP serves as a traditional biomarker that demonstrates significant elevation in response to inflammation, particularly during bacterial infections[33]. In the context of sepsis, CRP has been extensively validated as a prognostic marker and a contributing factor in both adult and neonatal sepsis[13,34,35]. However, its specificity is limited by physiological elevations following birth and increases linked to non-infectious conditions[36,37]. PLTs, specialized blood components essential for hemostasis and thrombosis[38], have emerged as key players in immune regulation. They are now recognized for their capacity to activate other immune cells and promote the generation of coagulation factors and inflammatory cytokines[39–41]. Research indicates a strong association between PLTs and sepsis, with thrombocytopenia commonly observed in affected patients[42–44].

Recent studies have explored biomarker ratios, including the neutrophil-to-lymphocyte ratio, CRP-to-albumin ratio, and PCT-to-albumin ratio[45–51], for their diagnostic and prognostic relevance in sepsis. Our prior research identified CPR as clinically significant in diagnosing sepsis-related conditions among neonates with suspected sepsis[52]. However, limited data exist regarding the diagnostic value of CPR in distinguishing neonatal LOS (positive blood culture) in NWP. CPR, calculated as the ratio of CRP to PLT count, reflects both inflammatory and coagulation dynamics. This study evaluated the diagnostic efficacy of CPR in differentiating neonatal LOS in NWP. Consistent with earlier findings[53], elevated CPR levels were observed in NWS compared to pneumonia cases, and higher CPR values correlated with prolonged hospital stays. Multivariate analysis identified CPR as an independent risk factor for sepsis detection in NWP, while ROC curve analysis demonstrated that CPR surpassed CRP levels and PLT count individually in differentiating NWS from NWP. However, CPR's diagnostic accuracy remains moderate, necessitating cautious interpretation. CRP values below the threshold do not exclude NWS, and neonates with elevated CPR require further diagnostic evaluation to confirm sepsis.

This study demonstrates that elevated CPR is associated with a heightened risk of NWS, offering potential for improving clinical decision-making and optimizing resource allocation in neonatal care. This study highlights the relevance of CPR as a biomarker for distinguishing between NWS and NWP, suggesting its incorporation into existing clinical workflows to enable earlier and more precise diagnoses. Prioritizing CPR assessment in neonates at risk may strengthen the ability to initiate timely interventions, a critical factor in mitigating severe morbidity and mortality associated with diagnostic delays.

This study has several limitations that require acknowledgment. First, as a single-center retrospective observational analysis, the generalizability of the results may be limited, highlighting the need for confirmation through multicenter studies. Second, the relatively small cohort of newborns diagnosed with LOS suggests that future research involving larger sample sizes is essential to derive more robust and reliable conclusions. Lastly, CPR measurements are restricted to admission values; longitudinal monitoring of CPR levels throughout disease progression could provide valuable insights into its diagnostic relevance for distinguishing sepsis from pneumonia in neonates.

Conclusions

This study demonstrates the potential of CPR as a diagnostic marker for distinguishing sepsis from pneumonia in neonates. Results indicate that CPR offers superior diagnostic accuracy compared to CRP or platelet count individually in differentiating NWS from NWP.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Received: 6 December 2024; Accepted: 17 March 2025
Published online: 28 March 2025

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Acknowledgements
We express our gratitude to Bullet Edits Limited for their editorial assistance and manuscript revision services.

Author contributions
Xiaojuan Li and Tiewei Li were responsible for project design and administration, manuscript writing, and funding acquisition. Fatao Lin, Ci Li, and Qingdao Bai contributed to data collection and statistical analysis. Tiewei Li, Hui Fu and Zhipeng Jin provided overall guidance and managed the project. All authors reviewed the manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (82200097), the Key Research, Development, and Promotion Projects of Henan Province (252102310054 and 232102310122), and the Medical Science and Technology Project of Henan Province (LHGJ20220774).

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
The investigation was executed per the standards of the Declaration of Helsinki, and it was approved by the Hospital Ethics Review Board of Henan Children's Hospital (No. 2024-009). The research ensures that participant identities and associated information remain anonymous and protected. Informed consent was waived due to its retrospective nature along with the institution name by which it has been waived.

Additional information
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