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Assessment of the diagnostic significance of pentraxin-3 in conjunction with procalcitonin (PCT) and C-reactive protein (CRP) for neonatal sepsis

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Abstract

Objective This study aimed to compare serum levels of pentraxin-3 (PTX-3) in neonates with sepsis against those without sepsis and to assess the diagnostic value of PTX-3 in relation to conventional inflammatory markers.

Methods Between June and December 2020, a total of 109 neonates aged 1 to 21 days, with birth weights ranging from 1795 g to 4200 g, and who met the diagnostic criteria outlined in the "Expert Consensus on the Diagnosis and Treatment of Neonatal Sepsis" (2019) were examined in this prospective study, including 35 with sepsis, 36 with localized infections, and 38 without any infections. Neonates with congenital malformations, intrauterine viral infections, prior antibiotic treatment or without parental consent were excluded from the study. Blood samples were collected and analyzed for routine blood parameters, liver and kidney function metrics, levels of C-reactive protein (CRP), procalcitonin (PCT), lactic acid, and PTX-3.

Results The incidence of premature rupture of membranes was significantly lower in the sepsis and localized infection groups compared to the non-infected group (22.86%, 11.11%, and 2.63%; $P<0.05$). White blood cell (WBC) counts were significantly elevated in both the sepsis and localized infection groups when compared to the non-infected group ($P<0.05$). Notable differences were also found in lactate dehydrogenase (LDH) and calcium (Ca) levels ($P<0.05$). Serum levels of CRP, PCT, and PTX-3 were significantly higher in the sepsis group ($P<0.05$). Additionally, PTX-3 levels demonstrated a strong correlation with both CRP and PCT ($P<0.01$). PTX-3, PCT, and platelet distribution width (PDW) emerged as independent risk factors for neonatal infection, while WBC, platelet count (PLT), CRP, PTX-3, PDW, and pH were identified as independent risk factors for sepsis ($P<0.05$). The combination of PTX-3, CRP, PCT, and WBC exhibited the highest diagnostic efficiency for neonatal infection (AUC = 0.954, sensitivity 97.4%, specificity 83.1%; $P<0.01$). For sepsis, the combined markers also demonstrated the best diagnostic performance (AUC = 0.855, sensitivity 83.3%, specificity 80.0%; $P<0.01$).

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Conclusion PTX-3 shows promise as a biomarker for neonatal sepsis, and when combined with WBC, CRP, and PCT, it significantly enhances both diagnostic sensitivity and specificity.

Clinical trial number Not applicable.

Significance

What is already known on this topic

1.The clinical signs of neonatal sepsis are nonspecific, as well as blood culture that is considered as a gold standard have a low positive rate in sepsis due to the widespread use of antibiotics

2.The serum PTX-3 plays an important role in the occurrence and progression of various infectious diseases

3.The specificity and sensitivity of serum PTX-3 was excellent in adult sepsis patients.

What this paper adds

1.The diagnostic value of PTX-3 combined with WBC, CRP, and PCT was firstly evaluated through receiver operating characteristic (ROC) analysis for the early diagnosis of neonatal infection and sepsis.

2.It is the first study to report the sensitivity, specificity, and cut-off points of the combined indicators relevant to PTX-3 for neonatal infection and sepsis.

3.For the diagnosis of neonatal sepsis, CRP was the most sensitive single indicator, and PTX-3 had the strongest specificity. The combination of WBC, CRP and PTX-3 could significantly improve the sensitivity and specificity of diagnosis.

Keywords Neonatal sepsis, Early diagnosis, Pentraxin-3, Procalcitonin, Receiver operating characteristic analysis

Introduction

Neonatal sepsis is a systemic inflammatory response triggered by pathogenic microorganisms entering the bloodstream of neonates through various routes [1]. It represents a critical condition observed in neonates following infections [2]. Recent population-level studies over the past two decades suggest that the global incidence of neonatal sepsis is approximately 22.02 cases (95% confidence interval [CI] 1099–4360) per 1,000 live births (LBs), with mortality rates ranging from 11–19% [3–4]. Early identification and timely intervention are crucial for improving survival rates and minimizing mortality.

The clinical diagnosis of neonatal sepsis incorporates both clinical signs and laboratory indicators. However, the clinical manifestations of neonatal sepsis are often non-specific. While laboratory markers such as C-reactive protein (CRP), procalcitonin (PCT), and white blood cell count (WBC) can serve as supplementary diagnostic tools [5–6], they can easily be misinterpreted due to other non-infectious conditions. Blood culture remains the gold standard for diagnosing neonatal sepsis; however, the positive yield of cultures is only about 3% due to the prevalent use of antibiotics [7]. This significantly limits the effectiveness of culture methods for diagnosis. Additionally, WBC counts typically stabilize only 12 h after birth [8], and PCT levels physiologically increase within the first 24 h post-birth, returning to normal by 96 h [9]. These factors contribute to delays in diagnosing neonatal sepsis. Hence, there is an urgent need for the identification of novel biomarkers that can facilitate early diagnosis of neonatal sepsis to better guide treatment.

Pentraxin-3 (PTX-3), located at the q25 region of chromosome 3, is composed of 2 introns and 3 exons [10]. This protein is secreted by various cells, including endothelial cells, neutrophils, mononuclear phagocytes, chondrocytes, renal innate cells, and dendritic cells, in response to inflammatory stimuli such as interleukin-1β and tumor necrosis factor-α. PTX-3 plays a significant role in the development and progression of infectious diseases, as well as kidney, cardiovascular, and cerebrovascular disorders [11–12]. Previous research has indicated that serum PTX-3 demonstrates a specificity and sensitivity of 0.77 and 0.68, respectively, in adult sepsis patients [13]. Moreover, PTX-3 has been shown to be more reliable than PCT, CRP, and other biomarkers for prognostic purposes [14]. However, studies investigating the role of PTX-3 in the diagnosis of neonatal sepsis are limited. Therefore, this study aims to compare serum PTX-3 levels in cases of neonatal sepsis versus non-septic conditions, as well as to evaluate the diagnostic advantages and value of serum PTX-3 in conjunction with WBC, CRP, and PCT in neonatal patients diagnosed with sepsis.

Methods

Study enrollment

This prospective and non-recruitment-based study included 109 neonates admitted between June and December 2020 to the Second Affiliated Hospital of Xi'an Jiaotong University and the Department of Neonatology of Shaanxi Sengong Hospital. The patients were categorized into three groups according to their conditions:

1. **Sepsis Group**: Consisted of 35 neonates diagnosed with neonatal sepsis within 48 h of admission (including both early-onset sepsis and late-onset sepsis), which included 33 cases of clinical sepsis and 2 cases of confirmed sepsis. Among the confirmed cases, one was due to *Escherichia coli* infection, and the other was caused by *Staphylococcus epidermidis* infection.
2. **Local Infection Group**: Comprised 36 neonates who had mild infections but did not meet the diagnostic criteria for sepsis. This group included 34 cases of infectious pneumonia and 2 cases of omphalitis.
3. **Non-Infection Group**: Included 38 neonates with no infection. This group consisted of 5 infants born to diabetic mothers, 10 born to mothers with gestational hypertension, 7 with intrauterine distress, 5 macrosomic infants, 2 with hypothyroidism during pregnancy, 5 premature infants, and 4 with oligohydramnios at birth.

Inclusion criteria

- Age: 1 to 21 days after birth.
- Gestational age ranging from 34 + 6 weeks (244 days) to 41 + 5 weeks (292 days) including preterm neonates.
- Birth weight: 1795 g to 4200 g.
- Fulfilled the diagnostic criteria outlined in the "Expert Consensus on the Diagnosis and Treatment of Neonatal Sepsis" by the Neonatal Group of the Chinese Pediatric Society, Chinese Medical Association, 2019 [15]. Among them, the diagnostic criteria for culture-negative sepsis, namely clinical sepsis, are as follows: clinical symptoms (non-specific systemic manifestations of infection) plus non-specific inflammatory markers (white blood cell count, platelet count, C-reactive protein, procalcitonin) with at least two positive indicators.

Exclusion criteria

- Presence of congenital malformations.
- Intrauterine viral infections.
- Prior antibiotic treatment of the infant.
- Absence of parental consent.
- Prolonged exposure to mechanical ventilation, intravenous catheter use or total parenteral nutrition.

The study is registered in the Chinese Clinical Trials Registry (Registration No: ChiCTR2300072179).

Data collection

The following data were collected from the participants:

- **General Information**: Gender, delivery mode, gestational age at birth, birth weight, premature rupture of membranes, and amniotic fluid contamination.
- **Laboratory Parameters**: White blood cell count (WBC), platelet count (PLT), platelet distribution width (PDW), lactate (Lac), calcium (Ca), lactate dehydrogenase (LDH), albumin (ALB), serum creatinine (Scr), C-reactive protein (CRP), procalcitonin (PCT), and pentraxin-3 (PTX-3).

The laboratory tests were performed within 6–12 h after admission for all neonates.

Specimen collection and testing

Upon admission, venous blood was collected for routine blood tests, including CRP, PCT, liver and kidney function, and lactate levels. Blood cultures were also performed. Additionally, 1 mL of venous blood was centrifuged at 3000 g for 6 min, and the serum was transferred to a sterile tube and stored at -80 °C until further analysis. Serum PTX-3 levels were measured using the double antibody sandwich method with ABC-ELISA (R&D Systems, Minneapolis, MN, USA). PCT was quantified via electrochemiluminescence immunoassay using a Roche Cobas 8000 e602 automatic analyzer (Roche Diagnostics, Mannheim, Germany). CRP levels were determined with the QuikRead Go CRP System (Orion Diagnostica, Finland).

Statistical analysis

Data analysis was conducted using SPSS version 26.0. The normality of measurement data was assessed using the Kolmogorov-Smirnov test. Data with a normal distribution were expressed as mean ± standard deviation (SD). Comparisons between two groups were made using the T-test, while ANOVA was used to compare data across multiple groups with homogeneous variances, followed by Bonferroni post-hoc tests. Categorical data were presented as frequencies and percentages, and Pearson correlation was used to analyze the relationship between two sets of data. Binary logistic regression was applied to identify relevant biological markers for neonatal infection and sepsis. The optimal diagnostic cutoff values for WBC, CRP, PCT, and PTX-3 in distinguishing neonatal infection and sepsis were determined using receiver operating characteristic (ROC) curves. A p-value of < 0.05 was considered statistically significant.

Results

Comparison of general characteristics among the three groups

The incidence rates of maternal premature rupture of membranes were 22.86%, 11.11%, and 2.63% in the sepsis,

Table 1 Comparison of the general situation among the three groups

General Information	Sepsis group(35)	Local infection group(36)	Non-infection group(38)	x^2/F	*P*
Gender: n(%)					
Male	23 (65.71)	25 (69.44)	18 (47.37)	4.347	0.114
Female	12 (34.29)	11 (30.56)	20 (52.63)		
Mode of delivery: n(%)					
Vaginal delivery	18 (51.43)	20 (55.56)	13 (34.21)	3.829	0.148
Caesarean section	17 (48.57)	16 (44.44)	25 (65.79)		
Gestational age at birth (weeks)	38.9 ± 1.4	39.1 ± 1.2	38.3 ± 1.7	19.129	0.160
Birth weight (g)	3322 ± 477	3358 ± 386	3140 ± 671	1.819	0.167
Premature rupture of membranes: n(%)					
yes	8 (22.86)	4 (11.11)	1 (2.63)	7.129	0.028
no	27 (77.14)	32 (88.89)	37 (97.37)		
Amniotic fluid contamination: n(%)					
yes	4 (11.43)	6 (16.67)	7 (18.42)	0.723	0.696
no	31 (88.57)	30 (83.33)	31 (81.58)		

Table 2 Comparison of PTX3 levels and infection indicators among the three groups

Detection Indicator	Sepsis group (*n*=35)	Local infection group (*n*=36)	Non-infection group (*n*=38)	F	*P*
WBC ($\times 10^9$/L)	18.19 ± 6.13 **	15.93 ± 5.12*	12.92 ± 4.31	6.703	0.002
PLT ($\times 10^9$/L)	277.29 ± 91.54	255.56 ± 53.87	249.74 ± 58.97	1.558	0.215
PDW (fL)	10.73 ± 0.85	11.21 ± 1.88	10.84 ± 0.95	1.399	0.251
Lac (mmol/L)	2.72 ± 0.90	2.60 ± 0.85	2.28 ± 0.72	2.038	0.135
Ca (mmol/L)	2.22 ± 0.22 **#	2.31 ± 0.10	2.35 ± 0.12	6.945	0.001
LDH (U/L)	542.03 ± 179.87**	493.86 ± 157.04	427.08 ± 134.22	3.980	0.022
ALB (g/L)	38.21 ± 6.16	36.79 ± 4.05	36.1 ± 2.73	2.001	0.140
Scr (umol/L)	54.17 ± 14.04	49.26 ± 15.71	52.00 ± 13.42	1.037	0.358
CRP (mg/L)	17.94 ± 5.83 **##	6.26 ± 2.02	2.95 ± 0.92	11.203	0.000
PCT (ng/ml)	3.50 ± 1.11 **#	2.02 ± 0.68**	0.23 ± 0.07	13.002	0.000
PTX-3 (ng/ml)	25.89 ± 4.58 **##	22.11 ± 4.28**	17.00 ± 3.89	40.407	0.000

Note: WBC, white blood cell. PLT, platelet. PDW, platelet distribution width. Lac, lactic acid. Ca, calcium. LDH, lactate dehydrogenase. ALB, albumin. Scr, serum creatinine. CRP, C-reactive protein. PCT, procalcitonin. PTX-3, pentraxin-3

* $p < 0.05$, ** $p < 0.001$, compared with Non-infection group. #$p < 0.05$, ## $p < 0.001$, compared with Local infection group

local infection, and non-infection groups, respectively, with significant differences observed between the groups ($P < 0.05$). However, no significant differences were found in terms of gender, mode of delivery, gestational age, birth weight, or the presence of amniotic fluid contamination at birth ($P > 0.05$) (Table 1).

Comparison of PTX-3 levels and infection markers among the three groups

There were no significant differences in platelet count (PLT), platelet distribution width (PDW), lactate (Lac), albumin (ALB), or serum creatinine (Scr) across the three groups ($P > 0.05$). However, the white blood cell (WBC) count in both the sepsis and local infection groups was significantly higher compared to the non-infection group ($P < 0.05$). Lactate dehydrogenase (LDH) levels in the sepsis group were significantly elevated compared to the non-infection group ($P < 0.01$). Additionally, serum calcium (Ca), CRP, PCT, and PTX-3 levels in the sepsis group were significantly higher than those in both the local infection and non-infection groups ($P < 0.01$ or $P < 0.05$). Furthermore, PCT and PTX-3 levels in the local infection group were significantly higher than those in the non-infection group ($P < 0.05$) (Table 2).

Correlation between PTX-3 and WBC, CRP, and PCT across the three groups

Pearson correlation analysis was performed to evaluate the relationship between serum PTX-3 levels and WBC, CRP, and PCT. The results showed that PTX-3 levels were positively correlated with CRP and PCT ($P < 0.01$), with correlation coefficients of $r = 0.275$ and $r = 0.318$, respectively (Fig. 1B and C). However, no significant correlation was found between PTX-3 and WBC ($P > 0.05$) (Fig. 1A).

Multivariate logistic regression analysis of neonatal infection-related inflammatory markers

Multivariate logistic regression analysis was performed with the infection group (comprising the sepsis and local infection groups) as the dependent variable, and WBC,

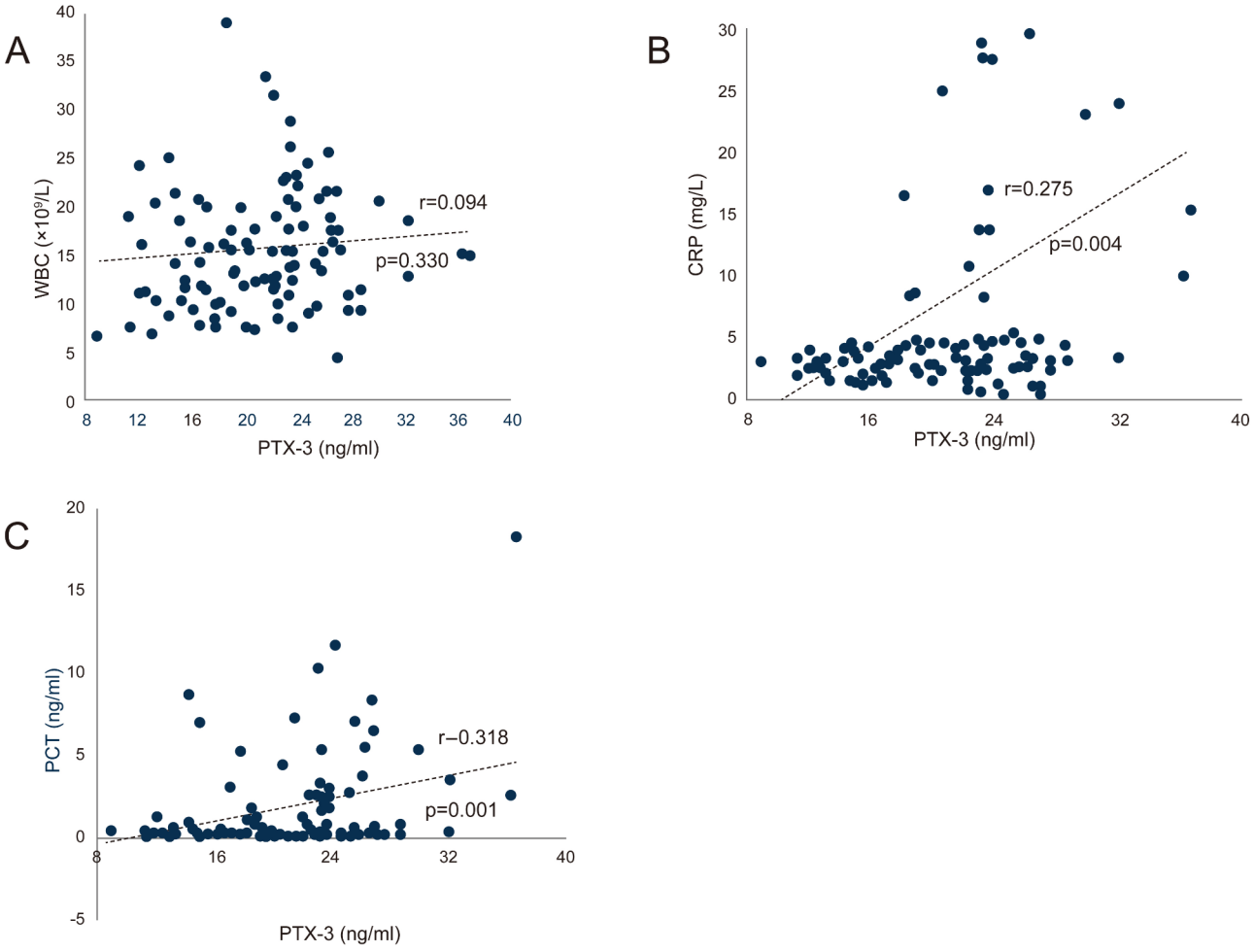

Fig. 1 Correlation analysis of PTX-3 levels with WBC, CRP, and PCT among the three groups. (**A**) Correlation between serum PTX-3 and WBC. (**B**) Correlation between serum PTX-3 and CRP. (**C**) Correlation between serum PTX-3 and PCT

Table 3 Multivariate logistic regression analysis of neonatal infection-related inflammatory indicators

Variables	B	S.E	Wald	df	*P*	OR	95% CI
PCT	0.242	0.126	3.670	1	0.049	0.238	0.006 ~ 0.490
WBC	0.104	0.067	2.756	1	0.067	1.045	0.856 ~ 1.345
PLT	0.145	0.055	1.452	1	0.084	1.058	0.976 ~ 1.254
PDW	0.056	0.547	1.054	1	0.123	0.987	0.567 ~ 1.764
Lac	0.156	0.342	0.987	1	0.085	0.867	0.979 ~ 1.043
Ca	0.087	0.567	0.876	1	0.067	1.243	0.786 ~ 1.271
LDH	0.097	0.054	1.354	1	0.075	1.045	0.875 ~ 1.143
ALB	0.825	0.067	0.896	1	0.068	1.154	0.768 ~ 1.354
Scr	0.046	1.786	0.567	1	0.074	0.874	0.467 ~ 1.175
PTX-3	0.652	0.186	12.267	1	0.000	1.919	1.332 ~ 2.763
PDW	0.550	0.265	4.299	1	0.038	1.733	1.031 ~ 2.915

Note: PCT, procalcitonin. PTX-3, pentraxin-3. PDW, platelet distribution width

PLT, CRP, PCT, PTX-3, PDW, Lac, Ca, LDH, ALB, and Scr as independent variables. The analysis revealed that PCT, PTX-3, and PDW were independent risk factors for neonatal infection (OR: 0.238, 1.919, and 1.733, respectively; 95% CI: 0.006–0.490, 1.332–2.763, and 1.031–2.915, respectively; $P<0.05$ or $P<0.001$) (Table 3).

Multivariate logistic regression analysis of neonatal sepsis-related markers

Similarly, multivariate logistic regression analysis was conducted with the sepsis group and local infection group as dependent variables, and the same set of inflammatory markers as independent variables. The

Table 4 Multivariate logistic regression analysis of inflammatory indicators related to neonatal sepsis

Variables	B	S.E.	Wald	df	*P*	OR	95% CI
ALB	0.133	0.240	0.305	1	0.581	1.142	0.713 ~ 1.829
LDH	0.001	0.006	0.010	1	0.922	1.001	0.989 ~ 1.012
Ca	3.162	5.223	0.367	1	0.545	23.619	0.001 ~ 659435.805
WBC	0.114	0.137	0.700	1	0.403	1.121	0.858 ~ 1.466
PLT	0.021	0.012	3.244	1	0.072	1.022	0.998 ~ 1.046
Scr	-0.017	0.060	0.086	1	0.770	0.983	0.874 ~ 1.104
CRP	0.104	0.023	19.953	1	0.000	1.110	1.060 ~ 1.162
PTX-3	0.280	0.068	16.923	1	0.000	1.323	1.158 ~ 1.512
PDW	-0.602	0.248	5.890	1	0.015	0.548	0.337 ~ 0.891
Lac	-8.850	4.419	4.011	1	0.045	0.000	0.000 ~ 0.828
PCT	5.268	2.911	3.275	1	0.070	194.064	0.645 ~ 58346.047

Note: WBC, white blood cell. PLT, platelet. CRP, C-reactive protein. PTX-3, pentraxin-3. PDW, platelet distribution width. PH: Pondus Hydrogenii. PCT, Procalcitonin. Lac, Lactate. Scr, Serum Creatinine. Ca, Calcium. LDH, Lactate Dehydrogenase. ALB, Albumin

Table 5 The diagnostic value of WBC, CRP, PCT, and PTX-3 combined indicators for neonatal infection

Predictive value	AUC	S.E.	*P*	95%CI	Best cut-off value	Sensitivity%	Specificity%
WBC + CRP + PCT + PTX-3	0.954	0.018	0.000	0.918 ~ 0.990	0.714	97.4	83.1
WBC	0.678	0.052	0.002	0.577 ~ 0.780	16.87	84.2	46.5
CRP	0.727	0.047	0.000	0.634 ~ 0.819	4.85	100	42.3
PCT	0.776	0.043	0.000	0.691 ~ 0.861	0.52	92.1	63.4
PTX-3	0.878	0.035	0.000	0.810 ~ 0.946	20.36	84.2	84.5

Note: WBC, white blood cell. CRP, C-reactive protein. PCT, procalcitonin. PTX-3, pentraxin-3

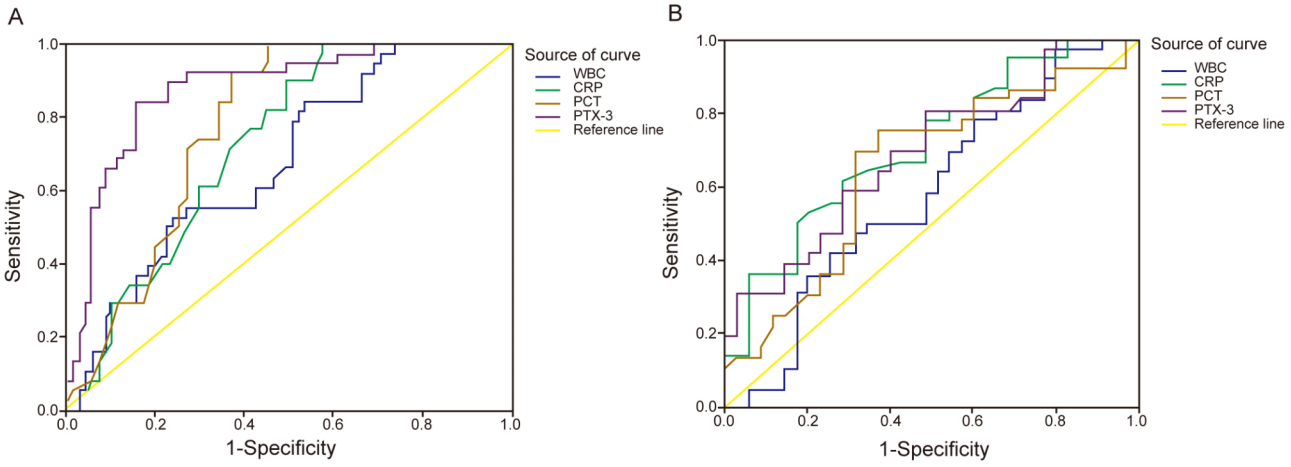

Fig. 2 ROC curve predicts the diagnostic value of WBC, CRP, PCT, and PTX-3 in neonatal infection and sepsis. (**A**) ROC curve to determine the best cut-off value of WBC, CRP, PCT, and PTX-3 for neonatal infection. (**B**) ROC curve to determine the best cut-off value of WBC, CRP, PCT, and PTX-3 for neonatal sepsis

results indicated that WBC, PLT, CRP, PTX-3, and PDW were independent risk factors for neonatal sepsis (OR: 1.146, 1.013, 1.110, 1.323, and 0.548, respectively; 95% CI: 1.049–1.252, 1.005–1.021, 1.060–1.162, 1.158–1.512, and 0.337–0.891, respectively; $P < 0.05$ or $P < 0.001$) (Table 4).

Diagnostic value of ROC curve for WBC, CRP, PCT, and PTX-3 in predicting neonatal infection

ROC curve analysis was performed for WBC, CRP, PCT, and PTX-3 to assess their diagnostic value in predicting neonatal infection (i.e., sepsis and local infection groups vs. non-infection group). The combined indices of PTX-3, CRP, PCT, and WBC demonstrated the highest diagnostic performance (AUC = 0.954, sensitivity 97.4%, specificity 83.1%, cutoff value 0.714, $P < 0.01$). Individually, PTX-3, PCT, and CRP also showed strong diagnostic performance, though slightly lower than the combined index (AUC = 0.878, 0.776, and 0.727, respectively; sensitivity 84.2%, 92.1%, and 100%; specificity 84.5%, 63.4%, and 42.3%; cutoff values 20.36, 0.52, and 4.85, respectively; $P < 0.01$) (Table 5; Fig. 2A).

Table 6 Diagnostic value of the combined indicators WBC, CRP, PCT, and PTX-3 for neonatal sepsis

Predictive value	AUC	S.E.	*P*	95%CI	Best cut-off value	Sensitivity%	Specificity%
WBC + CRP + PTX-3	0.855	0.028	0.000	0.800 ~ 0.909	0.614	83.3	80.0
WBC	0.582	0.043	0.065	0.497 ~ 0.666	20.21	40	77.8
CRP	0.710	0.039	0.000	0.634 ~ 0.787	5.35	82.9	50.0
PCT	0.650	0.067	0.030	0.566 ~ 0.733	1.55	68.6	69.4
PTX-3	0.689	0.040	0.000	0.610 ~ 0.768	25.39	51.4	80.6

Note: WBC, white blood cell. CRP, C-reactive protein. PCT, procalcitonin. PTX-3, pentraxin-3

Diagnostic value of ROC curve for WBC, CRP, PCT, and PTX-3 in predicting neonatal Sepsis

ROC curve analysis was also performed for WBC, CRP, PCT, and PTX-3 in distinguishing sepsis from local infection. The combined indices of PTX-3, CRP, PCT, and WBC provided the best diagnostic efficiency (AUC = 0.855, sensitivity 83.3%, specificity 80.0%, cut-off value 0.614, $P < 0.01$). For individual markers, CRP, PTX-3, and PCT showed good diagnostic performance, but were less effective than the combined indices (AUC = 0.710, 0.689, and 0.650, respectively; sensitivity 82.9%, 51.4%, and 68.6%; specificity 50.0%, 80.6%, and 69.4%; cutoff values 5.35, 25.39, and 1.55, respectively; $P < 0.05$) (Table 6; Fig. 2B).

Discussion

The significant differences observed in the incidence rates of maternal premature rupture of membranes (PROM) across the sepsis, local infection, and non-infection groups underline the clinical importance of these findings. The sepsis group exhibited the highest incidence of 22.86%, followed by 11.11% in the local infection group and only 2.63% in the non-infection group. This variation suggests that infection may play a pivotal role in the pathophysiology of PROM. Previous studies have demonstrated that infections can lead to inflammation of the membranes, weakening their structure and precipitating premature rupture, thereby increasing the risk of adverse neonatal outcomes [16].

The higher incidence of PROM in the sepsis group may be attributed to the systemic inflammatory response triggered by infection. This response leads to the release of various pro-inflammatory cytokines and mediators, which can compromise the integrity of the membranes. Additionally, sepsis may reflect a more severe underlying infection, further weakening the amniotic membranes and increasing the likelihood of PROM [17]. In contrast, the lower incidence of PROM in the non-infection group suggests that the absence of infection may help preserve membrane integrity during labor. It's worth noting that amniotic fluid contamination, specifically meconium-stained amniotic fluid, was not significantly associated with neonatal infection in our study. This finding was consistent with the understanding that while meconium passage into the amniotic fluid can trigger a sterile inflammatory response due to fetal distress, it does not necessarily lead to infection. Meconium itself is sterile within the uterus, and bacterial colonization occurs only after birth. Therefore, the presence of meconium-stained amniotic fluid, although indicative of fetal distress, does not directly correlate with an increased risk of neonatal infection.

Apart from differences in PROM incidence, infection markers across the three groups revealed significant variations, particularly in white blood cell (WBC) counts, C-reactive protein (CRP), procalcitonin (PCT), and PTX-3 levels. Elevated WBC counts in the sepsis and local infection groups compared to the non-infection group reflect a heightened inflammatory response associated with infection. These findings align with the well-established role of infection in stimulating an increase in WBCs as part of the immune defense.

WBC count is a commonly used diagnostic tool for infection in clinical practice [18]. While it is simple to measure and produces rapid results, WBC count can be influenced by various external factors, which may complicate clinical decisions. Both PCT and CRP are acute-phase reactants that respond to inflammation, with PCT levels rising significantly during bacterial infections due to microbial toxins, interleukins, and tumor necrosis factor-α [19]. In contrast, PCT levels are inhibited by interferon-gamma during viral infections [20]. When bacterial infections occur, serum PCT levels increase, with higher levels correlating with more severe infection [21]. CRP, a non-specific acute-phase protein synthesized by the liver, is also widely used in diagnosing and prognosticating bacterial infections [22]. In this study, WBC counts were significantly higher in the sepsis group compared to the local infection and non-infection groups. However, correlation analysis did not reveal a significant relationship between WBC and PCT, CRP, or PTX-3 levels. Several factors may explain this discrepancy.

Firstly, WBC count is the most commonly used laboratory marker for infection, but various factors, including breastfeeding, strenuous exercise, and emotional stress, can influence WBC levels [23]. Moreover, normal newborns have higher baseline WBC counts compared to older children [24]. In the case of acute infection, especially bacterial infections, WBC levels can increase significantly, often correlating with the severity of infection

[19]. However, in severe infections, toxins produced by pathogens can damage tissues and blood cells, leading to bone marrow suppression or immune dysfunction, which may result in reduced WBC production [25]. These factors could explain the lack of a strong correlation between WBC counts and other inflammatory markers like PCT, CRP, and PTX-3.

PTX-3 is a relatively new inflammatory biomarker that belongs to the same superfamily as CRP but differs in its cellular origin, regulatory mechanisms, and ligands [26]. While CRP is produced by the liver in response to interleukin-6, PTX-3 is primarily induced by immune cells and tissues at the site of inflammation through tumor necrosis factor-α and interleukin-1β (rather than IL-6) [27]. Neonates have lower CRP levels due to underdeveloped immune systems [28], which makes PTX-3 a potentially more reliable marker for inflammation in this population. Compared to CRP, PTX-3 reflects local tissue inflammation and injury more rapidly. Furthermore, PTX-3 levels are closely associated with the severity of the inflammatory response, with levels rising in patients with sepsis, severe sepsis, and septic shock [29].

The results of this study confirm significant differences in CRP and PTX-3 levels across the three groups. Multivariate logistic regression analysis revealed that WBC, platelets (PLT), CRP, PCT, PTX-3, and platelet distribution width (PDW) were all closely related to neonatal infection, with PTX-3 being most strongly associated with neonatal sepsis and infection. These findings suggest that PTX-3 may provide a more rapid and reliable indication of neonatal infection compared to CRP, as its levels rise more swiftly in response to infection.

ROC curve analysis demonstrated that the combined use of PTX-3, CRP, PCT, and WBC provided the highest diagnostic accuracy for neonatal infection, outperforming each marker individually. Among these, PTX-3 was the most effective single marker for diagnosing neonatal infection. When PTX-3 levels exceeded 20.36 ng/ml, this strongly indicated the presence of neonatal infection. The rapid response of PTX-3 to inflammation underscores its potential diagnostic value [30–31]. Additionally, the combination of WBC, CRP, and PTX-3 provided the best diagnostic performance for neonatal sepsis and local infection, with CRP showing the highest sensitivity as a single marker [32]. CRP is a stable protein, produced mainly during systemic or severe infections, and its elevated levels in neonatal sepsis are indicative of significant ongoing inflammation [33].

To the best of our knowledge, this study is the first to assess the diagnostic value of PTX-3 combined with WBC, CRP, and PCT for early diagnosis of neonatal infection and sepsis using ROC curve analysis. This is also the first study to report the sensitivity, specificity, and cut-off values of these combined markers for neonatal infection and sepsis. Our findings suggest that PTX-3 is the most valuable single marker for early diagnosis of neonatal sepsis. However, the combination of WBC, CRP, PCT, and PTX-3 markedly improves diagnostic sensitivity and specificity for neonatal infection. For diagnosing neonatal sepsis, CRP was the most sensitive marker, while PTX-3 demonstrated the strongest specificity. The combination of WBC, CRP, and PTX-3 significantly enhanced both sensitivity and specificity.

Despite these promising findings, there are several limitations to this study. First, the sample size of 109 neonates may limit the generalizability of our results. A larger sample would provide more robust conclusions regarding the role of PTX-3 as a diagnostic marker for neonatal sepsis. Second, although the study was prospective, it lacked long-term follow-up data on neonates to evaluate outcomes beyond the initial diagnosis. This would have offered additional insights into the clinical relevance of PTX-3 over time. Additionally, variations in laboratory methods and patient demographics could have impacted the results, particularly for traditional inflammatory markers like CRP and PCT. Furthermore, while correlations between PTX-3 and other markers were explored, the study did not investigate the underlying biological mechanisms or the impact of potential confounding factors such as the timing of sample collection. What's more, it is plausible that delivery mode may affect the baseline levels of PTX-3 to some extent. During vaginal delivery, neonates are exposed to a greater number of microbes while passing through the birth canal, which may trigger a stronger inflammatory response and consequently elevate PTX-3 levels. In contrast, neonates delivered by cesarean section, who are directly extracted from the uterus with minimal microbial exposure, may exhibit weaker inflammatory reactions and lower PTX-3 levels. The sample size in this study may not be sufficient to detect a significant impact of delivery mode on PTX-3 levels. Similarly, fetal distress may trigger a certain degree of inflammatory response, which can lead to elevated levels of PTX-3. However, this inflammatory response is usually mild and may gradually subside shortly after birth, so its impact on PTX-3 levels may be limited. In this study, only 7 neonates in the non-infection group experienced intrauterine distress. The small sample size may have limited our ability to detect significant differences. In future multicenter studies, we will include a larger sample and document perinatal events such as intrauterine distress in detail to more comprehensively assess the impact of these factors on PTX-3 levels and further explore the biological mechanisms of PTX-3 in fetal distress, such as by studying the expression of inflammatory cytokines and the activation status of immune cells to reveal the specific impact mechanisms of intrauterine distress on PTX-3 levels. Lastly, the study

was conducted at a single institution, which may limit the applicability of these findings to different clinical settings. Larger, multicenter studies are needed to confirm these results and explore the role of PTX-3 in diverse neonatal populations.

Conclusion

PTX-3 holds promise as a novel biomarker for neonatal sepsis with best cutoff value of 20.36, and its diagnostic utility can be further enhanced when combined with WBC, CRP, and PCT. This combination significantly improves both sensitivity and specificity for diagnosing neonatal infection and sepsis.

Abbreviations

ALB	Albumin
Ca	Calcium
CRP	C-reactive protein
Lac	Lactic acid
LBs	Live births
LDH2	Lactate dehydrogenase
PCT	Procalcitonin
PDW	Platelet distribution width
PLT	Platelet
PROM	Premature rupture of membranes
PTX-3	Pentraxin-3
ROC	Receiver operating characteristic
Scr	Serum creatinine
WBC	White blood cell count

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Author contributions

YJ and SG contributed to the conception and design of the study; YF X and CY Y performed the experiments, collected and analyzed data; YJ wrote the manuscript; SG and YF X revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The current study was conducted in accordance with the Helsinki Declaration. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (Approval No: 2020245). Informed consent was obtained from the parents or legal guardians of all neonates enrolled in this study, particularly for participants under the age of 16.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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