Original paper

Pentraxin 3 as a biomarker for early detection of fetal inflammatory response syndrome in preterm infants

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Abstract

Introduction: Fetal inflammatory response syndrome (FIRS) is observed in preterm infants, characterised by inflammation of the umbilical cord and elevated levels of pro-inflammatory cytokines in circulation.
Aim of the research: To assess pentraxin 3 (PTX3) as a sensitive biomarker for the early detection of FIRS in preterm infants.
Material and methods: This prospective study was conducted at the Department of Neonatology, from September 2008 to March 2009, with the inclusion of 63 preterm infants (gestational age: 28–36 weeks) in the Neonatal Intensive Care Unit (NICU). Data were collected on demographics and clinical history, and infections were assessed based on clinical findings and laboratory results. FIRS was defined by IL-6 levels exceeding 11 pg/ml in umbilical vein blood to categorise the infants into FIRS-positive and FIRS-negative groups.
Results: It was determined that 46.1% of the infants with RDS and 19.2% of those with neonatal pneumonia were FIRS positive, indicating a statistically significant relationship between these conditions and FIRS positivity ($p < 0.05$). PTX3 levels in cord blood were significantly higher in the FIRS-positive infants compared to the FIRS-negative infants ($p = 0.001$). IL-6 levels were also elevated in the FIRS-positive group, especially in cord blood ($p = 0.001$). TNF-α levels did not differ significantly between the groups. PTX3 and sepsis were significant predictors of FIRS positivity, with PTX3 having an OR of 1.131 (95% CI: 1.026–1.246, $p < 0.05$). PTX3 levels had a cutoff value of > 4.45 (AUC = 0.76, 95% CI: 0.64–0.86, $p < 0.001$).
Conclusions: PTX3 can serve as a useful biomarker for detecting FIRS, and PTX3 levels appear to be linked to conditions such as RDS and sepsis.

Introduction

Inflammation is a key factor in preterm birth, with the fetal inflammatory response playing a critical role. Fetal inflammatory response syndrome (FIRS), commonly seen in preterm infants, is characterised by funisitis and elevated pro-inflammatory cytokines, leading to adverse outcomes such as neonatal sepsis, intraventricular haemorrhage, and neurodevelopmental impairments [1–4].

Pentraxin 3 (PTX3) has emerged as a significant biomarker for early inflammatory responses. Beyond its role as a marker, PTX3 actively participates in inflammation by recruiting immune cells and promoting pathogen clearance [5, 6]. In diseases like Crohn's and COVID-19, PTX3 levels correlate with disease severity, highlighting its diagnostic potential [5–7].

In sepsis, PTX3 levels rise rapidly, often surpassing traditional biomarkers like C-reactive protein (CRP), and they reflect localised inflammation more accurately [8, 9].

This rapid response makes PTX3 a promising early marker for FIRS because it peaks earlier than CRP and closely correlates with inflammation severity in conditions like chorioamnionitis [10, 11].

PTX3's localised production at infection sites enhances its sensitivity and specificity, making it a reliable biomarker for neonatal sepsis and a predictor of mortality risk in septic patients [12, 13].

Aim of the research

This study aims to evaluate the diagnostic and prognostic potential of PTX3 in preterm newborns with FIRS by analysing PTX3 levels in cord blood.

Material and methods

This was a prospective study conducted at the Department of Neonatology, Medical Faculty, Eskişehir Osmangazi University, between September 2008 and March 2009.

Study population

The study population included a total of 63 preterm infants with a gestational age between 28 and 36 weeks, who were followed up in the Neonatal Intensive Care Unit (NICU). One patient was excluded due to congenital anomalies (shown in the flowchart CONSORT diagram) (Figure 1).

Sample selection and size determination

The sample size was determined based on expected differences in cytokine levels (PTX3, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and CRP) between infants with and without FIRS.

A power analysis was conducted, estimating that approximately 60 participants would be needed, accounting for potential exclusions. Patients were selected consecutively as they met the inclusion criteria during the study period.

Inclusion and exclusion criteria

Inclusion criteria: Preterm infants with a gestational age of 28–36 weeks admitted to the NICU during the study period.

Exclusion criteria: Infants with major congenital anomalies or chromosomal abnormalities.

Data collection

Upon enrolment, data were collected on demographics, clinical history, and relevant comorbidities, with a particular focus on morbidity rates in premature infants. The presence of infection in neonates was determined based on clinical manifestations, such as poor suckling, lethargy, altered muscle tone, respiratory distress, apnoea, poor perfusion, cyanosis, bradycardia, thermoregulatory disorders (including fever or hypothermia), food intolerance, and metabolic acidosis, combined with laboratory test results, including CRP, TNF-α, IL-6, PTX3, platelet count, and white blood cell (WBC) count.

Blood sampling and laboratory analysis

Blood samples were collected from both mothers and newborns for cytokine analysis. Maternal venous blood (2 ml) was collected immediately after delivery, and umbilical cord blood (1 ml) or peripheral blood samples (0.5 ml) were collected from newborns within the first 12 hours of life and on the third day. The levels of PTX3, CRP, and IL-6, and platelet and WBC count were determined in all blood samples, and additional measurements of PTX3, IL-6, and TNF-α were conducted on umbilical cord blood and third-day peripheral blood samples.

Serum samples were separated by centrifugation and stored at –80°C until analysis.

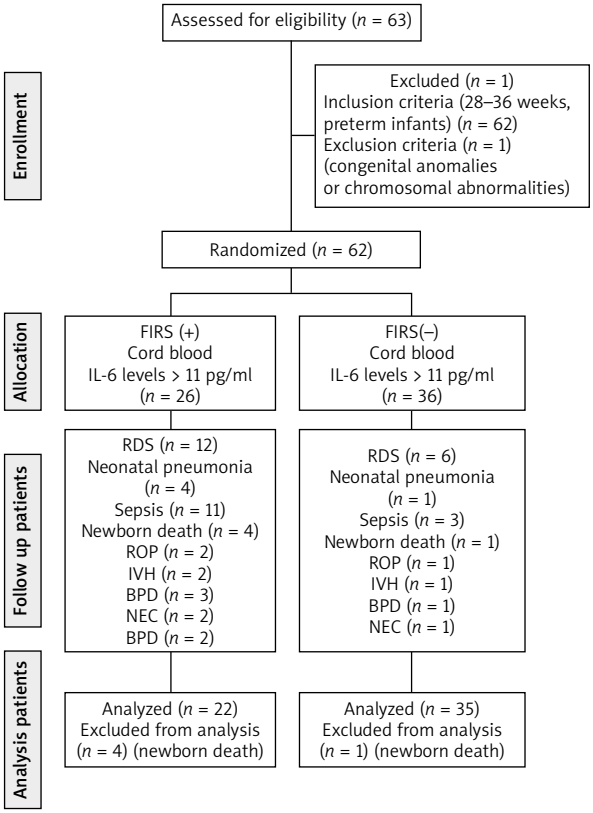

Figure 1. Flowchart for evaluating PTX3 levels in preterm infants

Fetal inflammatory response syndrome (FIRS) definition

FIRS was identified by IL-6 levels above 11 pg/ml in umbilical vein blood, and patients were classified into FIRS-positive and FIRS-negative groups [2].

Cytokine and PTX3 measurements

Cytokine and PTX3 levels were measured using enzyme-linked immunosorbent assay (ELISA) kits. Cytokine levels (TNF-α, IL-6) and PTX3 levels were measured using the Alfa Prime ELISA instrument with enzyme-linked immunosorbent assay (ELISA) kits. TNF-α measurements were performed using the Bender Medsystems TNF-α ELISA kit, IL-6 measurements with the BenderMedSystems-Human IL-6 ELISA kit, and PTX3 levels with the Quantakine-Human Pentraxin 3/TSG-14 Immunoassay ELISA kit. TNF-α and IL-6 levels were measured in pg/ml, and PTX3 levels were measured in ng/ml.

Statistical analysis

The data were evaluated using IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA) statistical package program. Descriptive statistics are given as number of units (*n*), percentage (%), mean ± standard deviation, median

(M), minimum (min.), maximum (max.), and interquartile range (IQR) values. The normal distribution of the numerical variables was evaluated using the Shapiro-Wilk normality test. The homogeneity of variance was evaluated using Levene's test. Comparisons for FIRS groups in numerical variables were made by *t*-test in independent samples if the data were normally distributed, and by Mann-Whitney *U* test if the data were not normally distributed. The χ^2 tests were used to compare groups on categorical variables. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. Factors affecting FIRS positivity were evaluated using a multiple binary logistic regression analysis. The Backward Wald method was used as the elimination method. The goodness of fit for the latest model was assessed using the Hosmer-Lemeshow test. The performance of PTX3 in predicting opportunity positivity was evaluated using receiver operating characteristic (ROC) curve analysis. Differences were considered statistically significant at $p < 0.05$.

Ethical approval

The study was approved by the Bioethics Committee of Faculty of Medicine (Approval No. 2008/40). Written informed consent was obtained from the parents of all participants.

Results

The general characteristics of participants in the FIRS-positive and FIRS-negative groups are shown in Table 1. According to the data, there were no significant differences in age and gender between the groups with and without FIRS ($p = 0.25$, $p = 0.20$).

According to Table 1, 12 (46.1%) of the children with RDS and 5 (19.2 %) with neonatal pneumonia were found to be FIRS positive. The incidence of FIRS positivity was statistically higher in those with RDS and neonatal pneumonia ($p < 0.05$). Among those with FIRS positivity, levels of white blood cells, ALT, cord IL-6, and cord PTX3 were statistically significantly different (Table 1).

In Table 2, comparisons of PTX3, IL-6, TNF-α, and CRP levels between the FIRS-positive (FIRS (+) and FIRS-negative (FIRS (–)) groups are presented for both mothers and newborns. In mothers, the mean IL-6 levels were higher in the FIRS (+) group (25.4 ±46.3 pg/ml, median 10.3) compared to the FIRS (–) group (15 ±40.3 pg/ml, median 3.6), although this difference was not statistically significant ($p = 0.07$). TNF-α levels showed no significant difference between the two groups (FIRS (+): 1.3 ±0.6 pg/ml, median 1.2; FIRS (–): 1.6 ±1.3 pg/ml, median 1; $p = 0.86$). PTX3 levels in mothers were similar between the FIRS (+) and FIRS (–) groups (FIRS (+): 12.9 ±10.4 ng/ml, median 9; FIRS (–): 13.9 ±10.4 ng/ml, median 12.3; $p = 0.96$) (Table 2).

In newborns, significant differences were observed in PTX3 levels. PTX3 levels measured from cord blood were significantly higher in the FIRS (+) group (12.3 ±11.1 ng/ml, median 8.9) compared to the FIRS (–) group (5 ±4.9 ng/ml, median 3.7), with a *p*-value of 0.001. Similarly, PTX3 levels measured on the third day were significantly higher in the FIRS (+) group (13.3 ±10.4 ng/ml, median 8.3) compared to the FIRS (–) group (8.1 ±7.4 ng/ml, median 5.8; $p = 0.02$) (Table 2). IL-6 levels in newborns were also significantly higher in the FIRS (+) group both in cord blood (41.3 ±38.1 pg/ml, median 25.7) and on the third day (10.6 ±6.9 pg/ml, median 8.5) compared to the FIRS (–) group (cord: 3.3 ±2.9 pg/ml, median 1.9; $p = 0.001$). However, the IL-6 levels on the third day did not show a significant difference ($p = 0.09$) (Table 2).

TNF-α levels did not show significant differences between the FIRS (+) and FIRS (–) groups in both cord blood and third-day measurements (cord: $p = 0.86$; third day: $p = 0.34$). CRP levels on the first day were higher in the FIRS (+) group (1.23 ±2.6 mg/dl, median 0.34) compared to the FIRS (–) group (0.79 ±1.4 mg/dl, median 0.17), but this difference was not statistically significant ($p = 0.06$) (Table 2). The evaluation of PTX3 levels in cord blood and on day 3, along with IL-6 and TNF-α levels in both the infants' and mothers' blood, is shown in Figure 2.

In premature infants with morbidity, PTX3 levels in cord blood and on day 3 differed between those with and without respiratory distress syndrome (RDS) ($p = 0.02$, $p = 0.001$). Additionally, neonatal pneumonia, sepsis, and neonatal death were associated with differences in PTX3 levels only on day 3 ($p = 0.001$, $p = 0.001$, $p = 0.002$, respectively) (Table 3). No correlation was found for PTX3 levels in cord blood and on day 3 with WBC counts ($r = 0.001$, $p = 0.99$; $r = –0.04$, $p = 0.76$) (Table 4).

Table 4 presents the results of a logistic regression analysis conducted to identify factors associated with FIRS positivity. The analysis included parameters with a *p*-value below 0.25 in the multivariable binary logistic regression model. The parameters incorporated into the model were PTX3, TNF-α, WBC, CRP, ALT, RDS, and sepsis. The results indicated that PTX3 was a significant predictor of FIRS positivity, with an odds ratio (OR) of 1.131 (95% CI: 1.026–1.246, $p < 0.05$). Additionally, sepsis was identified as a strong predictor, with an OR of 6.065 (95% CI: 1.058–34.770, $p < 0.05$). These findings highlight the importance of PTX3 and sepsis in assessing the risk of FIRS in neonates (Table 4).

The evaluation conducted through ROC analysis demonstrated that PTX3 has diagnostic value in predicting FIRS. The PTX3 level had a cutoff value of > 4.45, with an area under the curve (AUC) of 0.76 (95% CI: 0.64–0.86, $p < 0.001$). In contrast, IL-6 showed an AUC of 0.63 (95% CI: 0.50–0.75, $p = 0.076$) in predicting FIRS. The recommended cutoff values are presented in Table 5.

Table 1. General characteristics of preterm infants with FIRS (+) and FIRS (–)

Parameter	FIRS		Test statistics	
	Positive *N* = 26 (41.9%) Median IQR	Negative *N* = 36 (58.1%) Median IQR	Test value	*P*-value
Gender, *n* (%)				
Girls	12 (46.2)	23 (63.8)	1.932[&]	0.200
Boys	14 (53.8)	13 (36.2)		
Gestational age [weeks]	28.6 ±5.1	30.2 ±4.9	1.150[†]	0.255
Gravida	1 (1–6)	1 (1–6)	0.824[‡]	0.410
Para	1 (0–4)	1 (0–4)	0.263[‡]	0.793
Weight [g]	1672.5 (1060.0)	1855 (975.0)	1.106[‡]	0.269
Weight by age*				
SGA	3 (11.5)	7 (19.4)	0.698[&]	0.499
AGA	23 (88.5)	29 (80.6)		
Multiple pregnancy				
Yes	5 (19.3)	9 (25)	0.355[&]	0.759
No	21 (80.7)	27 (75)		
PROM**				
No	19 (73)	22 (61.1)	3.220[&]	0.209
Yes	7 (27)	14 (38.9)		
RDS				
Yes	12 (46.1)	6 (16.6)	6.371[&]	0.022
No	14 (53.9)	30 (83.4)		
Sulfactant				
Yes	12 (46.1)	6 (16.6)	6.371[&]	0.022
No	14 (53.9)	30 (83.4)		
Neonatal pneumonia				
Yes	5 (19.2)	1 (2.7)	7.332[&]	0.011
No	21 (80.8)	35 (97.3)		
Sepsis				
Yes	8 (30.7)	3 (8.3)	5.207[&]	0,02
No	18 (69.3)	33 (91.7)		
Placenta**	*N* = 21	*N* = 28	0.832[&]	0.398
Chorioamnionitis(+)	11 (52.3)	11 (39.2)		
Chorioamnionitis(–)	10 (47.7)	17 (60.8)		
CRP (serum reactive protein) [mg/dl]	0.375 (1.249)	0.179 (0.766)	1.864[‡]	0.062
APGAR 1st minute	6 (0–9)	7 (0–9)	0.829[‡]	0.407
APGAR 5th minute	8 (1–10)	8.5 (2–20)	1.488[‡]	0.137
PH_1 (cord)				
PO_2 [mm Hg]	7.27 ±0.09	7.29 ±0.08	0.802[†]	0.426
PCO_2 [mm Hg]	29.0 (24.2)	33.0 (22.0)	0.423[‡]	0.672
HCO_3 [mEq/l]	47.0 (17.2)	45.0 (15.0)	0.765[‡]	0.444
Lactate [mEq/l]	18.78 ±3.87	19.2 3±4.24	0.409[†]	0.684
BE [mmol/l]	27.5 (20.0)	27.0 (15.0)	0.077[‡]	0.939

Table 1. Cont.

Parameter	FIRS		Test statistics	
	Positive *N* = 26 (41.9%) Median IQR	Negative *N* = 36 (58.1%) Median IQR	Test value	*P*-value
PH_2 (peripheral blood sample)	–6.11 ±4.78	–4.23 ±6.40	1.179†	0.244
PO_2 [mm Hg]	74.0 (57.2)	74.0 (45.0)	0.336‡	0.737
PCO_2 [mm Hg]	41.5 (15.0)	35.0 (13.0)	1.482‡	0.138
HCO_3 [mEq/l]	17.53 ±3.48	18.57 ±3.34	1.171†	0.246
Lactate [mEq/l]	25.0 (22.5)	28.0 (15.0)	0.718‡	0.473
BE [mmol/l]	–8.47 ±4.29	–7.06 ±4.43	1.233†	0.223
Hb [gr/dl]	17.40 ±2.22	17.34 ±1.91	0.118†	0.906
White blood cell [10^9/l]	19.3 (922.4)	15.4 (13.6)	2.494‡	0.013
PLT [10^9/l]	205.5 (134)	233 (143)	1.517‡	0.129
AST [U/l]	64.0 (48.2)	56.0 (24.0)	1.428‡	0.153
ALT [U/l]	12.5 (7.0)	10.0 (4.0)	2.010‡	0.044
Newborn IL-6 [pg/ml]	25.7 (38.5)	1.99 (4.43)	6.676	< 0.001
Newborn TNF [pg/ml]	0.37 (1.30)	0.22 (1.60)	0.172‡	0.864
Newborn PTX3 [ng/ml]	8.87 (11.51)	3.75 (3.65)	3.459‡	0.001
Mother IL-6 [pg/ml]	10.38 (19.89)	3.64 (16.44)	1.819‡	0.069
Mother TNF [pg/ml]	1.17 (0.86)	1.03 (1.31)	0.172‡	0.863
MotherPTX3 [ng/ml]	9.02 (13.83)	12.33 (14.45)	0.048‡	0.962

*Nominal data are presented as count (row percent). Ordinal data are presented as median (minimum-maximum) values. Numerical data are presented as mean ± standard deviation or median (interquartile range) values. &χ^2, †Independent samples t test, ‡Mann-Whitney U test. SGA – small for gestational age, AGA – appropriate for gestational age, **PROM – premature rupture of membranes.*

Table 2. Comparison of PTX3 and other markers in FIRS (+) vs. FIRS (–) groups

Investigated group Blood parameters	FIRS (+) (*n* = 26)	FIRS (–) (*n* = 36)	*P*-value
Mothers	Mean ± SD (median)	Mean ± SD (median)	
IL-6 [pg/ml]	25.4 ±46.3 (10.3)	15 ±40.3 (3.6)	0.07
TNF-α [pg/ml]	1.3 ±0.6 (1.2)	1.6 ±1.3 (1)	0.86
PTXtx 3 [ng/ml]	12.9 ±10.4 (9)	13.9 ±10.4 (12.3)	0.96
Newborns	FIRS (+) (*n* = 26)	FIRS (–) (*n* = 36)	
PTX3 (cord) levels [ng/ml]	12.3 ±11.1 (8.9)	5 ±4.9 (3.7)	0.001
PTX3 3rd day [ng/ml]	13.3 ±10.4 (8.3)	8.1 ±7.4 (5.8)	0.02
IL-6 (cord) levels [pg/ml]	41.3 ±38.1 (25.7)	3.3 ±2.9 (1.9)	0.001
IL-6 3rd day [pg/ml]	10.6 ±6.9 (8.5)	12.8 ±27.6 (6)	0.09
TNF-α (cord) levels [pg/ml]	1.2 ±0.32 (0.4)	1.3 ±0.23 (0.2)	0.86
TNF-α 3rd day [pg/ml]	1.26 ±1.63 (0.39)	0.98 ±1.3 (0.22)	0.34
CRP 1st day [mg/dl]	1.23 ±2.6 (0.34)	0.79 ±1.4 (0.17)	0.06

The correlation analysis revealed a positive moderate correlation between PTX3 and IL-6 (r = 0.427, p = 0.001). In contrast, a negative weak correlation was found between PTX3 and base excess (BE) (r = –0.276, p = 0.04) (Table 6).

At the end of the 7-month follow-up, 2 of the FIRS-positive patients developed necrotising enterocolitis (NEC), 2 patients experienced intraventricular haemorrhage, 2 had retinopathy, and 4 had neonatal death. These complications typically arise during this period.

Discussion

In this study, FIRS was identified in 26 infants, with FIRS-positive infants exhibiting a higher incidence of respiratory distress syndrome (RDS), neonatal pneumonia, and sepsis compared to FIRS-negative infants. Notably, FIRS-positive infants had significantly elevated white blood cell counts, ALT levels, and cord blood levels of IL-6 and PTX3. When comparing biomarkers such as PTX3, IL-6, C-reactive protein (CRP), and TNF-α, we found that IL-6 levels were significantly elevated in cord blood of FIRS-positive

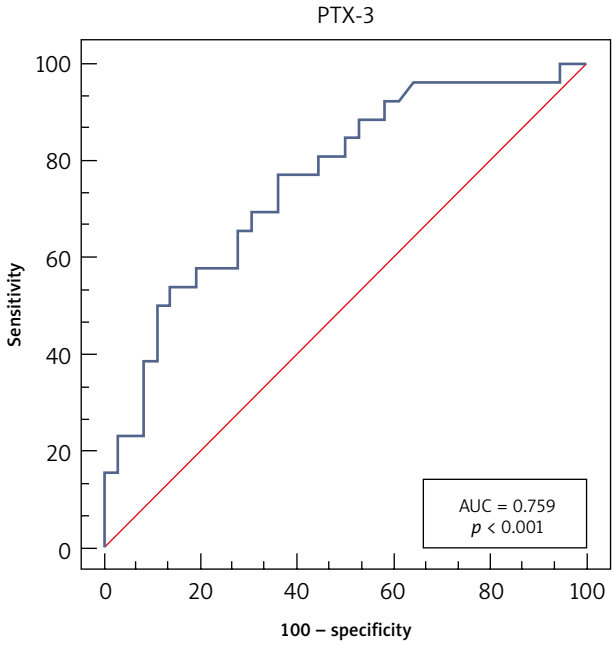

Figure 2. Evaluation of PTX3 performance in predicting FIRS positivity using ROC analysis

Table 3. PTX3 levels in cord and peripheral vein blood of preterm infants with morbidities

Morbidities *N*	PTX3 (cord) Median (min.–max.)	*P*-value	PTX3 (peripheral vein) Median (min.–max.)	*P*-value
RDS 18		0.02		0.001
Yes	10.1 (1.35–36.16)		19.9 (3.71–37.12)	
No	4.3 (0.95–7.0)		5.6 (2.1–5.8)	
Neonatal pneumonia 5		0.11		0.001
Yes	13.1 (1.42–35.2)		21.5 (12.69–32.7)	
No	4.4 (7.5–8.4)		7.4 (2.1–8.6)	
Sepsis 14		0.32		0.001
Yes	11.3 (1.35–35.2)		18.1 (12.5–32.87)	
No	4.5 (0.95–8.1)		6.3 (2.2–7.2)	
Newborn death 5				
Yes	17.2 (1.42–35.2)	0.59	27.2 (16.78–32.74)	0.002
No	4.6 (0.95–7.81)		7.5 (2.1–9.9)	
PTX 3 levels on a case-by-case basis				
Rop* 3				
Yes	13.2 (1.89–35.2)		15.8 (9.01–32.70)	
Intracranial haemorrhage				
Yes 3	4.2 (1.35–33.8)		15.2 (2.18–30.5)	
BPD*				
Yes 4	4.9 (2.3–13.75)		14.2 (9.01–18.1)	
NEC				
Yes 3	5.8 (1.4–10.7)		12.6 (8.2–32.8)	

Table 4. Correlation between WBC and PTX 3 levels. There is no correlation between cord blood and 3rd day PTX3 and WBC

		WBC	Cord blood PTX3
Cord blood PTX 3	Spearman's *r*	0.001	
	P-value	0.998	
3rd PTX 3	Spearman's *r*	–0.040	0.172
	P-value	0.763	0.189

infants. PTX3 levels were elevated in both cord and peripheral blood. A 1.13-unit increase in PTX3 and values above a cut-off of 4.45 ng/ml were associated with FIRS, indicating PTX3's potential as a valuable predictor. These findings underscore PTX3's role as a key biomarker for early detection and management of FIRS in preterm infants.

FIRS has been recognised as a significant risk factor for adverse neonatal outcomes, such as RDS and sepsis. The systemic inflammatory response initiated in the foetus leads to various complications. Our findings align with existing literature that highlights the detrimental impact of fetal inflammation on neonatal health. Research indicates that FIRS is linked to an increased incidence of severe neonatal morbidities. For instance, a study by Jain *et al.* highlighted that the occurrence of RDS and NEC was significantly higher in the FIRS group compared to non-FIRS counterparts, suggesting that FIRS is a critical risk factor for these conditions [14]. Similarly, Golubinskaya *et al.* found that histological signs of chorioamnionitis and FIRS are associated with severe neonatal morbidities, including brain injury and neurodevelopmental sequelae [15]. These findings are supported by a systematic review that emphasises the adverse outcomes associated with FIRS, including long-term neurodevelopmental issues [16]. The association between FIRS and increased rates of RDS, neonatal pneumonia, and sepsis has been well-documented, with various studies reporting similar risk ratios and correlations [3, 17–19].

PTX3 has emerged as a significant biomarker in various clinical contexts, particularly when compared to traditional markers like CRP and IL-6. PTX3 is produced by monocytes and macrophages in response to inflammatory signals, differentiating its production from CRP, which is primarily synthesised by hepatocytes [20]. Our study found PTX3 to be significantly elevated in both cord and peripheral blood in FIRS-positive infants, indicating its utility in detecting ongoing inflammatory processes. Previous studies have shown that PTX3 levels can rise rapidly following an inflammatory event, making it a crucial tool for early diagnosis and monitoring [21]. The ability to detect PTX3 in both cord and peripheral blood enhances its practicality in clinical settings, offering a non-invasive method for monitoring the inflammatory status of neonates.

PTX3's specificity in reflecting local inflammatory processes, compared to systemic inflammation indicated by CRP [10, 22, 23], provides more relevant and

Table 5. Logistic regression analysis of factors associated with FIRS positivity

Parameter	Regression coefficients*						
	β	Standard error	Wald statistics	*P*-value	OR	95% CI for OR	
						Lower	Upper
Constant	–1.487	0.457	10.604	< 0.001	0.226		
PTX-3	0.123	0.049	6.147	0.013	1.131	1.026	1.246
Sepsis (1)	1.803	0.891	4.093	0.04	6.065	1.058	34.770

*Variables entered on step 1: PTX3, PTX3, TNFα, WBC, CRP, ALT, RDS, and Sepsis. Model Summary: Hosmer and Lemeshow test χ^2 = 9.945; p = 0.269; Nagelkerke R^2 = 0.315. OR – odds ratio, CI – confidence interval; **variables with a p-value less than 0.25 were included in the multiple binary logistic regression analysis. The Backward Wald elimination method was used to eliminate non-significant variables, resulting in the final model.*

Table 6. ROC curve analysis of PTX3's performance in predicting FIRS

Parameter	AUC (95% CI)	*P*-value	Cut-off	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)
PTX-3	0.759 (0.634–0.859)	< 0.001	> 4.45	76.9 (56.4–91.0)	63.9 (46.2–79.2)	60.6 (48.7–71.4)	79.3 (64.6–89.0)
IL-6	0.628 (0.494–0.749)	0.076	> 3.99	92.0 (74.0–99.0)	40.0 (23.9–57.9)	52.3 (44.9–59.5)	87.5 (63.6–96.6)

AUC – area under the curve, CI – confidence interval, Sens – sensitivity, Spec – specificity, PPV – positive predictive value, NPV – negative predictive value.

actionable insights regarding the inflammatory status of the foetus. This specificity could enable tailored therapeutic approaches, improving care for preterm infants vulnerable to inflammation's harmful effects.

This study highlights the significant role of FIRS in preterm infants and its association with adverse neonatal outcomes such as RDS, neonatal pneumonia, and sepsis. Notably, PTX3 emerges as a promising biomarker for early detection and monitoring of FIRS, demonstrating superior specificity in reflecting local inflammatory processes compared to traditional markers like IL-6 and CRP. The ability to detect PTX3 in both cord and peripheral blood offers a practical, non-invasive approach to assessing inflammatory status, potentially facilitating timely and targeted therapeutic interventions.

The findings align with existing literature, underscoring the detrimental impact of fetal inflammation on neonatal health and reinforcing PTX3's utility as an early diagnostic tool. However, limitations such as the small sample size of FIRS-positive infants, absence of long-term neurodevelopmental follow-up, and potential unaddressed confounding factors should be acknowledged. Future research integrating a broader cohort, additional biomarkers, and comprehensive long-term outcomes could enhance understanding and clinical applicability.

Conclusions

This study contributes valuable insights into the pathophysiology of FIRS and its clinical management, emphasising PTX3's potential in improving outcomes for preterm infants affected by inflammation. Addressing the study's limitations in future work will further solidify the evidence base and support the development of more effective strategies for mitigating the impacts of FIRS.

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Ethical approval

The study was approved by the Bioethics Committee of Eskişehir Osmangazi University, Medical Faculty of Medicine (Approval No. 2008/40).

Conflict of interest

The authors declare no conflict of interest.

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