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Delta Neutrophil Index as a Predictive Biomarker for Chorioamnionitis in Pregnancies Complicated by PPROM

PPROM ile Komplike Olan Gebeliklerde Koryoamniyonit için Prediktif Biyomarker Olarak Delta Nötrofil İndeksi

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Abstract

Objective: Chorioamnionitis is an intra-amniotic infection involving the fetal membranes, amniotic fluid, or placenta, and is associated with adverse perinatal outcomes, particularly in pregnancies complicated by preterm premature rupture of membranes (PPROM). After membrane rupture; the risk of infection increases early diagnosis is essential to reduce the risks of neonatal sepsis, preterm birth, and maternal morbidity. Conventional diagnostic approaches are limited due to reliance on clinical signs and non-specific biomarkers. The delta neutrophil index (DNI), which reflects circulating immature granulocytes, has emerged as a rapid inflammatory marker. This study aimed to assess the diagnostic performance of DNI in predicting clinical chorioamnionitis in PPROM.

Method: Three hundred singleton pregnancies with PPROM diagnosed between 24+0 and 33+6 weeks were retrospectively analyzed at a tertiary perinatology center between May 2020 and July 2023. Patients were classified according to the presence of clinical chorioamnionitis using the American College of Obstetricians and Gynecologists criteria. Maternal blood samples were obtained within one hour of admission and before administration of antenatal corticosteroids. DNI values were automatically calculated as the proportion of circulating immature granulocytes.

Öz

Amaç: Koryoamniyonit, fetal membranları, amniyotik sıvıyı veya plasentayı içeren intra-amniyotik bir enfeksiyon olup, özellikle preterm erken membran rüptürü (PPROM) ile komplike gebeliklerde olumsuz perinatal sonuçların önemli bir nedenidir. Membran rüptürü sonrası enfeksiyon riski artar ve erken tanı yenidoğan sepsisi, preterm doğum ve maternal morbiditenin önlenmesinde kritik öneme sahiptir. Rutin tanı yöntemlerinin doğruluğu klinik bulgulara ve özgül olmayan belirteçlere dayanması nedeniyle sınırlıdır. Dolaşımdaki immatür granülosit düzeyini yansıtan delta nötrofil indeksi (DNI), enfeksiyon için hızlı bir biyobelirteç olarak öne çıkmaktadır. Bu çalışma, PPROM olgularında klinik koryoamniyoniti öngörmede DNI'nın tanısal performansını değerlendirmeyi amaçlamaktadır.

Yöntem: Mayıs 2020-Temmuz 2023 arasında, üçüncü basamak bir perinatoloji merkezinde 24+0 ile 33+6 hafta arasında PPROM tanısı almış 300 tekil gebelik retrospektif kesitsel olarak incelendi. Hastalar, Amerikan Kadın Hastalıkları ve Doğum Derneği kriterlerine göre klinik koryoamniyonit varlığına göre sınıflandırıldı. Maternal kan örnekleri başvurudan sonraki ilk bir saat içinde, antenatal kortikosteroid uygulanmadan önce alındı. DNI, hematoloji analizörü tarafından dolaşımdaki immatür granülosit oranı olarak otomatik hesaplandı.

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Abstract

Results: Maternal DNI levels were significantly higher in the chorioamnionitis group than in controls (p<0.01). Receiver operating characteristic analysis yielded an area under the curve of 0.627 (95% confidence interval: 0.515-0.739; p=0.026). At a cut-off of 0.11, sensitivity, specificity, likelihood ratios were 74.2%, 57.1%, 1.73, and 0.45, respectively. In the multivariable logistic regression model, platelet count, DNI, and international normalized ratio were identified as independent predictors of clinical chorioamnionitis.

Conclusion: DNI is significantly associated with clinical chorioamnionitis in PPROM and may support early detection of intrauterine infection. However, its diagnostic performance is limited, and DNI should not be used alone. Combined evaluation of clinical and laboratory findings is recommended. Larger prospective studies are needed to validate these results and clarify the role of DNI in infection risk assessment.

Keywords: Chorioamnionitis, delta neutrophil index, DNI, obstetric infection, preterm premature rupture of membranes

Öz

Bulgular: Maternal DNI düzeyleri, koryoamniyonit grubunda kontrol grubuna kıyasla anlamlı olarak daha yüksekti (p<0,01). Alıcı çalışma karakteristiği analizinde eğri altında kalan alan 0,627 bulundu (%95 güven aralığı: 0,515-0,739; p=0,026). 0,11 eşik değeri ile duyarlılık %74,2, özgüllük %57,1, pozitif olasılık oranı 1,73 ve negatif olasılık oranı 0,45 olarak hesaplandı. Çok değişkenli lojistik regresyon analizinde trombosit sayısı, DNI ve uluslararası düzeylendirilmiş oran, klinik koryoamniyonit ile bağımsız olarak ilişkili bulundu.

Sonuç: DNI, PPROM ile komplike gebeliklerde klinik koryoamniyonit ile anlamlı şekilde ilişkili olup intrauterin enfeksiyonun erken tanısında yardımcı bir biyobelirteç olabilir. Bununla birlikte tanısal gücü sınırlıdır ve tek başına kullanılmamalıdır. Klinik ve laboratuvar parametreleriyle birlikte değerlendirilmesi daha uygundur. Bulguların doğrulanması ve DNI'nın perinatal enfeksiyon risk değerlendirmesindeki rolünün netleştirilmesi için daha geniş, prospektif çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Delta nötrofil indeksi, DNI, erken membran rüptürü, koryoamniyonit, obstetrik enfeksiyon

Introduction

Preterm premature rupture of membranes (PPROM) is an important obstetric complication associated with high rates of perinatal morbidity and mortality (1). Inflammatory processes are increasingly recognized as key contributors to the pathogenesis of PPROM, and maternal inflammatory biomarkers such as interleukin (IL)-6 have been reported to correlate with the risk of intrauterine infection (2).

The delta neutrophil index (DNI) is a hematological parameter that reflects the proportion of circulating immature granulocytes and has been recognized as a valuable marker in the early detection of sepsis and systemic inflammatory conditions (3). Given its role in systemic inflammation, DNI has also been investigated as a potential biomarker for intrauterine infection. Previous studies have primarily evaluated its predictive value for histological chorioamnionitis in pregnancies complicated by PPROM (4), whereas data focusing on clinically diagnosed chorioamnionitis remain limited.

Chorioamnionitis is a serious clinical condition associated with significant maternal and neonatal complications, and timely diagnosis and management are essential to improving outcomes. In this context, DNI may serve as a rapid, non-invasive, cost-effective adjunct for the early identification of infection-related complications in PPROM. The aim of this study was to evaluate the clinical utility of DNI in predicting clinical chorioamnionitis among women with PPROM.

Materials and Methods

This retrospective, cross-sectional study included 300 pregnant women diagnosed with PPROM who were admitted to the Obstetrics and Gynecology Department of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital between May 2020 and July 2023.

The inclusion criteria were as follows:

- Maternal age between 18 and 45 years
- Singleton, live pregnancies between 24+0 and 33+6 weeks of gestation
- PPROM confirmed by speculum examination showing active leakage, pooling of amniotic fluid in the posterior fornix, vaginal pH >5, or a positive AmniSure® test.

Exclusion criteria included multiple gestations, major fetal anomalies (incompatible with life or requiring prenatal or postnatal surgery), intrauterine fetal demise, chromosomal or genetic syndromes, placental anomalies, systemic maternal infections, hematological or autoimmune disorders, and maternal smoking, alcohol use, or illicit drug use.

Maternal demographic and clinical data (age, parity, gestational age at delivery, vital signs, and laboratory parameters) and neonatal outcomes (1- and 5-minute Apgar scores) were retrieved from electronic hospital records.

Blood sampling and laboratory analysis: Maternal blood samples were collected within the first hour of admission and prior to administration of antenatal corticosteroids.

Complete blood count (CBC), DNI, white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP) were obtained. Samples were drawn into EDTA tubes and analyzed in the hospital laboratory. In addition to these parameters, maternal procalcitonin levels were measured.

DNI was measured using the ADVIA 2120 Hematology System (Siemens Healthcare Diagnostics, Forchheim, Germany). The DNI was automatically calculated by the analyzer as the difference between leukocyte subfractions measured in the myeloperoxidase and nuclear lobularity channels, which reflects the proportion of circulating immature granulocytes.

Treatment protocol: Following PPROM diagnosis, patients were managed according to institutional protocols based on international guidelines. Antenatal corticosteroids (betamethasone 12 mg intramuscularly, two doses 24 h apart) were administered for fetal lung maturation. Antibiotic prophylaxis consisted of intravenous ampicillin 2 g every 6 h for 48 h, followed by oral ampicillin 250 mg every 8 h for 5 days, in combination with a single oral dose of azithromycin 1 g (5). Vital signs were monitored regularly; clinical signs of infection (e.g., fundal tenderness, foul-smelling discharge) were assessed; and daily CBC and CRP measurements were obtained in patients with suspected infection.

Delivery planning: Unless urgent obstetric indications were present, delivery was planned for 34 weeks' gestation. Rescue corticosteroid therapy was administered if the initial course had been completed more than 14 days before delivery. Magnesium sulfate infusion (1 g/h for 24 h) was administered for fetal neuroprotection between 24 and 32 weeks of gestation.

Diagnostic criteria for chorioamnionitis: Clinical chorioamnionitis was diagnosed according to the American College of Obstetricians and Gynecologists criteria: Maternal fever ≥38.0 °C accompanied by at least two of the following—maternal tachycardia (>100 bpm), fetal tachycardia (>160 bpm), uterine tenderness, foul-smelling vaginal discharge, or maternal leukocytosis (>15.000/mm^3) (6).

Ethics: The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval no: 2023-610, date: 27.11.2023).

Statistical Analysis

Statistical analyses were performed using NCSS 2007 (Number Cruncher Statistical System, Kaysville, Utah, USA). Descriptive statistics (mean, standard deviation, median, frequency, percentage, minimum, maximum) were calculated. Normality was assessed using the Shapiro-Wilk test. Group comparisons were made with the Mann-Whitney U test for continuous variables and chi-square tests for categorical variables.

A post-hoc power analysis was performed using G*Power (version 3.1). Assuming a large effect size (d=0.8), α=0.05, and power =0.985, the required sample size was calculated to be n=300. Since the study cohort consisted of exactly 300 participants, the achieved statistical power was considered adequate.

Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) curve analysis: The area under the curve (AUC), the standard error, the 95% confidence interval (CI), the p-value, and the positive and negative likelihood ratios (LR^+, LR^-) were calculated. Logistic regression was performed to identify independent predictors of chorioamnionitis. In the logistic regression model, the dependent variable was coded as 0 for chorioamnionitis (–) and 1 for chorioamnionitis (+), following the standard binary coding approach. Therefore, regression coefficients (B) greater than zero correspond to odds ratios (OR) above 1 and indicate an increased likelihood of chorioamnionitis. Variables were selected for multivariate analysis if they demonstrated statistical significance in univariate testing or had established clinical relevance (inflammatory, coagulation, or hemodynamic parameters). OR with 95% CIs and p-values were reported. A p-value 0.05 was considered statistically significant.

Results

A total of 300 patients met the inclusion criteria and were analyzed. The mean maternal age was 30.12±6.40 years, and the mean gestational age at delivery was 30.65±3.06 weeks. Descriptive statistics for maternal demographics, laboratory findings, and perinatal outcomes are summarized in Table 1.

Among the patients included in the study, 39.3% (n=118) were primigravida, 18% (n=54) had two pregnancies, 20% (n=60) had three pregnancies, and 22.7% (n=68) had four or more pregnancies. In terms of parity, 46.7% (n=140) of patients were nulliparous, 20% (n=60) had one previous delivery, 22% (n=66) had two previous deliveries, and 11.3% (n=34) had three or more previous deliveries.

Amniotic fluid assessment revealed anhydramnios in 8.7% (n=26), normal amniotic fluid volume in 53.3% (n=160), oligohydramnios in 36% (n=108), and polyhydramnios in 2% (n=6) of patients. Regarding the mode of delivery, 52.7% (n=158) had a primary cesarean section, 24% (n=72) had a repeat cesarean section, 2% (n=6) had an induced vaginal delivery, and 21.3% (n=64) had a spontaneous vaginal delivery.

Table 1. Baseline maternal demographics, laboratory findings, obstetric characteristics, and neonatal outcomes in the study population (n=300)

	Mean ± SD	Min-max (median)
Age (years)	30.12±6.4	18-46 (29)
Height (cm)	161.61±5.58	149-175 (162)
Weight (kg)	75.85±13.71	44-119 (75)
Body mass index (kg/m^2)	29.06±5.29	18.510-45.31 (28.52)
Hemoglobin (g/dL)	11.36±1.27	7.4-13.8 (11.5)
Hematocrit (%)	34.25±3.35	25.5-41.8 (34.25)
Platelet count (10^9/L)	246.71±70.8	92-466 (244)
Neutrophils (10^9/L)	13.4±16.65	3.29-89.8 (8.91)
White blood cell (10^9/L)	12.17±3.46	5.7-24.92 (11.67)
Lymphocytes (10^9/L)	2.05±0.85	0.46-8.9 (2.01)
DNI (10^9//L)	0.14±0.14	0.02-0.96 (0.1)
DNI % (%)	1.13±0.94	0.2-5.7 (0.85)
CRP (mg/dL)	13.41±22.25	0.04-172.9 (6.1)
Procalcitonin (ng/mL)	0.06±0.05	0.02-0.42 (0.05)
PT (sec)	8.08±0.55	6.6-10.1 (8)
INR	0.93±0.06	0.8-1.1 (0.9)
aPTT (sec)	26.32±3.22	19.2-38.9 (26.2)
Birth weight (g)	1657.77±628	550-3230 (1690)
Apgar 1st min	5.29±2.12	0-8 (6)
Apgar 5th min	7.21±1.58	0-9 (7)
Gestational age at delivery (weeks)	30.65±3.06	24.14-34 (31.14)
Cervical length (mm)	32.35±9.6	10-50 (35)
Umbilical PI	0.98±0.23	0.45-1.83 (0.96)
Length of hospital stay (days)	14.23±11.86	2-60 (10)
Maternal temperature (°C)	36.02±0.14	36-38.8 (36)
Maternal systolic blood pressure (mmHg)	110.5±10.66	83-160 (110)
Maternal diastolic blood pressure (mmHg)	65.63±10.81	41-125 (61)

DNI: Delta neutrophil index, SD: Standard deviation, Min-max: Minimum-maximum, PI: Pulsatile index, PT: Prothrombin time, CRP: C-reactive protein, INR: International normalized ratio, aPTT: Activated partial thromboplastin time

Comorbidities were present in 17.3% (n=52) of patients; 82.7% (n=248) had no known comorbidities. Fetal growth restriction (FGR) was identified in 6% (n=18) of the patients; 94% (n=282) of the patients did not exhibit FGR.

Regarding antenatal corticosteroid use, 86% (n=258) received a full course, 8.7% (n=26) received a single dose, and 5.3% (n=16) received no steroids. Erythrocyte suspensiontransfusion at delivery was required in 7.3% (n=22) of patients; 92.7% (n=278) did not require transfusion. Placental abruption occurred in 16% (n=48) of patients, whereas placental separation was not observed in the remaining 84% (n=252).

As shown in Table 2, there were no statistically significant differences between the chorioamnionitis and non-chorioamnionitis groups with respect to maternal age, body mass index, hemoglobin, hematocrit, neutrophil count, WBC count, lymphocyte count, procalcitonin levels, or prothrombin time (PT) (all p>0.05).

In contrast, platelet count (PLT), DNI, DNI percentage, and CRP level were significantly higher in the chorioamnionitis group compared with the non-chorioamnionitis group (p=0.045, p=0.029, p=0.019, and p=0.018, respectively). The international normalized ratio (INR) and maternal body temperature were significantly higher in the chorioamnionitis group compared with the non-chorioamnionitis group (p=0.008 and p=0.017, respectively). Maternal diastolic blood pressure was also significantly elevated in the chorioamnionitis group (p=0.020). In contrast, no statistically significant differences were observed between the groups in terms of birth weight, Apgar scores at 1 and 5 minutes, duration of PPROM, gestational age at delivery, cervical length, umbilical artery pulsatility index (PI), length of hospital stay, or maternal systolic blood pressure (all p>0.05) (Table 3).

Correlation analysis further demonstrated a strong positive correlation between DNI and maternal fever (r=0.694, p<0.01), and a moderate positive correlation with maternal systolic blood pressure (r=0.578, p<0.05). No significant correlations were found between DNI and CRP, procalcitonin, PT, INR, aPTT, birth weight, Apgar scores, gestational age at delivery, cervical length, umbilical artery PI, length of hospital stay, or maternal diastolic blood pressure (all p>0.05). ROC analysis results and AUC values are summarized in Table 4.

Table 2. Comparison of measurements according to chorioamnionitis status

Parameters	Chorioamnionitis (+) (n=30)	Chorioamnionitis (-) (n=270)	p-value
Age (years)	27.77±6.85 (19-46; 25)	28.71±3.98 (18-35; 30)	0.056
BMI (kg/m^2)	28.74±6.17 (18.51-44.14; 27.89)	29.02±5.29 (11.69-45.31; 28.91)	0.401
Hb (g/dL)	11.47±1.14 (8.7-13.5; 11.6)	11.33±1.31 (7.4-13.8; 11.5)	0.788
Hct (%)	34.61±3.03 (27.7-39.9; 34.6)	34.30±3.43 (25.5-41.8; 34.2)	0.559
PLT (10^9/L)	**272.39±86.77 (92-439; 259)**	**240.03±64.79 (118-466; 236)**	**0.045***
Neutrophils (10^9/L)	14.78±19.33 (3.29-89.8; 10.75)	13.04±30.95 (4-85.6; 8.8)	0.322
WBC (10^9/L)	13.12±4.31 (5.7-24.92; 12.22)	11.93±3.17 (6.45-24.05; 11.53)	0.123
Lymphocytes (10^9/L)	2.00±0.60 (1.03-3.12; 1.99)	2.07±0.90 (0.46-8.9; 2.05)	0.774
DNI (10^9/L)	**0.27±0.29 (0.02-0.96; 0.12)**	**0.13±0.10 (0.02-0.66; 0.09)**	**0.029***
DNI (%)	**1.84±1.80 (0.11-5.7; 1.0)**	**0.93±0.68 (0.02-4.5; 0.7)**	**0.019***
CRP (mg/dL)	**22.16±47.03 (1.6-172.9; 5)**	**13.79±31.78 (0.04-172.9; 3.2)**	**0.018***
Procalcitonin (ng/mL)	0.05±0.04 (0.02-0.19; 0.04)	0.06±0.05 (0.02-0.42; 0.05)	0.456
PT (sec)	8.24±0.66 (7.4-10.1; 8.1)	8.05±0.51 (6.6-9.9; 8.0)	0.180

*: p<0.05, Hb: Hemoglobin, Hct: Hematocrit, BMI: Body mass index, PLT: Platelet count, WBC: White blood cell count, DNI: Delta neutrophil index, CRP: C-reactive protein, PT: Prothrombin time

Table 3. Comparison of measurements according to chorioamnionitis status

		n	Mean ± SD	Min-max (median)	p
INR	**With**	30	0.96±0.07	0.9-1.1 (0.9)	0.008**
	Without	270	0.92±0.06	0.8-1.1 (0.9)	
aPTT (sec)	**With**	30	27.35±3.99	19.2-38.9 (27.1)	0.087
	Without	270	26.05±2.95	19.2-35 (26.1)	
Birth weight (g)	**With**	30	1808.55±623.66	660-3100 (1800)	0.103
	Without	270	1618.49±625.76	550-3230 (1630)	
Apgar 1st min	**With**	30	5.42±2.2	1-8 (6)	0.672
	Without	270	5.25±2.11	0-8 (6)	
Apgar 5th min	**With**	30	7.32±1.6	2-9 (7)	0.728
	Without	270	7.18±1.58	0-9 (7)	
Gestational age at delivery (weeks)	**With**	30	29.74±3.01	24.29-34 (29.43)	0.300
	Without	270	30.76±3.06	24.14-34 (31.57)	
Cervical length (mm)	**With**	30	32.83±8.39	14-48 (33.5)	0.805
	Without	270	32.21±9.96	10-50 (35)	
Umbilical PI	**With**	30	1.01±0.17	0.84-1.83 (0.98)	0.446
	Without	270	0.97±0.11	0.45-1.5 (0.98)	
Length of hospitalization (days)	**With**	30	14.9±12.18	3-44 (9)	0.822
	Without	270	14.05±11.83	2-60 (10)	
Maternal temperature (°C)	**With**	30	38.55±0.23	38-39.4 (38.7)	0.017*
	Without	270	36.01±0.14	36-36.8 (36)	
Maternal systolic blood pressure (mmHg)	**With**	30	114.39±11.1	100-138 (130)	0.492
	Without	270	109.49±10.35	83-160 (110)	
Maternal diastolic blood pressure (mmHg)	**With**	30	65.1±13.75	44-125 (60)	0.02*
	Without	270	65.77±9.96	41-109 (61)	

*: p<0.05, **: p<0.01, SD: Standard deviation, Min-max: Minimum-maximum, PI: Pulsatile index, INR: International normalized ratio, aPTT: Activated partial thromboplastin time

A DNI cut-off value of 0.11 yielded a sensitivity of 74.2% and a specificity of 57.1% for predicting chorioamnionitis, representing a clinically relevant threshold that may contribute to early detection and proactive management strategies in PPROM cases (Table 4). Figure 1 illustrates the corresponding ROC curve, further demonstrating the diagnostic performance of DNI in distinguishing pregnancies complicated by chorioamnionitis.

Building upon the diagnostic performance demonstrated by the ROC analysis, a multivariate logistic regression model was subsequently applied to further delineate independent predictors of chorioamnionitis, the results of which are presented in Table 5.

A multivariable logistic regression analysis was performed to identify independent predictors of clinical chorioamnionitis. The overall model was statistically significant (χ^2=24.294, p=0.001), indicating an acceptable model fit. The explanatory power of the model was modest but clinically meaningful (Nagelkerke R^2=0.180).

Among the hematological and coagulation parameters evaluated, PLT, DNI, and INR were identified as independent predictors of chorioamnionitis. Higher PLT values were associated with a small but statistically significant increase in risk (OR=1.007, 95% CI: 1.001-1.013; p=0.016). DNI demonstrated the strongest association with chorioamnionitis (OR=53.255, 95% CI: 5.170-548.559; p=0.001), consistent with its role as an inflammatory marker.

INR was also significant (OR=7,956.218, 95% CI: 1.21–5.2×10^7; p=0.042), but its wide confidence interval indicates substantial variability and suggests the estimate should be interpreted with caution.

Overall, the model indicates that hematological inflammatory markers and coagulation parameters may serve as independent predictors of chorioamnionitis in pregnancies complicated by PPROM (Table 5).

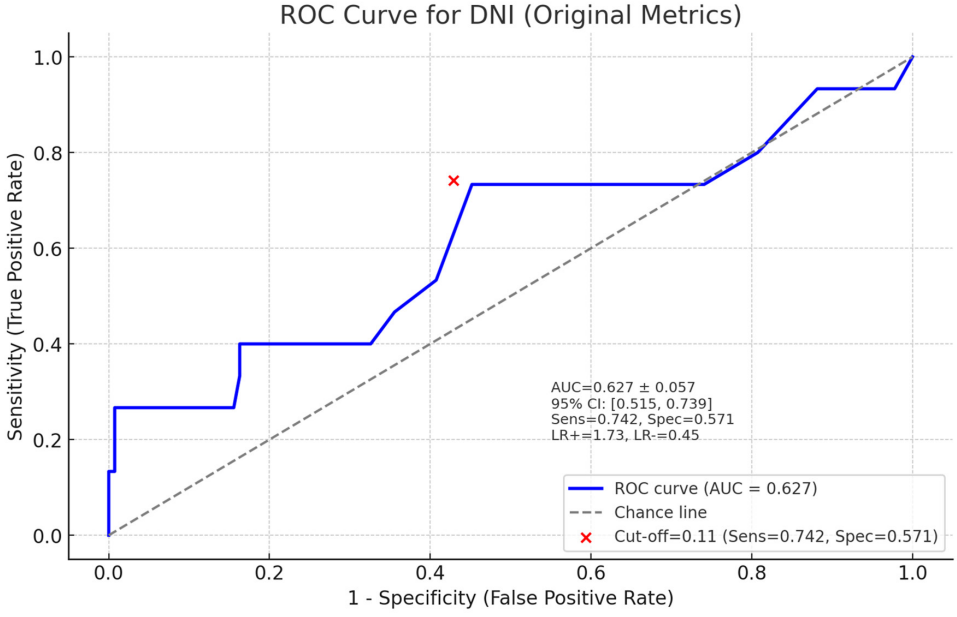

Figure 1. ROC curve of DNI for predicting chorioamnionitis in pregnancies complicated by PPROM

ROC: Receiver operating characteristic, DNI: Delta neutrophil index, AUC: Area under the curve, CI: Confidence interval, PPROM: Preterm premature rupture of membranes, LR: Likelihood ratios

Table 4. ROC analysis results and AUC values

Parameter (10^9/L)	Sens. %	Spec. %	Cut-off	AUC (95% CI)	SE	p-value	LR^+/LR^-
DNI	74.2	57.1	0.11	0.627 (0.515-0.739)	0.057	0.026*	1.73/0.45

*: p<0.05, LR: Likelihood ratios, ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, SE: Standard error, DNI: Delta neutrophil index

Table 5. Predictors of chorioamnionitis identified by multivariate logistic regression

		Multivariable				
Model	**Variables**	**B**	**SE**	**Exp(B)**	**95% CI**	**p**
	PLT	0.007	0.003	1.007	1.001-1.013	0.016*
	DNI (10^9/L)	3.975	1.190	53.255	5.170-548.559	0.001**
	INR	8.982	4.486	7956.218	1.21-5.2×10^7	0.042*
	R^2=0.180					
	X^2=24.294, p=0.001**					

*: p<0.05, **: p<0.01, DNI: Delta neutrophil index, SE: Standard error, PLT: Platelet count, CI: Confidence interval, INR: International normalized ratio

Discussion

This study highlights the potential role of the DNI as a biomarker for the early detection of chorioamnionitis in pregnancies complicated by PPROM. In clinical practice, where timely and reliable diagnostic tools are essential, DNI provides several practical advantages. It is derived automatically from a standard CBC, incurs no additional cost, requires no specialized laboratory processing, and can be reported in real time, thereby providing an accessible adjunct to infection surveillance protocols (7).

Our findings showed that DNI values were significantly elevated in patients with chorioamnionitis, consistent with DNI's proposed role as a marker of the release of immature granulocytes during acute inflammatory responses. This early hematologic shift may precede elevations in conventional markers such as CRP, WBC count, or procalcitonin (8). Unlike these delayed systemic markers, DNI reflects the an early increase in immature granulocytes of the innate immune system, thereby allowing earlier recognition of subclinical intrauterine infection.

Consistent with our results, Cho et al. (4) reported that increased DNI levels were independently associated with histological chorioamnionitis in patients with PPROM, suggesting its predictive utility in obstetric populations. Moreover, other hematologic indices, including platelet-to-lymphocyte and NLRs, have been investigated for their diagnostic value in PPROM and threatened preterm labor, further underscoring the relevance of readily available hematologic parameters in this context (9). Collectively, our data support the use of simple inflammatory indices, including DNI, as adjunctive tools in the evaluation of infection risk in PPROM.

Furthermore, the integration of other hematologic parameters—PLT, INR, and maternal diastolic blood pressure—into our predictive model strengthens the rationale for a combined assessment using routine hematologic parameters for early identification of chorioamnionitis. The association with elevated PLTs is noteworthy, raising the possibility that thrombocytosis reflects an active hematological response to systemic inflammation rather than a coincidental finding (10). This observation is consistent with the broader concept that platelets act as immunomodulatory cells in inflammatory cascades, rather than merely serving hemostatic functions (10).

Our findings suggest that incorporating DNI into routine assessment may help clinicians recognize infection earlier in the course of PPROM. The routine use of DNI—alone or in combination with complementary biomarkers—may allow obstetricians to anticipate infection, initiate timely interventions, and reduce neonatal exposure to inflammatory insults.

Inflammatory biomarkers such as CRP and procalcitonin have long been used in the diagnostic workup of chorioamnionitis; however, their delayed rise in levels and limited specificity reduce their reliability. By contrast, the DNI reflects early granulocytic activation and can be measured rapidly and at no additional cost as part of a standard CBC (11). In our study, CRP levels were significantly higher in the chorioamnionitis group, in line with previous reports. However, CRP is a non-specific acute-phase reactant that may increase in diverse infectious and non-infectious conditions, including tissue injury and autoimmune disorders (12). This inherent lack of specificity underscores the need for adjunctive biomarkers, with DNI offering a promising alternative.

Chorioamnionitis is a common complication of pregnancies with PPROM and an established risk factor for adverse fetal and neonatal outcomes. The inflammatory cascade underlying this condition is initiated by maternal immune activation—whether triggered by microbial invasion or sterile inflammation—and is characterized histologically by neutrophil infiltration of the amniotic membranes (13). In line with this pathophysiological

process, our findings revealed significantly higher DNI values in patients diagnosed with chorioamnionitis (p=0.029), suggesting enhanced neutrophil mobilization and increased levels of circulating immature granulocytes. This observation reinforces DNI's potential as a marker for early intrauterine inflammatory activity (7).

Collectively, these findings support the broader concept of using blood-based inflammatory indices—such as the NLR, CRP, lymphocyte count, and particularly DNI—in the early detection of chorioamnionitis during preterm labor. These markers are non-invasive, rapidly obtainable, and cost-effective, making them especially attractive in high-volume or resource-limited clinical settings. Ridout et al. (14) have emphasized the diagnostic potential of NLR in preterm labor management, particularly in low-income countries. In a similar vein, our data suggest that DNI, due to its higher specificity than traditional markers, may represent a more effective screening tool for early identification of chorioamnionitis in PPROM. The ability to intervene at an earlier stage could translate into reduced maternal and fetal morbidity.

These findings have meaningful clinical implications. Early administration of antibiotics for confirmed or suspected chorioamnionitis has been shown to significantly reduce rates of neonatal sepsis and maternal complications (15). The diagnostic cut-off of 0.11 identified for DNI via ROC analysis may provide a practical reference point for clinicians. This threshold, with its balanced sensitivity and specificity, could assist in risk stratification, guide timely initiation of antibiotic therapy, and even inform decisions regarding the optimal timing of delivery in at-risk pregnancies.

In our study, the significantly elevated maternal diastolic blood pressure observed in chorioamnionitis may reflect the interplay among systemic inflammation, sympathetic activation, and endothelial dysfunction. Pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) are known to impair endothelial tone and promote vasoconstriction, while systemic inflammation can activate the sympathetic nervous system and increase vascular resistance (16). Placental inflammation and hypoperfusion may further contribute to maternal hemodynamic instability, suggesting that chorioamnionitis extends beyond intrauterine infection and exerts systemic cardiovascular effects during pregnancy (17).

The incidence of chorioamnionitis in our cohort was 10% (n=30), aligning with reported rates of 1-5% at term and 20-30% in preterm pregnancies (18). This relatively high incidence likely reflects the tertiary referral nature of our center, where high-risk pregnancies are concentrated. In addition, INR values were slightly but significantly higher in affected patients, although still within normal limits. This finding may indicate subtle cytokine-mediated alterations in hepatic synthetic function or early coagulopathy, consistent with previous reports linking chorioamnionitis to coagulation disturbances (18,19).

Our study contributes to the limited literature on DNI in PPROM by combining a relatively large, well-characterized cohort with comprehensive hematologic profiling. These results reinforce the potential of DNI—together with dynamic markers such as PLT, INR, and blood pressure parameters—as part of an integrated, real-time infection surveillance strategy in obstetric practice.

Study Limitations

This study has some limitations. Its retrospective and single-center design may limit the generalizability of the results. Because of the retrospective design, an a priori power analysis could not be performed; however, a post-hoc power calculation demonstrated that the sample size (n=300) provided adequate statistical power to detect large effect sizes. In addition, DNI values were obtained using a specific hematology analyzer (ADVIA 2120), and inter-laboratory variations cannot be completely excluded. Another limitation is that DNI was measured only once during hospitalization, which did not allow for evaluation of temporal changes. Nevertheless, these findings provide meaningful preliminary evidence supporting the potential role of DNI in PPROM, and future multicenter prospective studies are needed to confirm and expand upon our results.

Conclusion

Our findings suggest that the DNI may serve as a useful biomarker for identifying the risk of chorioamnionitis in pregnancies complicated by PPROM. An elevated DNI level was significantly associated with infection, highlighting its potential role in early diagnosis. Because DNI is rapid, cost-effective, and easily accessible through routine blood counts, it may represent a practical adjunct in clinical decision-making. When interpreted together with other inflammatory markers, DNI could contribute to a more accurate and timely assessment of infection risk and guide prenatal management strategies in cases of PPROM. Nonetheless, confirmation in larger, multicenter prospective studies is essential before the integration of DNI into standardized care protocols can be recommended.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval no: 2023-610, date: 27.11.2023).

Informed Consent: This study was conducted retrospectively, Independent Ethics Committee University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital approved the waiver of informed consent. Patient confidentiality was maintained throughout the study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: T.A., Concept: T.A., K.K.B., Design: T.A., K.K.B., Data Collection or Processing: T.A., K.K.B., Analysis or Interpretation: T.A., Literature Search: T.A., Writing: T.A.

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