

LEUKOCYTE COUNT AND NEUTROPHIL-TO-LYMPHOCYTE RATIO IN PREGNANCIES WITH PREMATURE RUPTURE OF MEMBRANES: A COMPARATIVE STUDY

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Abstract: Background: Premature Rupture of Membranes (PROM) increases maternal and neonatal morbidity through inflammatory mechanisms. Hematological markers such as leukocyte count and neutrophil-to-lymphocyte ratio (NLR) may serve as cost-effective inflammatory indicators. Objective: To compare leukocyte levels and NLR values between pregnancies with PROM and normal pregnancies. Methodology: This cross-sectional study included 72 subjects (36 PROM, 36 normal pregnancies) at Adam Malik General Hospital and affiliated centers. Complete blood count data were analyzed using appropriate statistical tests ($p < 0.05$). Results: Leukocyte levels were significantly higher in the PROM group versus normal pregnancy (14.33 ± 4.59 vs 11.02 ± 2.25 thousand/ μL ; $p = 0.010$). NLR values were markedly elevated in term PROM (12.16 ± 6.86) and preterm PROM (11.08 ± 7.04) compared to normal pregnancy (median 4; $p < 0.001$). Post-hoc analysis confirmed significant differences between PROM/PPROM versus normal groups. Conclusions: NLR demonstrates potential as a simple, accessible biomarker for detecting inflammatory conditions in PROM, supporting early clinical assessment in resource-limited settings.

Keywords: inflammation, leukocyte, neutrophil-to-lymphocyte ratio, premature rupture of membranes, pregnancy

INTRODUCTION

Premature Rupture of Membranes (PROM) is defined as the spontaneous rupture of fetal membranes before the onset of labor, occurring either at term (≥ 37 weeks) or preterm (< 37 weeks) gestation (Schmitz et al., 2019). This condition represents a significant obstetric concern due to its association with increased risks of maternal and neonatal infections, preterm delivery, and subsequent morbidity and mortality (Tchirikov et al., 2018). Globally, PROM affects approximately 5–10% of all pregnancies, with nearly one-third of cases resulting in preterm birth (World Health Organization, 2014). In Indonesia, hospital-based reports indicate varying incidence rates, ranging from 5.1% to 11.2%, underscoring the need for accessible diagnostic tools to support timely clinical decision-making (Rohmawati & Ika, 2018).

The etiology of PROM is multifactorial, with intrauterine infection and inflammatory processes recognized as central contributors (Andalas et al., 2019). Bacterial pathogens such as *Escherichia coli*, *Streptococcus* group B, and *Staphylococcus aureus* have been implicated in membrane weakening through enzymatic degradation and cytokine-mediated pathways (Harger et al., 1990). In response to infection or sterile inflammation, the maternal immune system activates neutrophils and other leukocyte subpopulations, leading to measurable changes in peripheral blood parameters (Choltus et al., 2021).

Among hematological indicators, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a practical, cost-effective marker of systemic inflammation. NLR is calculated from routine complete blood count results and has demonstrated utility in predicting adverse pregnancy outcomes, including preeclampsia and preterm birth (Esercan & Demir, 2023). Several studies have reported elevated NLR values in women with preterm PROM compared to controls, suggesting its potential role in early detection of inflammatory activity associated with membrane rupture (Toprak et al., 2017; Lazarosony et al., 2023).

Despite growing evidence, data comparing NLR and leukocyte levels across term PROM, preterm PROM, and normal pregnancies remain limited, particularly in Indonesian clinical settings. Furthermore, most prior studies have focused exclusively on preterm PROM, potentially overlooking inflammatory patterns specific to term presentations. This study aimed to address this gap by comparing leukocyte counts and NLR values among pregnancies with term PROM, preterm PROM, and normal term pregnancies at Adam Malik General Hospital and affiliated centers. Findings from this research may support the integration of NLR into routine hematological screening for PROM, particularly in resource-constrained healthcare environments.

METHODS

Study Design and Setting

This analytical cross-sectional study was conducted at Adam Malik General Hospital and its affiliated network hospitals (Prof. dr. CPL USU Hospital and Pirngadi General Hospital, Medan, Indonesia) from April 2025 until the required sample size was achieved.

Population and Sampling

The target population comprised pregnant women with confirmed PROM (both term and preterm) and normal term pregnancies (≥ 37 weeks). Participants were recruited using consecutive non-probability sampling. Inclusion criteria included: confirmed gestational age by ultrasound and last menstrual period; fluid leakage confirmed by positive nitrazine test; no history of trauma, abdominal massage, or heavy physical activity; no chronic diseases (malignancy, autoimmune disorders, diabetes, chronic hypertension); no prior PROM; no use of uterotonics, NSAIDs, steroids, immunomodulators, or antibiotics; no active infections; and signed informed consent. Exclusion criteria included incomplete medical records or laboratory data. Based on power analysis for comparing two independent means, a minimum of 36 subjects per group was determined.

Variables and Measurements

The independent variables were leukocyte count (thousand/ μL) and NLR, calculated as the ratio of absolute neutrophil count to absolute lymphocyte count from the most recent complete blood count performed at the clinical pathology laboratory of Adam Malik General Hospital. Leukocyte levels were categorized as low ($< 4,000/\text{mm}^3$), normal ($4,000\text{--}11,000/\text{mm}^3$), or high ($> 11,000/\text{mm}^3$). The dependent variable was PROM status, classified as term PROM (≥ 37 weeks), preterm PROM (< 37 weeks), or normal pregnancy.

Data Analysis

Data were analyzed using SPSS version 26. Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed data were presented as mean \pm standard deviation; non-normal data were presented as median (range). Group comparisons for normally distributed variables used independent t-tests; non-parametric comparisons used Mann–Whitney U tests. Post-hoc analysis for multiple groups employed Dunn's method. Statistical significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

Demographic Characteristics

Table 1. Demographic Characteristics

Demographic Characteristics	PROM	
	Yes (n= 36)	No (n = 36)
Age, n (%)		
< 20 years	7 (19,4)	7 (19,4)
20 – 30 years	19 (52,8)	17 (47,2)
> 30 years	10 (27,8)	12 (33,3)
Gestational Age, weeks		
≥ 37 weeks	17 (47,2)	33 (91,7)
< 37 weeks	19 (52,8)	3 (8,3)
Parity, n (%)		
Primigravida	7 (19,4)	6 (16,7)
Sekundigarivida	16 (44,4)	16 (44,4)
Multigravida	2 (5,6)	2 (5,6)
Grande Multigravida	11 (30,6)	12 (33,3)

A total of 72 pregnant women were included: 36 with PROM (17 term, 19 preterm) and 36 with normal term pregnancies. Maternal age distribution was comparable across groups, with the majority aged 20–30 years (PROM: 52.8%; PPRM: 52.6%; normal: 47.2%). As expected by definition, all term PROM cases occurred at ≥37 weeks, while all preterm PROM cases occurred at <37 weeks. Parity distribution showed secundigravida and grande-multigravida predominance in PROM groups, consistent with prior reports suggesting cumulative biomechanical stress may influence membrane integrity (Sharma et al., 2021).

Hematological Parameters

Table 2. Distribution of Maternal Demographic Characteristics Based on the Type of Premature Rupture of Membranes (PROM, PPRM) and the Normal Group

Demographic Characteristics	PROM (n = 17)	PPROM (n = 19)	Normal (n = 36)
Age, n (%)			
< 20 years	3 (17,6)	4 (21,1)	7 (19,4)
20 – 30 years	9 (52,9)	10 (52,6)	17 (47,2)
> 30 years	5 (29,4)	5 (26,3)	12 (33,3)
Gestational age, weeks			
≥ 37 weeks	17 (100)	0	33 (91,7)
< 37 weeks	0	19 (100)	3 (8,3)
Parity, n (%)			
Primigravida	3 (17,6)	4 (21,1)	6 (16,7)
Sekundigarivida	10 (58,8)	6 (31,6)	16 (44,4)
Multigravida	0	2 (10,5)	2 (5,6)
Grande Multigravida	4 (23,5)	7 (36,8)	12 (33,3)

Leukocyte levels differed significantly among groups ($p=0.010$), with higher means in PROM (14.33 ± 4.59 thousand/ μL) and PPRM (14.31 ± 6.90 thousand/ μL) compared to normal pregnancy (11.02 ± 2.25 thousand/ μL). This finding aligns with prior evidence linking leukocytosis to inflammatory activation in PROM (Margono et al., 2021; Rahmayanti & Nurdin, 2023).

Table 3 presents the differences in leukocyte, neutrophil, and lymphocyte levels among the three study groups.

Table 3. Differences in Leukocyte, Neutrophil, and Lymphocyte Levels Between PROM, PPRM, and Normal Pregnancy

Variable	PROM	PPROM	Normal	p
Leucocyte, ribu/ μ L	14,33 \pm 4,59	14,31 \pm 6,9	11,02 \pm 2,25	0,010 ^a
Neutrophil	11,14 \pm 4,47	10,2 \pm 6,91	7,15 (4-17,67)	0,073 ^b
Lymphocyte	1,54 \pm 0,65	1,57 \pm 0,57	1,73 (0,72-3,75)	0,429 ^b

NLR values showed a highly significant difference across groups ($p < 0.001$). Both PROM (12.16 \pm 6.86) and PPRM (11.08 \pm 7.04) exhibited markedly elevated NLR compared to normal pregnancy (median 4; range 1.6–17). Post-hoc analysis confirmed significant differences between PROM versus normal ($p = 0.001$) and PPRM versus normal ($p = 0.005$), but not between PROM and PPRM ($p = 1.000$). These results corroborate international studies reporting NLR elevation in PROM contexts (Sultana & Karim, 2024; Toprak et al., 2017; Lazarosony et al., 2023).

Table 4. Differences in Neutrophil-to-Lymphocyte Ratio (NLR) Values Between PROM, PPRM, and Normal Pregnancy

Variable	NLR	p^b	Posthoc ^b	
			PPROM	Normal
PROM	12,16 \pm 6,86	<0,001	1,000	0,001
PPROM	11,08 \pm 7,04			0,005
Normal	4 (1,6 – 17)			

The comparable NLR elevation in term and preterm PROM suggests that systemic inflammatory activation may follow similar pathways regardless of gestational age at membrane rupture. This observation supports the biological plausibility of NLR as a universal inflammatory indicator in PROM, rather than a gestational-age-specific marker.

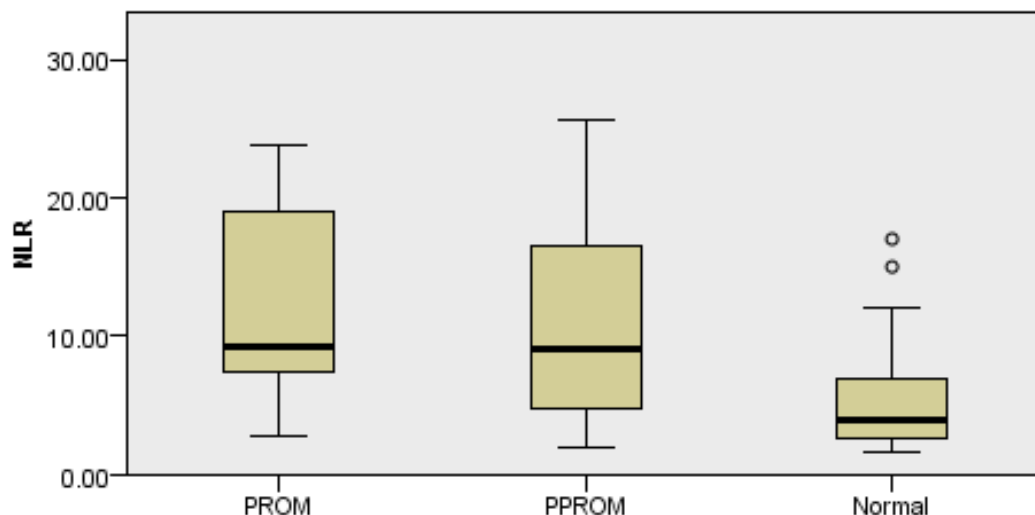


Figure 1. Box Plot Graph of the Comparison of Neutrophil-to-Lymphocyte Ratio (NLR) Values in PROM, PPROM, and Normal Pregnancy

Clinical Implication

The practical advantage of NLR lies in its derivation from routine, low-cost complete blood count testing, making it particularly valuable in settings with limited access to specialized inflammatory biomarkers. Elevated NLR may prompt clinicians to initiate closer monitoring, antibiotic prophylaxis, or timely delivery planning in PROM cases. However, NLR should be interpreted alongside clinical assessment, as non-infectious inflammatory conditions may also elevate this ratio.

Limitations

This study has several limitations. The cross-sectional design precludes causal inference between NLR elevation and PROM onset. Consecutive sampling may introduce selection bias, limiting generalizability. Potential confounders such as subclinical infection, nutritional status, and environmental exposures were not fully controlled. Additionally, strict exclusion criteria may reduce applicability to broader pregnant populations. Future prospective studies with larger, multicenter samples are recommended to validate NLR cutoff values and assess its predictive utility in clinical algorithms.

CONCLUSION

This study demonstrated that the neutrophil-to-lymphocyte ratio reflects systemic inflammatory activity and shows potential as a hematological biomarker to distinguish pregnancies with premature rupture of membranes from normal pregnancies. The similar NLR elevation in both term and preterm PROM suggests a comparable inflammatory response regardless of gestational age. These findings support the integration of NLR into routine hematological assessment for early detection of inflammatory complications in PROM, particularly in healthcare settings with limited diagnostic resources.

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