DOI: 10.7860/JCDR/2024/68722.19077

Original Article

Pathology Section

Evaluation of the Predictive Role of Neutrophil Lymphocyte Ratio and Mean Platelet Volume in Preterm Deliveries: A Cross-sectional Study

DISHA SAI M CHANDAVAR[1], JESSICA MINAL[2], KS RASHMI[3]

ABSTRACT

Introduction: Preterm birth is associated with high perinatal morbidity and mortality. Identifying women at risk for preterm labour early in pregnancy may improve pregnancy outcomes. Neutrophil-Lymphocyte Ratio (NLR) and Mean Platelet Volume (MPV) can be helpful in predicting preterm labour, as infection is an important factor in early preterm deliveries, with immunity playing a key role in preterm labour.

Aim: To evaluate the predictive role of the NLR and MPV in preterm deliveries.

Materials and Methods: This cross-sectional study was conducted in a tertiary care and research hospital from August 2022 to October 2023. Haematological and clinical data were retrieved for preterm deliveries (n=79, group I) and term deliveries (n=151, group II). The two groups were compared in terms of demographic characteristics, obstetric and laboratory findings, including maternal age, gravida, parity, birth weight, NLR, MPV, and haemoglobin levels. The data were analysed using Statistical Package for the Social Sciences (SPSS) version 29.0. One-way Analysis of Variance (ANOVA) was used to compare the mean values among different groups. Categorical values were evaluated with Pearson's Chi-square test. Receiver Operating Characteristic (ROC) curve was used to assess the diagnostic properties of the tests.

Results: The two groups showed no statistical difference in terms of demographic parameters such as the mother's age (p-value=0.611), parity (p-value=0.798), and gravida (p-value=0.583). The NLR was higher in group I (5.8±5.01) compared to group II (4.3±1.75), and this difference was statistically significant with a p-value of <0.001. MPV was observed to be lower in group II (8.7±0.96) compared to group I (8.9±1.07); however, this difference was not statistically significant (p-value=0.128). The mean baby weight and mean maternal haemoglobin in group I were significantly lower compared to group II.

Conclusion: In this study, the NLR value was significantly higher in patients with preterm deliveries compared to term deliveries. This study highlights the role of NLR as an emerging predictor of preterm deliveries and emphasises that NLR, obtained from an inexpensive and routinely conducted haemogram, has the potential to be used as an early indicator of preterm deliveries.

Keywords: Complete blood count, Inflammation, Labour, Pregnancy outcome

INTRODUCTION

Preterm delivery, defined as delivery before 37 weeks or 259 days of gestation, is classified into early preterm (<34 weeks) and late preterm (34-37 weeks) and is a significant factor contributing to perinatal morbidity and mortality [1,2]. In addition to the increased risk of mortality, children born preterm also face numerous challenges such as neurological deficits, learning disabilities, and respiratory problems [1]. Predicting preterm birth becomes crucial for healthcare workers to be prepared for timely interventions [3]. Developing strategies to improve access to effective care should be a research and operational priority, especially in developing countries like India [1]. Inflammation and infection play important roles in the aetiology of preterm birth, and identifying non invasive methods or markers associated with these conditions may be crucial [2]. Unfortunately, currently, there is a lack of effective diagnostic parameters for predicting preterm labour and its outcomes [1].

An increase in the number of leukocytes or neutrophils in subclinical inflammation is due to the systemic response to intrauterine infection regulated by the natural immune system. Neutrophil counts increase, and lymphocyte counts decrease, resulting in an increased NLR in spontaneous preterm birth. NLR is an affordable, simple, and readily available parameter of stress and inflammation that reflects the potent relationship between the innate (neutrophils) and adaptive (lymphocytes) immune response during illness and diseased conditions [2]. Clinical research has established the sensitivity of NLR for the diagnosis of systemic infection, sepsis, and its strong predictive and prognostic value [4]. The role of NLR as an inflammatory parameter for the early prediction of preterm delivery has been explored in several studies; however, the results of these studies have been conflicting [4-7]. The normal range of NLR in healthy non geriatric adults is between 0.78 and 3.58 [8]. Women with a high NLR may be more likely to experience preterm labour progressing to preterm birth [2].

MPV, a routinely performed automated whole blood count parameter, is indicative of platelet function and activity, and it reflects the size of platelets. It plays an important role in immunological and inflammatory events [2]. The normal value of MPV is between 7.2 and 11.7 fL [9]. In some chronic inflammatory disorders, an inverse correlation between disease activity and MPV has been demonstrated [2]. In preterm labour, which is a highly inflammatory state, the consumption of large platelets at the site of inflammation causes a decrease in MPV levels [2].

Both of these indices, NLR and MPV are inexpensive and easily accessible parameters and they may serve as pivotal proinflammatory biomarkers in patients who experience preterm deliveries [2]. Therefore, interpreting the possible role of NLR and MPV based on routinely conducted Complete Blood Count (CBC) parameters may help predict the occurrence of preterm labour and preterm deliveries, enabling better preparedness for pregnant women, obstetricians, and the healthcare team to perform the necessary interventions [4]. Although the role of NLR in predicting preterm labour has been studied, regional research on the utility of this parameter is limited. The utility of MPV in predicting preterm labour also needs further exploration, as it is an area that has not been

adequately researched. The current study may provide possible indications for identifying surrogate first-line indicators of preterm deliveries, which could be useful in facilities that lack resources or have limited resources to manage preterm deliveries and care for preterm babies. The aim of the study was to evaluate the predictive role of the NLR and MPV for preterm deliveries, and to assess if a cut-off value can be established for these two parameters to predict delivery outcomes.

MATERIALS AND METHODS

This was a cross-sectional study conducted in the Central Laboratory, Haematology section at Dr. Chandramma Dayananda Sagar Institute of Medical Education and Research, a tertiary care centre in Ramanagara, Karnataka, India, from August 2022 to October 2023. Ethics committee clearance for the study was obtained from the Institutional Ethics Committee (IEC) (CDSIMER/MR/0048/IEC/2022). Since this was a retrospective study, a waiver of consent was granted.

Inclusion criteria: Pregnant women aged ≥18 years with available haematological records from the last/third trimester were included in the study.

Exclusion criteria: Patients with induced labour, multiple pregnancies, anomalies of the female genital tract, and a history of smoking were excluded from the study.

Sample size: A convenience sample of 230 patients was selected for the study from August 2022 to December 2023. These patients were classified into two groups: preterm (delivery before 37 weeks, group I= 79) and term (delivery at or after 37 weeks, group II=151).

Study Procedure

Patient medical records and electronic data were retrieved, and the two groups were compared with respect to demographic specifications and obstetric findings such as maternal age, gravida, parity, infant gender, mode of delivery, and laboratory findings including NLR, MPV, and haemoglobin levels. Relevant patient details were obtained from the laboratory database and medical case records. All samples were analysed on a Beckman five-part haematology analyser, and the results were standardised by conducting external and internal quality control checks daily in accordance with laboratory protocols. CBC parameters from the third trimester were retrieved, and laboratory parameters including haemoglobin, NLR, and MPV were recorded for all participants during the third trimester. NLR was calculated by dividing the neutrophil count by the lymphocyte count obtained from the same run.

STATISTICAL ANALYSIS

The data were collected and analysed using the statistical software, SPSS version 29.0. The results were expressed as the mean±Standard Deviation (SD). Baseline demographic specifications of the study groups were described in terms of frequency, percentage, mean, and SD. Mean values between the groups were compared using one-way ANOVA. Categorical values were evaluated using Pearson's Chi-square test. A two-tailed p-value <0.05 was considered statistically significant. The diagnostic properties of significant tests were assessed using ROC curves. The optimal cut-off value for significant variables was determined, followed by the assessment of sensitivity, specificity, and the area under the ROC curve.

RESULTS

A total of 230 patients were included in the study, consisting of 79 patients who gave birth before 37 weeks of gestation (preterm, group I) and 151 patients who delivered at or after 37 weeks of gestation (term, group II).

The mothers' ages in the entire dataset ranged from 18 to 37 years, with an average age of 25.1±4.4 years. The average birth weight of the babies was 2.7±0.54 kg, ranging from 0.9 kg to 4.3 kg. The average NLR was 4.8±3.3, and the average MPV was 8.8±1.01 fL for the entire dataset of 230 patients. There were no statistically significant differences between group I and group II in terms of demographic parameters such as mother's age, parity, and gravida [Table/Fig-1].

There were statistically significant differences between the groups in terms of baby's birth weight and haemoglobin. The mean birth weight in group I was lower (2.3±0.59 kg) compared to group II (2.9±0.37 kg), and this difference was statistically significant (p-value <0.001). The mean maternal haemoglobin in group I was 11.5±1.51 g/dL, which was significantly lower compared to group II (12.0±1.43 g/dL) (p-value=0.013). NLR was higher in the preterm group I (5.8±5.01) compared to the term group I (4.3±1.75), and this difference was statistically significant with a p-value <0.001. MPV was slightly lower in the term group (8.7±0.96 fL) compared to the preterm group (8.9±1.07 fL), but this difference was not statistically significant (p=0.128) [Table/Fig-1].

Parameters	Total (n=230)	Group I (Preterm <37 weeks/<259 days) (n=79)	Group II (Term ≥37 weeks ≥259 days) (n=151)	p-value
Mothers age in years mean±SD	25.1±4.4 (18-37)	24.9±4.8 (18-37)	25.2±4.2 (18-37)	0.611[a]
Mean gestational age (\in days)	261.4±15.6 (201-287)	244.4±14.4 (201-258)	270.3±5.9 (259-287)	<0.001[a]
Gravida±SD	1.8±0.96 (1-6)	1.9±1.16 (1-6)	1.8±0.84 (1-4)	0.583[a]
Parity±SD	0.6±0.71 (0-3)	0.5±0.77 (0-3)	0.6±0.68 (0-3)	0.798[a]
Baby's birth weight (kg) mean±SD	2.7±0.54 (0.9-4.3)	2.3±0.59 (0.9-3.6)	2.9±0.37 (2.1-4.3)	<0.001[a]
Baby's gender %				
Female	116	39/79=49.4%	77/151=51%	0.815[c]
Male	114	40/79=50.6%	74/151=49%	
Mode of delivery, %				
FTNVD	125	44/79=55.7%	70/151=46.4%	0.767[c]
LSCS	105	35/79=44.3%	81/151=53.6%	
Mother's haemoglobin gm/dL mean±SD	11.8±1.48 (7.1-15.9)	11.5±1.51 (7.1-15.9)	12.0±1.43 (7.2-15.5)	0.013[a]
Neutrophils % mean±SD	73.9±7.06 (49.3-95.9)	75.6±8.59 (53.5-95.9)	73.1±5.96 (49.4-88.6)	0.010[a]
Lymphocytes % mean±SD	18.3±6.95 (2.6-79.3)	17.1±6.73 (2.6-35.6)	18.9±6.99 (7.6-79.3)	0.048[a]
NLR mean±SD	4.8± 3.3 (1.0-37.2)	5.8± 5.01 (1.5-37.2)	4.3± 1.75 (1-11.6)	<0.001[a]
MPV (Fl) mean±SD	8.8±1.01 (6.4-13.7)	8.9±1.07 (6.4-13.1)	8.7±0.96 (7.1-13.7)	0.128[a]

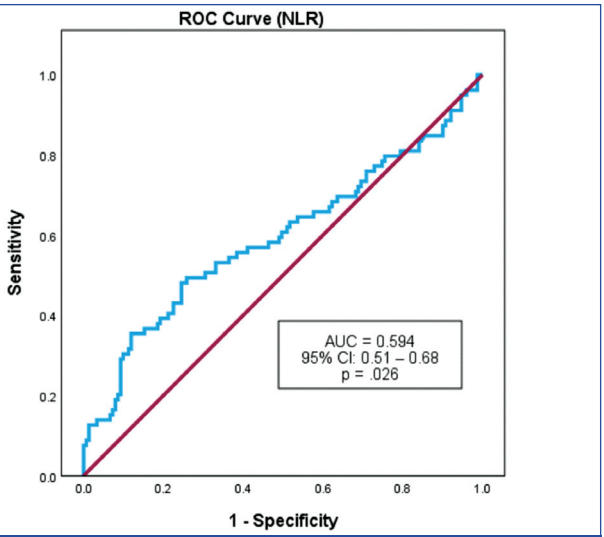
[Table/Fig-1]: Characteristics of descriptive and clinical data amongst different groups.
n: Number; %: Percentage; SD: Standard deviation; a: one-way variance analysis; c: Chi-square test; FTNVD: Full term normal vaginal delivery; LSCS: Lower segment ceasarean section; NLR: Neutrophil-lymphocyte ratio; MPV: Mean platelet volume

Further analysis of the preterm groups with respect to early preterm (<34 weeks) and late preterm (34-37 weeks) showed no significant differences between the different laboratory parameters [Table/Fig-2].

Laboratory parameters	<34 weeks n=18	34-37 weeks n=61	p-value
Haemoglobin (gm/dL) mean±SD	11.4±1.66 (7.1-13.5)	11.6±1.48 (7.9-15.9)	0.611[a]
Neutrophils (%) mean±SD	73.8±12.1 (53.5-95.9)	76.1±7.3 (62.3-95.2)	0.324[a]
Lymphocytes (%) mean±SD	18.6±9.95 (2.6-35.6)	16.6±5.46 (4-28.9)	0.271[a]
NLR mean±SD	6.89±8.27 (1.5-37.2)	5.5± 3.59 (2.3-23.8)	0.318[a]
MPV (fL) mean±SD	8.9±1.05 (6.4-10.7)	9.0±1.08 (7.1-13.1)	0.758[a]

[Table/Fig-2]: Detailed distribution of lab parameters amongst different subgroups of preterm.
n: Number; %: Percentage; SD: Standard deviation; a: one way variance analysis; c: Chi-square test; NLR: Neutrophil-lymphocyte ratio; MPV: Mean platelet volume

ROC curve analysis to study the diagnostic value of NLR in predicting preterm deliveries showed that an NLR >4.33 had a sensitivity of 53% and specificity of 67% [Table/Fig-3,4].



[Table/Fig-3]: Receiver Operating Characteristic (ROC) curve for NLR values.
AUC: Area under curve; CI: Confidential interval

Cut-off	Sensitivity (%)	Specificity (%)
3.83	65	45
3.90	63	48
3.95	61	50
3.99	58	54
4.01	57	56
4.15	56	60
4.24	56	62
4.33	53	67
4.48	51	70
4.71	49	72
4.86	47	75

[Table/Fig-4]: Diagnostic sensitivity and specificity of NLR at different cut-offs.

Among the other laboratory parameters for the total samples, the mother's haemoglobin was positively correlated with the baby's birth weight and negatively correlated with MPV. Neutrophil count and NLR were positively correlated as expected. Other observations included a negative correlation between NLR and the baby's birth weight [Table/Fig-5].

DISCUSSION

In the current study, the predictive role of inflammatory markers such as NLR and MPV in preterm and term deliveries was investigated. It was observed that NLR was significantly higher in group I compared to group II. The diagnostic value of NLR in predicting preterm deliveries before 37 weeks demonstrated that an NLR >4.33 had a sensitivity of 53% and specificity of 67%. On the other hand, MPV was found to be lower in group II compared to group I, but this difference was not statistically significant. Therefore, MPV did not have a role in predicting the timing of deliveries. The observation of lower MPV in group II compared to the preterm group I is intriguing and warrants further validation in future studies.

Preterm delivery, defined as delivery before 37 weeks of gestation, is a significant factor contributing to perinatal morbidity and mortality, with long-term implications [1]. Various factors such as stress, infection, placental disorders like abruption and placenta previa, prior history of preterm birth or abortion, and inadequate maternal care contribute to preterm labour. Foetal inflammatory response syndrome, characterised by systemic inflammation and elevated interleukin-6 levels, is a key event in preterm labour initiation [10]. Given the crucial role of inflammation in triggering preterm labour, markers associated with neutrophils may have a predictive role in preterm deliveries [4]. This study aimed to investigate novel inflammatory markers for their predictive value in preterm and term deliveries.

The NLR has been found to have a correlation with the prognosis of systemic inflammatory diseases [3]. NLR is a simple marker derived from a CBC and has previously been observed to be increased in pregnancy complications such as preeclampsia, gestational diabetes mellitus, intrahepatic cholestasis of pregnancy, and hyperemesis gravidarum [11]. MPV, on the other hand, reflects platelet function and activity and plays a significant role in immunological and inflammatory events [3]. In highly inflammatory conditions like preterm labour, the consumption of large platelets at the site of inflammation leads to a reduction in MPV [2].

In a study conducted by Kurban Y et al., NLR was found to be higher in preterm births, which was consistent with the findings of present study [2]. Similarly, Melissa CL et al., observed a significant elevation of NLR in patients with preterm labour [12]. However, a study by Khatoon F et al., in the Indian population reported that although neutrophil levels were significantly elevated and lymphocytes were reduced in pregnant women with preterm labour, the NLR ratio itself was not significantly increased in the preterm labour group [13].

In a study by Christoforaki V et al., the NLR of pregnant women in the first trimester was compared between those who had a live birth at 37 weeks and those who experienced a miscarriage. There was no statistically significant difference in NLR between the two groups, with

Correlation table								
Variables		Mothers_age	Baby_weight	Mother-HB	Mothers-N	Mothers-LY	Mothers-NLR	Mothers- MPV
Mothers_age	Pearson correlation	1	-0.008	0.037	-0.057	-0.048	-0.063	0.063
	Sig. (2-tailed)		0.907	0.580	0.386	0.466	0.341	0.339
Baby_Weight	Pearson correlation	-0.008	1	0.151*	0.012	-0.036	-0.137*	-0.054
	Sig. (2-tailed)	0.907		0.022	0.853	0.591	0.038	0.419
Mother-HB	Pearson correlation	0.037	0.151*	1	-0.118	0.084	-0.116	-0.141*
	Sig. (2-tailed)	0.580	0.022		0.075	0.205	0.080	0.033

Mothers-N	Pearson correlation	-0.057	0.012	-0.118	1	-0.715**	0.752**	0.064
	Sig. (2-tailed)	0.386	0.853	0.075		<0.001	<0.001	0.338
Mothers-LY	Pearson correlation	-0.048	-0.036	0.084	-0.715**	1	-0.645**	-0.042
	Sig. (2-tailed)	0.466	0.591	0.205	<0.001		<0.001	0.529
Mothers-NLR	Pearson correlation	-0.063	-0.137*	-0.116	0.752**	-0.645**	1	0.092
	Sig. (2-tailed)	0.341	0.038	0.080	<0.001	<0.001		0.165
Mothers- MPV	Pearson correlation	0.063	-0.054	-0.141*	0.064	-0.042	0.092	1
	Sig. (2-tailed)	0.339	0.419	0.033	0.338	0.529	0.165	

[Table/Fig-5]: Correlation across different variables for the entire sample.
*Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed); HB: Haemoglobin; N: Neutrophil; LY: Lymphocytes; NLR: Neutrophil-lymphocyte ratio; MPV: Mean platelet volume

values of 2.5±1.0 and 2.9±1.5, respectively. However, NLR values higher than 5.8 were only found in the miscarriage group, suggesting a potential clinical utility that requires further validation [11].

Hershko Klement A et al., investigated NLR values during pregnancy in both high-risk and normal-risk populations and found no difference between the two groups. They also noted that the peak value of NLR is reached during the second trimester, with these values positively correlating with age [14].

Another study by Ozel A et al., suggested that NLR values were significantly higher in the Preterm Premature Rupture of Membranes (PPROM) group compared to the threatened preterm labour group and the healthy control group. They concluded that NLR can be a cost-effective parameter in the management of PPROM [15].

In the current study, MPV was observed to be lower in group II compared to group I; however, this difference was not statistically significant. This finding contradicts the results of Kurban Y et al., where a significant decrease in MPV was found in the preterm birth group compared to the term group (p-value <0.05) [2]. Abd El-Rhaman Abd El-Fattah I et al., also investigated the role of MPV in predicting PPROM and found a positive correlation between these parameters, highlighting the potential of MPV in identifying patients at risk for PPROM [16]. Platelet activation plays a significant role in the pathophysiology of infection, inflammation, and malignancy. However, there is a limited number of studies examining the role of MPV in term and preterm labour, which suggests the need for further research in this area. Ekın A et al., demonstrated that women with PPROM had significantly lower MPV values in the first trimester compared to controls [17]. In present study, MPV was lower in the term group compared to the preterm group; however, this difference was not statistically significant. It's worth noting that present study specifically examined MPV values in the third trimester.

Limitation(s)

The study was conducted as an exploratory research to identify and determine the predictive role of NLR and MPV in preterm deliveries, given the intriguing yet controversial literature on this topic. The limitations of the present study were the small size of the study group and the lack of adjustment for potential confounders such as medications, chronic diseases like coronary heart disease, stroke, diabetes, and stress among the study groups. Although this study was cross-sectional, only patients without risk factors have been included. However, it cannot exclude certain subgroups with elevated NLR due to underlying conditions. The authors' preliminary observations in the present study therefore call for larger prospective case-control studies that may provide better insights and stronger evidence regarding the predictive role of these parameters.

CONCLUSION(S)

Preterm deliveries remain a critical healthcare issue, especially in developing countries like India. There is a need to predict these events to enhance preparedness and improve access to effective care for preterm deliveries. The findings of this study demonstrate that the NLR value was significantly higher in patients with preterm delivery compared to term deliveries. Present study aimed to emphasise the role of NLR as an emerging predictor of preterm deliveries. Authors believe that NLR, obtained from an inexpensive and routinely performed haemogram has the potential to serve as an early indicator of preterm deliveries. Prospective studies with larger datasets and rigorous methodologies are necessary to validate the observations made in this study.

Acknowledgement

Authors would like to acknowledge the laboratory staff especially the non-teaching staff for their role and help in this study.

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PARTICULARS OF CONTRIBUTORS:
1. Undergraduate, Dr. Chandramma Dayananda Sagar Institute of Medical Education and Research, Dayananda Sagar University, Harohalli, Karnataka, India.
2. Associate Professor, Department of Pathology, Dr. Chandramma Dayananda Sagar Institute of Medical Education and Research, Dayananda Sagar University, Harohalli, Karnataka, India.
3. Associate Professor, Department of Obstetrics and Gynaecology, Dr. Chandramma Dayananda Sagar Institute of Medical Education and Research, Dayananda Sagar University, Harohalli, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Jessica Minal,
Associate Professor, Department of Pathology, Dr. Chandramma Dayananda Sagar Institute of Medical Education and Research, Dayananda Sagar University, Harohalli, Karnataka, India.
E-mail: jes.minal@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Nov 24, 2023
- Manual Googling: Dec 11, 2023
- iThenticate Software: Dec 23, 2023 (15%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Nov 22, 2023**
Date of Peer Review: **Dec 08, 2023**
Date of Acceptance: **Dec 27, 2023**
Date of Publishing: **Feb 01, 2024**