



## A RETROSPECTIVE STUDY

# Do the Neutrophil/Lymphocyte Ratio and the Platelet/Lymphocyte Ratio Have an Effect on Birthweight, Gestational Age and Severity of Prematurity?

Ayca Nazli Bulut\*  and Venhar Ceyhan, MD 

Department of Obstetrics and Gynecology, Kayseri Training and Research Hospital, Kayseri, Turkey

\*Corresponding author: Ayca Nazli Bulut, MD, Department of Obstetrics and Gynecology, Kayseri Training and Research Hospital, Kayseri, Turkey, Tel: +90-505-625-1433, Fax: +90-352-315-77-00



## Abstract

**Purpose:** There are studies in literature which have reported that the neutrophil to lymphocyte ratio (NLR) is associated with gestational diabetes, pre-eclampsia, the severity of pre-eclampsia, premature prelabour rupture of membranes (PPROM) and hyperemesis gravidarum. There may also be an association with healthy pregnancies without any pathological conditions. The aim of this study was to investigate whether the neutrophil/lymphocyte ratio (NLR) and the platelet/lymphocyte ratio (PLR) have an effect on birthweight, gestational age and the severity of prematurity.

**Methods:** Data of 15000 women who delivered at the Kayseri Training and Research Hospital between May 2018 and December 2019 were retrospectively scanned. The complete blood count (CBC) values taken from the patients at least 1 month before the birth were used in the study. Primary outcome was to evaluate the effect of NLR and PLR on prematurity severity, birthweight and gestational week.

**Results:** A total of 637 patients who were randomly selected among the patients who met the criteria were included in the study. The gestational age at birth was determined to be associated with an increase in maternal Hb value and a decrease in PLR. A decrease in Hb, PLR, and neutrophil count, and an increase in BMI and NLR were each determined to be independent factors for birthweight.

**Conclusion:** This is the first study to have investigated the effect of PLR and NLR on the severity of prematurity. While no correlation was determined between the severity of prematurity and NLR, there was seen to be a weak positive correlation with PLR.

## Keywords

Birthweight, Inflammation, Neutrophil/Lymphocyte ratio, Platelet/Lymphocyte ratio, Prematurity

## Abbreviations

AGA: Appropriate for Gestational Age; CBC: Complete Blood Count; CRP: C-Reactive Protein; IUGR: Intrauterine Growth Retardation; NLR: Neutrophil to Lymphocyte Ratio; PLR: Platelet/Lymphocyte Ratio; PPRM: Premature Pre labour Rupture of Membranes; SD: Standard Deviation; SGA: Small for Gestational Age; LGA: Large for Gestational Age

## Introduction

Fetal growth is one of the signs of fetal health. Maternal inflammatory and thrombotic factors can affect the fetus through fetoplacental-maternal circulation [1]. For the determination of fetal growth abnormalities, definitions of small for gestational age (SGA) and large for gestational age (LGA) are applied using weight percentiles according to the gestational week [2]. Premature birth is defined as birth < 37 weeks and is associated with maternal inflammation [3].

SGA, LGA, and prematurity negative perinatal outcomes are closely related. Fetal growth may also be affected by ethnic and racial factors [4].

There are significant changes in the maternal hematological system throughout the process of pregnancy [5]. The most frequently seen hematological change is anemia (Hb < 12 g/dL), the cause of which is increased plasma volume resulting in hemodilution [6]. Another variable is an increase in white blood cells. Leukocytosis develops because of physiological stress

in pregnancy. Major leukocytes are neutrophils. While the leukocyte count decreases in the first and second trimester of pregnancy, it increases in the third trimester [7]. In platelet count, especially because of platelet aggregation occurring in the 8<sup>th</sup> week of pregnancy, a significant decrease is seen from the 32<sup>nd</sup> week onwards [6]. The role of these variables on fetal growth has still not been fully clarified.

There are studies in literature which have reported that the neutrophil to lymphocyte ratio (NLR) is associated with gestational diabetes, pre-eclampsia, the severity of pre-eclampsia, premature prelabour rupture of membranes (PPROM) and hyperemesis gravidarum [8-11]. In addition, the NLR and platelet to lymphocyte ratio (PLR) are known to be a sign of primarily various malignancies [12-16], several inflammatory processes like major cardiac events [17], cerebral hemorrhage [18], ischemic stroke [18], sepsis and infectious pathologies [19]. There may also be an association with healthy pregnancies without any pathological conditions [20,21].

Deviations in hematological variables may become significant problems in pregnancy and afterwards, but if variations in hematological parameters are known, these negative events can be minimalised from the beginning.

It was suggested that all these variables have an effect on infant birthweight and gestational age [22].

The aim of this study was to investigate whether the NLR, PLR and other CBC variables have an effect on birthweight, gestational age and the severity of prematurity.

## Material and Method

The data of 15000 women who gave birth at Kayseri Research and Training Hospital between May 2018 and December 2019 were retrospectively scanned. The patients included in the study were those aged 18-40 years, women who give birth between 31<sup>+0</sup>-41<sup>+</sup> weeks with a singleton pregnancy, with no systemic disease in the obstetric history, and who were not taking any vitamins, iron prepartes or other medication for any reason. Patients with multiple pregnancies or any congenital anomalies were excluded from the study. Patients with high sedimentation, CRP, fibrinogen or procalcitonin, evidence of any infection, and a history of cervical insufficiency and premature birth at previous pregnancy were excluded from the study.

Approval for the study was granted by the Ethics Committee of Erciyes University. Informed consent for participation in the study was obtained from all the participants. (Ethical approval; Date: 29.01.2020. Reference number: 2020/53). All the study procedures were applied in compliance with the Helsinki Declaration.

The complete blood count (CBC) values taken from

the patients at least 1 month before the birth were used in the study and the CBC values immediately before or after birth were not used. Blood collection time corresponded to the gestational week at least 4 weeks before the birth week. Therefore, the blood draw time of the patients who gave birth at different gestational weeks corresponded to different gestational weeks. A record was made for each patient of maternal age, weight and BMI, gravida, parity, a history and number of abortus, a history of cervical insufficiency and premature birth, infant gender and birthweight, and the FBC variables of Hb, neutrophils, lymphocytes, NLR, platelets, PLR, PDW, RDW-sd, MPV, c-reactive protein (CRP), sedimentation, fibrinogen and procalcitonin values.

## Statistical Analysis

Data obtained in the study were analysed statistically using SPSS vn. 25.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables with normal distribution ( $p > 0.05$  in Kolmogorov-Smirnov test or Shapiro-Wilk [ $n < 30$ ]), were reported as mean  $\pm$  standard deviation (SD) values, and those not showing normal distribution were stated as median values. Comparisons between groups were made using the Student's t-test or the One-way ANOVA test for normally distributed data, and the Mann Whitney U-test or Kruskal Wallis test were used for the data not normally distributed. Since analysis of variance was significant, comparisons were applied using the Post Hoc test and the Mann Whitney U-test.

Categorical variables were analyzed between the groups using the Chi square test. Multiple linear regression analysis was applied to determine associations between birthweight, gestational age at birth and other measurements, with birthweight or gestational age at birth as dependent variables. Correlations between variables were tested with Spearson's correlation coefficient. Correlation coefficients were interpreted as either an excellent relationship  $r \geq 0.91$ ; good  $0.90 \geq r \geq 0.71$ ; fair  $0.70 \geq r \geq 0.51$ ; weak  $0.50 \geq r \geq 0.31$ ; little or none  $r \leq 0.3$ .

## Results

According to the sample calculation, 637 people who met the criteria with 95% CI and 90% power were randomly selected and included in the study [22]. G-Power 3.1 program was used for sample calculation. The 637 patients were separated into groups according to birthweight and gestational age at birth. Those who gave birth at  $< 37$  weeks were accepted as the preterm group, which was divided into 3 subgroups of 31<sup>+0</sup>-32<sup>+6</sup> weeks, 33<sup>+0</sup>-34<sup>+6</sup> weeks, and 35<sup>+0</sup>-36<sup>+6</sup> weeks. Birthweight according to gestational age at birth was accepted as SGA  $< 10$ th percentile [23], AGA 10<sup>th</sup>-90<sup>th</sup> percentile, and LGA  $> 90$ th percentile [24].

## Demographic Data

Birth was preterm in 21.7% (n: 138) of the patients

**Table 1:** Demographics of the patients.

Demographics	Values (n = 637)
Age (year) (mean ± sd)	26.5 ± 5.9
BMI (kg/m <sup>2</sup> ) (mean ± sd)	28.6 ± 4.9
Graida [median (min-max)]	3 (1-11)
Parity [median (min-max)]	2 (1-8)
Smokingstatus [n, (%)]	76 (11.9)
Fetal growth status according to gestational age [n, (%)]	
SGA	198 (31.1)
AGA	242 (38)
LGA	197 (30.9)
Preterm Labour [n, (%)]	138 (21.7)
31 <sup>+0</sup> -32 <sup>+6</sup>	16/138 (11.6)
33 <sup>+0</sup> -34 <sup>+6</sup>	33/138 (24)
35 <sup>+0</sup> -36 <sup>+6</sup>	89/138 (64.4)
Gestational week at labour (week) (mean ± sd)	37.9 ± 2.1
Birthweight (gram) (mean ± sd)	2974.4 ± 757.4
Fetalgender [n, (%)]	
Female	304 (47.7)
Male	333 (52.3)
Laboratory data (mean ± sd)	
Hb (gr/dL)	12.1 ± 1.3
Wbc (X10 <sup>9</sup> /L)	10.8 ± 3.9
Platelet (X10 <sup>9</sup> /L)	241178.9 ± 63333.1
Neutrophil(10 <sup>3</sup> /μL)	10.3 ± 5.76
Lymphocyte(10 <sup>3</sup> /μL)	2.5 ± 0.56
PDW (%)	12.3 ± 2.6
MPV (fL)	10.4 ± 1.1
RDW (%)	14.3 ± 2.4
N/L ratio	4.1 ± 2.2
P/L ratio	25608.4 ± 10808.7

BMI: Body Mass Index; SGA: Small for Gestational Age; AGA: Appropriate for Gestational Age; LGA: Large for Gestational Age; Hb: Hemoglobin; Wbc: White Blood Cell; PDW: Platelet Distribution Width; RDW: Red Cell Distribution Width; MPV: Mean Platelet Volume; N/L: Neutrophil to Lymphocyte Ratio; P/L: Platelet to Lymphocyte Ratio

**Table 2:** Comparative data of groups formed based on infant weight according to gestational age.

	AGA (n = 242)	LGA (n = 197)	IUGR (n = 198)	p
Age (year) (mean ± sd)	26.7 ± 6.0	27.1 ± 6.1	26.3 ± 5.6	0.137
Height (cm) (mean ± sd)	162.1 ± 20.8	164.1 ± 21.9	159.9 ± 5.4	0.259
Weight (kg) (mean ± sd)	73.4 ± 12.8	80.4 ± 14.5	69.7 ± 11.7	<b>0.0001</b>
BMI (kg/m <sup>2</sup> ) (mean ± sd)	28.3 ± 5.0	30.2 ± 5.3	27.2 ± 4.1	<b>0.0001</b>
Gravida [median (min-max)]	3 (1-9)	3 (1-11)	2 (1-7)	<b>0.001</b>
Parity [median (min-max)]	2 (1-8)	3 (1-8)	2 (1-6)	<b>0.001</b>
Abortion [median (min-max)]	0 (0-3)	0 (0-4)	0 (0-3)	0.988
Smoking status ([n, (%)]	25 (10.3)	12 (6.09)	42 (21.2)	<b>0.001</b>

BMI: Body Mass Index; AGA: Appropriate for Gestational Age; LGA: Large for Gestational Age; SGA: Small for Gestational Age. P < 0.05; Statistically Significant.

and term in 78.3% (n: 499). The demographic data of the patients are shown in [Table 1](#).

### Data of the Group Comparisons

The comparative demographic data of the groups showing different growth patterns according to the gestational age are shown in [Table 2](#).

When the LGA group and the other groups were compared, no difference was observed in the N/L ratio and P/L ratio. When the SGA group and other groups were compared, there was no difference in the N/L ratio and P/L ratio. In SGA group, the Hb value was observed to be statistically significantly higher than that of the

other groups ( $p = 0.0001$ ). A statistically significantly higher rate of female infants was seen in the SGA group ( $p = 0.007$ ), and of male infants in the LGA group ( $p = 0.007$ ). Infant gender was not seen to have any effect on the hematological parameters.

The rate of SGA infants in this Turkish population was statistically significantly higher than in other ethnic groups ( $p = 0.001$ ).

### Comparison of the Laboratory Test Results

A statistically significant difference was determined only in the Hb value, with the highest value determined in the SGA group ( $p = 0.025$ ). No other statistically significant difference was observed between the groups in respect of the other laboratory results. The lowest NLR was observed in the SGA group. The highest PLR was observed in the SGA group and the lowest PLR in the LGA group.

When maternal age and CBC variables were evaluated separately, no statistically significant effect was determined on birthweight or gestational age at birth ([Table 3](#)). In the multivariate linear regression analysis, gestational age at birth was determined to be associated with an increase in maternal Hb value and a decrease in PLR ([Table 4](#)) while a decrease in Hb, PLR, and neutrophil count, and an increase in BMI and NLR were each determined to be independent factors for birthweight ([Table 5](#)).

In the comparison of term and preterm groups, the Hb value in the preterm group was observed to be

**Table 3:** Correlations among the variables.

		Birth Week	Birth Weight
Age	r	0.04	0.09
Hb	r	0.14*	-0.07
Neutrophil	r	-0.06	-0.03
Lymphocyte	r	0.04	0.03
WBC	r	-0.06	-0.08
Platelets	r	-0.02	-0.07
PDW	r	0.07	-0.01
RDW	r	0.01	0.12*
MPV	r	0.07	-0.02
N/L Ratio	r	-0.05	-0.04
P/L Ratio	r	-0.09*	-0.09*

N/L: Neutrophil to Lymphocyte Ratio, P/L: Platelets to Lymphocyte Ratio; r = Correlation Coefficients; \* $P < 0.05$

**Table 4:** Multivariate linear regression analysis to determine independent variables affecting birth week.

Model		Unstandardized Coefficients		Standardized Coefficients	t	p	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	36.78	0.813		45.2	0.0001	35.2	38.4
	Hb	0.11	0.063	0.073	1.8	0.026	0.034	0.281
	P/L oranı	-3.06	0.000	-0.085	-2.2	0.031	0.000	0.000

a. Dependent Variable: Birth week

P/L: Platelets to Lymphocyte Ratio

**Table 5:** Multivariate linear regression analysis to determine independent variables affecting birth weight.

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	2630.877	333.533		7.888	0.000	1975.909	3285.846
	Hb	-60.300	21.754	-0.105	-2.772	0.006	-103.019	-17.581
	P/L ratio	-0.026	0.008	-0.197	-3.425	0.001	-0.040	-0.011
	BMI	50.227	5.817	0.327	8.634	0.000	38.803	61.650
	Neutrophile	-4.158	1.739	-0.137	-2.390	0.017	-7.573	-0.742
	N/L ratio	66.542	26.074	0.192	2.552	0.011	15.340	117.744

a. Dependent variable: Birthweight

BMI: Body Mass Index; P/L: Platelets to Lymphocyte Ratio; N/L: Neutrophil to Lymphocyte Ratio



statistically significantly lower ( $p = 0.005$ ). Although no statistically significant difference was observed between the groups in respect of the other variables, the WBC, platelet, RDW values and PLR were seen to be higher in the preterm group, and the neutrophil, lymphocyte, PDW and MPV values were observed to be lower. No difference was determined between the groups in respect of the NLR.

In the evaluation of the preterm subgroups, the Hb value was statistically significantly lowest in the 35<sup>+0</sup>-36<sup>+6</sup> gestational weeks age group, and the highest value was in the 31<sup>+0</sup>-32<sup>+6</sup> gestational weeks group ( $p = 0.005$ ). The statistically significantly highest RDW value was observed in the 31<sup>+0</sup>-32<sup>+6</sup> gestational weeks group ( $p = 0.001$ ). The highest NLR was observed in the 35<sup>+0</sup>-36<sup>+6</sup> gestational weeks group but not at a statistically significant level ( $p = 0.387$ ). The highest PLR value was observed in the 35<sup>+0</sup>-36<sup>+6</sup> gestational weeks group but not at a statistically significant level ( $p = 0.118$ ). No difference was observed between the groups in respect of other CBC variables.

## Discussion

In this study, it was investigated whether or not there was any relationship between CBC variables and birthweight, gestational week at birth and preterm severity. A weak negative correlation was determined between PLR and birthweight and gestational week at birth, and NLR was determined to be a weak, positive independent variable for birthweight.

NLR is a simple parameter which easily evaluates the inflammatory status of any event. An increase in NLR measured in the first trimester may be related to various complications of pregnancy associated with underlying inflammatory processes [8-11]. For example, an increase in NLR has been observed in pre-eclampsia, especially in its severe form. Therefore, NLR is recommended as a marker which can be useful in the first trimester of pregnancy [22]. In a study by Mannaerts, et al. of 164 pre-eclampsia patients and a control group of 1886 subjects, the NLR and MPV value were reported to be higher and the PLR lower in the pre-eclampsia group compared to the control group [9]. Gezer, et al. found neutrophils, platelets, NLR, and PLR to be higher in the pre-eclampsia group [10]. In a study of diabetic pregnant patients, Yilmaz, et al. reported similar results with higher NLR determined [11], and as in the current study, no increase was determined in the NLR in the healthy pregnant patients who had no pregnancy complications. In the current study, the low PLR was concluded to be an independent risk factor for birthweight. Akgun, et al. stated that this showed a relationship between PLR and early births because of prematurity rather than birthweight [22], whereas in the current study, there was seen to be a greater relationship with birthweight according to gestational week at birth rather than prematurity.

There is only one study in literature related to the effect of NLR and PLR on birthweight and the gestational week at birth [22]. In that study, there was concluded to be a relationship between increased NLR and low birthweight. It has been reported in literature that maternal inflammation affects birthweight according to gestational week mediated by various inflammatory cytokines, and leads to low birthweight [25]. In a study by Amarilyo, et al. there were reported to be more inflammatory cytokines in small for gestational age (SGA) infants compared to appropriate for gestational age (AGA) infants [26]. Peiris, et al. analysed the amniotic fluid of women with preterm births and reported an increased concentration of prostoglandins [27]. To the best of our knowledge, the current study is the first to have evaluated whether NLR and PLR have any effect on preterm severity. Although there are many factors affecting prematurity, the population of the current study comprised healthy pregnant patients with no disease, no history of cervical insufficiency and premature birth and thus it was aimed to minimise additional factors.

Anaemia is one of the most frequently encountered conditions in pregnancy. In a study by Levy, et al. a relationship was shown between maternal anaemia, and preterm birth and IUGR [28]. While the results of the current study support previous findings in literature in respect of the relationship between anaemia and prematurity, there was no evidence of a relationship with IUGR. According to the current study results, the highest Hb level was obtained in the SGA group, and according to the analysis results, anaemia was not correlated with prematurity severity.

In literature, RDW, PDW and MPV have been associated with both IUGR and prematurity. In a study by Erkenekli et al, increased MPV and RDW values were seen in the IUGR group, and RDW showed a negative correlation with gestational age at birth [29-31]. In the current study, the lowest RDW value was observed in the SGA group. When comparisons were made within the preterm group, the lowest value was statistically significant in the 31<sup>+0</sup>-32<sup>+6</sup> gestational weeks group ( $p = 0.001$ ). This result suggests that RDW is directly proportional to both gestational week and prematurity severity. In literature, some authors have shown a higher RDW in IUGR and preterm infants [29,31], and some in studies of a neonatal population have reported a negative correlation between RDW and gestational week [32].

While Akgun, et al. determined a higher leukocyte value in male fetal gender [22], in the current study a higher value was seen in female infants, although not at a statistically significant level. This contradictory result suggests caution about concluding that there could be a relationship between CBC variables and fetal gender.

A limitation of the current study can be said to be that the study group was heterogenous as there were patients of different ethnic origins.

In conclusion, the results of this study showed that there was a negative correlation between NLR and birthweight and gestational week at birth and a negative correlation between PLR and birthweight and gestational week at birth. Although the results showed that low Hb was associated with early birth, it was not related to low birthweight and the highest Hb values were observed in low birthweight infants. There is a need for further studies to determine whether maternal CBC variables have any effect on perinatal outcomes, and this easy-to-apply method could be useful in the early determination of perinatal outcomes.

### Acknowledgement

None.

### Declarations

### Funding

None.

### Conflicts of interest/Competing interests

The authors certify that they have NO affiliations with or involvement any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

### Availability of data and material

Available.

### Code availability (software application or custom code)

None.

### Authors' contributions

Ayca Nazli Bulut: Conception or design of the work, drafting the work, final approval of the version to be published, revising it critically for important intellectual content; Venhar Ceyhan: Interpretation of data for the work, revising it critically for important intellectual content.

### Ethics approval

Approval for the study was granted by the Ethics Committee of Erciyes University. (Ethical approval; Date:29.01.2020. Reference number: 2020/53). All the study procedures were applied in compliance with the Helsinki Declaration.

### Informed consent

Informed consent for participation in the study was obtained from all the participants.

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