Do the Neutrophil/Lymphocyte ratio and the Platelet/Lymphocyte ratio have an Effect on Birthweight, Gestational Age and Severity of Prematurity?

Ayca Nazli Bulut[1] and Venhar Ceyhan[1]

[1]Kayseri Education and Research Hospital

April 28, 2020

Abstract

ABSTRACT Objective: 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. Design: Retrospective cohort study Setting: Kayseri Education and Research Hospital Methods: The 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. Main Outcome Measures: Primary outcome was to evaulate the effect of NLR and PLR on prematurity severity, birthweight and gestational week. Results: A total of 637 patients 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. Key Words: neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, prematurity, inflammation, birthweight Funding: None

INTRODUCTION

Fetal growth is one of the signs of fetal health. Maternal inflammatory and thrombotic factors can affect the fetus through feto-placental-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, 6). The most frequently seen hematological change is anemia (Hb<12 g/dL), the cause of which is increased plasma volume resulting in hemodilution (7). 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 (8). In platelet count, especially because of platelet aggregation occurring in the 8th week of pregnancy, a significant decrease is seen from the 32nd week onwards (7). The role of these variables on fetal growth has still not been fully clarified.

There are studies in literature which have reported that the neutrophile to lymphocyte ratio (NLR) is associated with gestational diabetes, pre-eclampsia, the severity of pre-eclampsia, PPROM and hyperemesis gravidorum (9-13). In addition, the NLR and platelet to lymphocyte ratio (PLR) are known to be a sign

of several inflammatory processes, primarily various malignancies (14-23). There may also be an association with healthy pregnancies without any pathological conditions (24, 25).

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.

In a recently published study it was suggested that all these variables have an effect on infant birthweight and gestational age (25).

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

Material and Method

A retrospective scan was made of the data of 15000 women who gave birth at Kayseri Research and Training Hospital between May 2018 and December 2019. The patients included in the study were those aged 18-40 years, with a singleton pregnancy, with no systemic disease in the obstetric history, and who were not taking any vitamins, iron preparates or other medication for any reason. Patients with multiple pregnancies or any congenital anomalies 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. 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. A record was made for each patient of maternal age, weight and BMI, gravida, parity, number of abortus, infant gender and birthweight, and the FBC variables of Hb, neutrophils, lymphocytes, NLR, platelets, PLR, PDW, RDW-sd and MPV 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±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 distrubited. 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 [?] 0.91; good 0.90 [?] r [?]0.71; fair 0.70 [?] r [?] 0.51; weak 0.50 [?] r [?] 0.31; little or none r [?] 0.3.

Results

According to the sampling calculation made with G-Power 3.1 program, for 90% and 95% confidence interval (CI), a total of 637 subjects were included in the study (25). 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+0-32+6 weeks, 33+0-34+6 weeks, and 35+0-36+6 weeks. Birthweight according to gestational age at birth was accepted as SGA <10th percentile, AGA 10th-90th percentile, and LGA >90th percentile.

Demographic Data

Of the total patient group, 31.1% (n:198) were defined as SGA, 38% (n:242) as AGA, and 30.9% (n:197) as LGA. Birth was preterm in 21.7%(n:138) of the patients and term in 78.3% (n:499). In the subgroups of the preterm patient group, 11.6% (n:16/138) gave birth at 31+0-32+6 weeks, 24% (n:33/138) at 33+0-34+6 weeks, and 64.4% (n:89/138) at 35+0-36+6 weeks. The infants born were 52.3% (n:333) males and 47.7% (n:304) females.

Of the whole patient group, the mean age was 26.5+-5.9 years, BMI was 28.6+-4.9 kg/m^2 , mean infant birthweight was 2974.4+-757.4 gr, and mean gestational age at birth was 37.9+-2.1 weeks. Of the CBC variables, the mean values were determined as Hb 12.1+-1.3 g/dl, neutrophils 73.3+-24.9 (%), lymphocytes 20.1+-5.9 (%), WBC 10.8+-3.9 (x10^9/L), platelets 241178.9+-63333.1 (x10^3/L), PDW 12.3+-2.6 (%), RDW 14.3+-2.4 (%), and MPV 10.4+-1.1 (fL). The mean NLR was calculated as 4.1+-2.2 and mean PLR as 13108.4+-5808.7.

Data of the group comparisons

Statistically significantly higher BMI (p=0.0001), gravida (p=0.003) and parity (p=0.001) values were determined in the LGA group compared to the other groups. No significant difference was observed in respect of CBC variables, NLR and PLR.

Statistically significantly lower BMI (p=0.0001), gravida (p=0.0001) and parity (p=0.0001) values were determined in the SGA group compared to the other groups. The Hb value was observed to be statistically significantly higher than that of the other groups (p=0.0001). No significant difference was observed in respect of other variables, NLR and PLR. 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 sepatrately, no statistically signficant effect was determined on birthweight or gestational age at birth (Table 1). 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 2) 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 3).

In the comparison of term and preterm groups, the Hb value in the preterm group was observed to be 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+0-36+6 gestational weeks age age group, and the highest value was in the 31+0-32+6 gestational weeks group (p=0.005). The statistically significantly highest RDW value was observed in the 31+0-32+6 gestational weeks group (p=0.001). The highest NLR was observed in the 35+0-36+6 gestational weeks group but not at a statistically significant level (p=0.387). The highest PLR value was observed in the 35+0-36+6 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

The aim of this study was to investigate whether CBC variables were correlated with birthweight, gestational age at birth and severity of prematurity. The results demonstrated that there was a weak negative correlation of PLR with birthweight and gestational age at birth and NLR was a weak positive independent variable for birthweight.

The Hb value was determined to be lower in the preterm group. When the groups were separated on the basis of infant birthweight according to gestational week, the highest Hb value was observed in the SGA group and the lowest Hb value in the AGA group.

There is only one study in literature related to the effect of NLR and PLR on birthweight and gestational age at birth (25). In that study, it was concluded that an increased NLR was associated with early birth and low birthweight. In the current study, no correlation was determined between increased NLR and preterm births, but a weak positive relationship was determined with birthweight. When the increase in NLR is measured in the first trimester of pregnancy, it may be associated with various pregnancy complications as a link with underlying inflammatory processes (9-13).

For example, the NLR has been observed to be increased in pre-eclampsia and especially in the severe form. Therefore, it has been recommended that it could be a useful marker in the first trimester of pregnancy (26). Moreover, in healthy pregnancies with no complications, as in the current study population, no increased NLR values have been observed (27).

In a study by Akgun et al, a negative correlation was observed between the PLR and birthweight and gestational age at birth (25). In the current study, a similar result was obtained in this context. However, while there was no significant relationship in the comparisons made according to preterm, term, or birthweight, a correlation was determined when all the patients were examined independently of the groups. Furthermore, it was concluded in this study that low PLR was an independent risk factor for birthweight. While Akgun et al stated that PLR was related to early births because of prematurity rather than birthweight (25), the results of the current study showed that in contrast there was a greater relationship with birthweight according to gestational age rather than prematurity. In literature, it has been reported that maternal inflammation affects birthweight according to gestational age through various inflammatory cytokines, and leads to low birthweight (28). The results of the current study support these findings in literature.

In the current study, the lowest RDW value was observed in the SGA group, which was consistent with the findings of Akgun et al (25). In addition, in the comparison of the preterm subgroups, the lowest value was observed in the 31+0-32+6 weeks gestational age group, at a statistically signficant level (p=0.001). This suggested that the RDW was directly proportional to both gestational age and the severity of prematurity. In literature, some authors have reported a higher result of RDW in IUGR and preterm infants (29, 30), while others in studies of neonatal populations have shown a negative correlation of RDW and gestational age (31).

In the study by Akgun et al, although PDW and MPV values were observed to be lower in preterm and IUGR groups, a positive correlation was determined with birthweight (25). In the currrent study, while PDW and MPV values were observed to be lower in the preterm group, the highest value was seen in the LGA group. The relationship between PDW and MPV values and prematurity has been reported in literature (32, 33). However, no clear data have been obtained in respect of the effect on birthweight.

In the study by Akgun et al, the leukocyte value was determined to be higher in male fetal gender (25), and in the current study, although not statistically significant, a higher value was seen in female infants. These conflicting results lead to hesitation in suggesting that there could be a relationship between CBC variables and fetal gender.

There is only one study in literature about the effect of NLR and PLR on gestational age at birth and birthweight (25). However, the current study is the first to have evaluated whether or not there is an effect of NLR and PLR on the severity of prematurity. There are of course many factors affecting prematurity, but the patients included in this study were healthy pregnant patients with no other disease, and thus it

was attempted to minimise additional factors. A limitation of the current study could be said to be that the study group was heterogenous as it included patients of different ethnic origins.

From the results of the current study, it was concluded that elevated NLR was an independent risk factor for birthweight. Although not statistically significant, the lowest NLR was obtained in the SGA group. This result is consistent with the only study in literature on this subject, but as Akgun et al also stated, this result should be investigated independently of gestational week, and there is a need for further studies on this subject. In the current study, no relationship was observed of the NLR with preterm or term pregnancies and no correlation was determined with the severity of prematurity. A negative correlation was determined between the PLR and both gestational age at birth and birthweight, and it was concluded that a decreased PLR was an independent risk factor for birthweight. Furthermore, although not statistically significant, the PLR was determined to be directly proportional to the severity of prematurity.

CONCLUSION

In conclusion, the results of this study revealed a negative correlation between NLR and gestational age at birth and birthweight, and although this does not support the findings of Akgun et al (25), in the first study published on this subject, similar results were obtained in respect of the negative correlation between PLR and gestational age at birth and birthweight. In addition, the current study results showed that although low Hb was associated with early births, there was no association with low birthweight and the highest Hb value was observed at low birthweight. There is a need for further studies to determine the effects of maternal CBC variables on perinatal outcomes, and this easily applicable method can be considered useful for the pre-determination of perinatal outcomes.

ACKNOWLEDGEMENT

None

CONFLICIT OF INTEREST

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, affi liations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

CONTRIBUTION TO AUTHORSHIP

Planning and writing carried out by A.N.Bulut

Data scanning carried out by V.Ceyhan

ETHICS APPROVAL

This study has received the approval of erciyes university ethics committee.

Date:29.01.2020. Referance number: 2020/53.

FUNDING

None

REFERANCES

1. Roland MCP, Friis CM, Godang K, Bollerslev J, Haugen G, Henriksen T. Maternal Factors Associated with Fetal Growth and Birthweight Are Independent Determinants of Placental Weight and Exhibit Differential Effects by Fetal Sex. Plos One. 2014;9(2):1-5.
2. Naeye RL, Dixon JB. Distortions in Fetal Growth Standards. Pediat. Res.1978;*12:* 987-991.
3. Romero R, Dey SK, Fisher SJ. Preterm labor: One syndrome, many causes. SCIENCE 2014 ;345(6198):760-766.

4. Mayer C, Joseph KS. Fetal growth: a review of terms, concepts and issues relevant to obstetrics. Ultrasound Obstet Gynecol 2013; 41: 136–145.
5. Patrick Chukwuyenum Ichipi-Ifukor,1 Juliet Jacobs,2 Rita Ngozi Ichipi-Ifukor,3 and Oberhiri Lawrence Ewrhe4,5. Changes in Haematological Indices in Normal Pregnancy. Physiology Journal. 2013:1-5
6. R. Yip, "Significance of an abnormally low or high hemoglobin concentration during pregnancy: special consideration of iron nutrition," The American Journal of Clinical Nutrition. 2000;72(1):272-79.
7. Chandra S, Tripathi AK, Mishra S, Amzarul M, Vaish AK. Physiological Changes in Hematological Parameters During Pregnancy. Indian J Hematol Blood Transfus. 2012;28(3):144-46.
8. Kaur S, Khan S, Nigam A. Hematological profile and pregnancy: a review. Int. J Adc. Med. 2014;1(2):68-70.
9. Mannaerts D, Heyvaert S, De Cordt C, Macken C, Loos C, Jacquemyn Y. Are neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and/or mean platelet volume (MPV) clinically useful as predictive parameters for preeclampsia? The Journal of Maternal-Fetal & Neonatal Medicine. 2017;32(9):1412-1419.
10. Gezer C, Ekin A, Ertas IE, Ozeren M, Solmaz U, Mat E, Taner CE. High first-trimester neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are indicators for early diagnosis of preeclampsia. Ginekologia Polska. 2016;87(6):431-435.
11. H. Yilmaz, H. T. Celik, M. Namuslu, O. Inan, Y. Onaran, F. Karakurt, A. Ayyildiz, M. A. Bilgic, N. Bavbek, A. Akcay. Benefi ts of the Neutrophil-to Lymphocyte Ratio for the Prediction of Gestational Diabetes Mellitus in Pregnant Women. Exp Clin Endocrinol Diabetes. 2014;122:39-43.
12. Caglayan EK, Engin-Ustun Y, Gocmen AY, Sarı N, Seckin L, Kara M, Polat MF. 2016. Is there any relationship between serum sirtuin-1 level and neutrophil-lymphocyte ratio in. hyperemesis gravidarum? Journal of Perinatal Medicine 44:315–320.
13. Kim MA, Lee YS, Seo K. 2014. Assessment of predictive markers for placental inflammatory response in preterm births. PLoS One 9:e107880.
14. Huang QT, Zhou L, Zeng WJ, Ma QQ, Wang W, Zhong M, Yu YH. 2017. Prognostic significance of neutrophil-to-lymphocyte ratio in ovarian cancer: a systematic review and meta-analysis of observational studies. Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology 41: 2411–2418.
15. Akinci Ozyurek B, Sahin Ozdemirel T, Buyukyaylaci Ozden S, Erdogan Y, Kaplan B, Kaplan T. 2017. Prognostic value of the neutrophil to lymphocyte ratio (NLR) in lung cancer cases. Asian Pacific Journal of Cancer Prevention 18:1417–1421.
16. Iwase T, Sangai T, Sakakibara M, Sakakibara J, Ishigami E, Hayama S, et al. 2017. An increased neutrophil-to-lymphocyte ratio predicts poorer survival following recurrence for patients with breast cancer. Molecular and Clinical Oncology 6:266–270.
17. Piciucchi M, Stigliano S, Archibugi L, Zerboni G, Signoretti M, Barucca V, et al. 2017. The neutrophil/lymphocyte ratio at diagnosis is significantly associated with survival in metastatic pancreatic cancer patients. International Journal of Molecular Sciences 18:pii:730.
18. Tang X, Du P, Yang Y. 2017. The clinical use of neutrophil-to-lymphocyte ratio in bladder cancer patients: a systematic review and meta-analysis. International Journal of Clinical Oncology 22:817–8255.
19. Brooks SD, Spears C, Cummings C, VanGilder RL, Stinehart KR, Gutmann L, Domico J. 2014. Admission neutrophil-lymphocyte ratio predicts 90 day outcome after endovascular stroke therapy. Journal of NeuroInterventional Surgery 6:578–583.
20. Lattanzi S, Cagnetti C, Rinaldi C, Angelocola S, Provinciali L, Silvestrini M. 2018. Neutrophil-to-lymphocyte ratio improves outcome prediction of acute intracer
21. Aktas G, Sit M, Dikbas O, Erkol H, Altinordu R, Erkus E, Savli H. 2017. Elevated neutrophil-to-lymphocyte ratio in the diagnosis of Hashimoto's thyroiditis. Revista da Associacao Medica Brasileira (1992) 63:1065–1068.
22. Hwang SY, Shin TG, Jo IJ, Jeon K, Suh GY, Lee TR, et al. 2017. Neutrophilto- lymphocyte ratio as a prognostic marker in critically-ill septic patients. The American Journal of Emergency Medicine

35:234–239.
23. Surendar J, Indulekha K, Mohan V, Pradeepa R. 2016. Association of neutrophil- lymphocyte ratio with metabolic syndrome and its components in Asian Indians (CURES-143). Journal of Diabetes and its Complications 30:1525–1529.
24. Kirbas A, Biberoglu E, Daglar K, _Iskender C, Erkaya S, Dede H, et al. Neutrophil-to-lymphocyte ratio as a diagnostic marker of intrahepatic cholestasis of pregnancy. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2014;180:12–15.
25. Akgun N, Kalem MN, Yuce E, Kalem Z, Aktas H. Correlations of maternal neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) with birth weight. The Journal of Maternal-Fetal & Neonatal Medicine 2019;30(17):2086-2091.
26. Serin S, Avcı F, Ercan O , Köstü B, Bakacak M, Kıran H. Is neutrophil/lymphocyte ratio a useful marker to predict the severity of pre-eclampsia? Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health . 2016;6: 22–25.
27. Kurtoglu E, Kokcu A, Celik H, Migraci Tosun M, Malatyalioglu E. May ratio of neutrophil to lymphocyte be useful in predicting the risk of developing preeclampsia? A pilot study. The Journal of Maternal-Fetal & Neonatal Medicine 2014;28(1):97-99.
28. Amarilyo G, Oren A, Mimouni FB, Ochshorn Y, Deutsch V, Mandel D. Increased cord serum inflammatory markers in small-for-gestational-age neonates. Journal of Perinatology 2011;31:30–32 .
29. Erkenekli K, Öztaş E, Özler S, Yücel A, Uygur D, Danışman N. Complete Blood Count Indices in Pregnancies With Isolated Intrauterine Growth Restriction. The Journal of Gynecology - Obstetrics and Neonatology 2015;12(1):18 – 21.
30. Shehata HA, Ali MM, Evans-Jones JC, Upton GJG, Manyonda IT. Red cell distribution width _RDW. changes in pregnancy. International Journal of Gynecology & Obstetrics 1998;62:43-46.
31. Garofoli F, Ciardelli L, Mazzucchelli I, Borghesi A, Angelini M, Bollani L, Genini E, Manzoni P, Paolillo P, Tinelli C, Merlini G, Stronati M. The red cell distribution width (RDW): Value and role in preterm, IUGR (intrauterine growth restricted), full-term infants. Hematology 2014;19(6);365-370.
32. Ulkumen BA, Pala HG, Calik E, Koltan So. Platelet distribution width (PDW): A putative marker for threatened preterm labour. Pak J Med Sci 2014;30(4):745-748.
33. Farhan FS. Mean Platelet Volume and Platelet Distribution Width as Predictors for Preterm Labour. Iraqi Medical Journal 2016;62(2);95-99.

Hosted file

`Table 1.docx` available at https://authorea.com/users/309765/articles/440623-do-the-neutrophil-lymphocyte-ratio-and-the-platelet-lymphocyte-ratio-have-an-effect-on-birthweight-gestational-age-and-severity-of-prematurity

Hosted file

`Table 2.docx` available at https://authorea.com/users/309765/articles/440623-do-the-neutrophil-lymphocyte-ratio-and-the-platelet-lymphocyte-ratio-have-an-effect-on-birthweight-gestational-age-and-severity-of-prematurity

Hosted file

`Table 3.docx` available at https://authorea.com/users/309765/articles/440623-do-the-neutrophil-lymphocyte-ratio-and-the-platelet-lymphocyte-ratio-have-an-effect-on-birthweight-gestational-age-and-severity-of-prematurity