International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Khan JA et al. Int J Reprod Contracept Obstet Gynecol. 2023 Feb;12(2):448-451
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20230133

Original Research Article

Neutrophil-lymphocyte ratio as inflammatory marker for clinical prediction and disease severity evaluation of preeclampsia

Javid Ahmed Khan[1]*, Aadil Ashraf[2], Waseem Qureshi[3], Faizana Fayaz[4]

[1]Department of Medicine, GMC Srinagar, Jammu and Kashmir, India
[2]Department of Gastroenterology, AIG Hospital, Hyderabad, Telangana, India
[3]GMC Srinagar, Jammu and Kashmir, India
[4]Delhi University, India

Received: 14 December 2022
Accepted: 05 January 2023

***Correspondence:**
Dr. Javid Ahmed Khan,
E-mail: khanjaved69@yahoo.com

ABSTRACT

Background: Pre-eclampsia (PE) is a multisystem disorder that complicates 4-6% of pregnancies and constitutes a major source of morbidity and mortality worldwide. About 10-15% of maternal deaths are directly associated with PE and eclampsia. The aim of this study is to compare the neutrophil-lymphocyte ratio (NLR) values of mild and severe PE with the healthy normotensive pregnant women, in order to study the predictive role of NLR for PE and whether the NLR value has significant difference between normotensive pregnancy, severe and mild PE.
Method: A cross-sectional study conducted from January to July 2022 after proper informed consent and ethical clearance. The study population included 194 pregnant women divided into three groups (97 normotensive, 55 mild PE, 42 with severe PE). All the study participants were statistically compared in respect to NLR and the baseline data including age, parity and gestational age.
Results: Maternal NLR in mild PE group was statistically increased when compared to normotensive healthy women ($p<0.05$). Similarly, NLR was significantly higher in severe PE group when compared with normotensive pregnancy group ($p=0.00$). A statistically significant positive correlation was also seen between SBP (systolic blood pressure) and NLR in PE group ($p<0.05$).
Conclusions: NLR can be used as an inflammatory marker for clinical prediction and disease severity evaluation of PE but further cohort studies are required to determine and establish its role.

Keywords: NLR, Pre-eclampsia, Morbidity, Mortality

INTRODUCTION

Pre-eclampsia (PE) is a pregnancy-specific hypertensive disorder which affects 4-6% of all pregnancies.[1] Overall, 10-15% of maternal deaths are directly associated with PE and eclampsia.[2] PE is diagnosed after 20 weeks of gestation with a deterioration of the disease state throughout the rest of the pregnancy up to delivery. However, starting events that lead to the development of the disease are assumed to begin during implantation. In normal pregnancy, immune cells in the decidua, including macrophages, uterine natural killer (NK) cells and dendritic cells (DCs), facilitate migration and invasion of trophoblasts into the uterine wall during establishment of the placenta.[3,4] PE is associated with chronic immune activation that results in elevated levels of inflammatory cytokines released by proinflammatory helper T-cell subsets.[5] The proinflammatory cytokines tumor necrosis factor α (TNF-α), interleukin (IL) 6, and IL-17 are typically secreted by activated T_H1 and T_H17 cells to instigate a cytotoxic and inflammatory immune response to foreign pathogens or injury. During PE, these cytokines are significantly increased in the maternal circulation and the placenta, resulting in chronic systemic and local placental inflammation, which contributes to the pathophysiologic complications that manifest during PE.[6,7]

Interleukin 17 activates and promotes proliferation of TH17 cells in a feedback loop and is a key cytokine essential for proliferation, recruitment, activation, and migration of neutrophils.[8] With these background studies this study was aimed to evaluate the relationship between NLR ratio in patients with PE and severity of PE.

METHODS

Study population

This was a cross sectional study, in the department of obstetrics and gynecology of Govt. medical college, Srinagar, from November 2021 to July 2022 after written informed consent. Pregnant females more than 18 years of age who reported to the OPD, admitted in ward and labour room of Lal Ded hospital were selected as study population. Total 194 subjects were enlisted as the study population divided into three groups (97 normotensive, 55 mild PE, 42 with severe PE). All the subjects of the study were included after taking proper relevant history and informed consent.

The subjects were classified as PE if they had de novo hypertension of ≥140/90 mmHg after 20 weeks gestation accompanied by proteinuria and/or evidence of maternal acute kidney injury, liver dysfunction, neurological or cerebral features like headache, visual disturbances, hemolysis or thrombocytopenia, and/or fetal growth restriction. They were further divided into two groups with patients with SBP≥140-160 mmHg and/or DBP≥90-110 mmHg classified as mild PE while those with SBP>160 mmHg and/or DBP 110 mmHg classified as severe PE.

Exclusion criteria

Exclusion criteria consisted of multiple pregnancy, chronic hypertension, diabetes mellitus, women with cardiovascular diseases, chronic liver disease, patients taking steroids or diuretics, gestational trophoblastic diseases. Chronic inflammatory diseases like SLE, rheumatoid arthritis etc. Patients with history of medication related to inflammatory condition of patient such as corticosteroids which could alter the maternal NLR values were also excluded from the study.

Blood sample were collected from patients after thorough history and complete blood count was done using three-part haematology analyser and neutrophil lymphocyte ratio was calculated manually.

Statistical analysis

Data was compiled in MS office excel and statistical analysis was done by statistical program for social sciences (SPSS, version 17, statistics for windows, version 26.0. Chicago: SPSS Inc) software. Statistical comparison was made of the control group and all the PE patients in respect of NLR. Variables stated as mean ± standard deviation. For comparison of data between patient and control group, ANOVA test used. Moreover, for comparing intergroup difference, Sidak test used. Associations with $p<0.05$ considered statistically significant.

RESULTS

The demographic characteristics such as age of subjects and gestational age of the subjects showed no statistically significant differences between cases and controls ($p>0.05$) but in case of parity there was statistically significant difference of mean between the cases and control ($p=0.025$, $p<0.05$), (Table 1).

Table 1: Demographic characteristics of PE and normotensive pregnant females, (n=97).

Variables	PE, mean ± SD	Normal, mean ± SD	P value
Age (Years)	29.44±3.78	28.97±3.28	0.303
Gest. age (Weeks)	33.52±4.01	34.51±3.97	0.201
Parity	2.55±1.45	2.19±1.12	0.025*

Table (2) shows that the mean NLR value of the mild PE group (mean ± SD) (4.07±1.25) was higher than the control group (3.50±1.24) and further higher in severe PE group (4.72±1.27).

Table 2: Mean and SD of NLR in control, mild PE and severe PE group.

NLR	N	Mean	SD
Normal	97	3.50	1.24
Mild PE	55	4.07	1.25
Severe PE	42	4.72	1.27
Total	194	3.93	1.33

Table 3: A one way ANOVA to compare the means of NLR in control, mild PE and severe PE group.

Variables	Sum of squares	Df	Mean square	F	Sig.
Between groups	45.45	2	22.72	14.4	0
Within groups	299.98	191	1.57		
Total	345.44	193			

A one way ANOVA (Table 3) was performed between subjects to compare the means of NLR, There was a significant difference of NLR mean at the $p<0.01$ for 3 groups [$F(2,191)=14.471$, $p=0.00$]. Post hoc comparisons using Sidak test for multiple comparisons found that there was statistically significant difference in NLR between means of normotensive, mild PE and severe PE group with $p=0.00$ and 95% confidence interval of (-1.2676, -0.0304) in case of mild versus severe PE; CI of (-1.0832, -0.0641) in case of control versus mild and CI of (-1.7803, -0.6650) in case of control vs severe group (Table 4).

Table 4: Post hoc comparisons using the Sidak test for multiple comparisons.

Sidak test						
(I) SBP category	(J) SBP category	Mean difference (I-J)	Std. error	Sig.	95% CI	
					Lower bound	Upper bound
Normal	Mild	-0.57363*	0.211	0.022*	-1.0832	-0.0641
	Severe	-1.22263*	0.231	0.000*	-1.7803	-0.6650
Mild	Normal	0.57363*	0.211	0.022*	0.0641	1.0832
	Severe	-0.64900*	0.256	0.036*	-1.2676	-0.0304
Severe	Normal	1.22263*	0.231	0.000*	0.6650	1.7803
	Mild	0.64900*	0.256	0.036*	1.0304	1.2676

*The mean difference is significant at the 0.05 level.

The correlation coefficient r had a value of +0.205, indicating a low positive correlation. In this case, the p value was statistically significant (Table 5) and thus, it can be suggested that the increase in the SBP leads to the increase in the NLR in PE.

Table 5: Pearson correlation table between systolic blood pressure (SBP) and NLR in PE showing low positive correlation, (r=0.20).

Correlations		SBP	NLR
SBP	Pearson correlation	1	0.205*
	Sig. (2-tailed)		0.044
	N	97	97
NLR	Pearson correlation	0.205*	1
	Sig. (2-tailed)	0.044	
	N	97	97

*Correlation is significant at the 0.05 level (2-tailed).

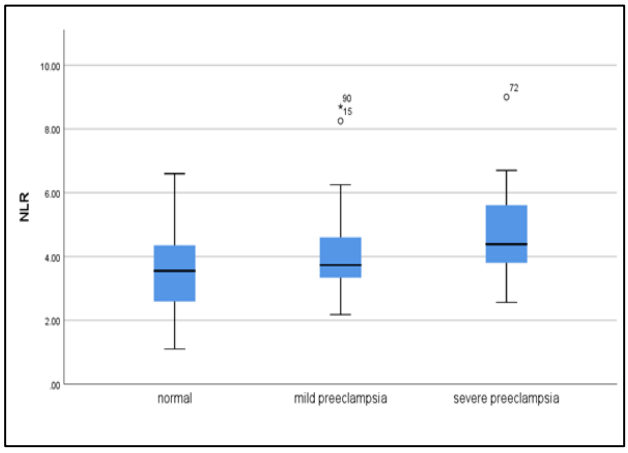

Figure 1: Boxplot of NLR in normotensives, mild PE and severe PE.

DISCUSSION

PE is a multisystemic disorder whose aetiology, pathogenesis and pathophysiology are poorly understood. Traditionally, PE is considered to progress through a "two-stage" theory; an abnormal spiral artery remodeling in early pregnancy causes placental hypoxia (stage 1) and the ischemic placenta releasing large amounts of soluble factors, such as reactive oxygen species (ROS), proinflammatory cytokines, and anti-angiogenic factors, into the maternal circulation, leading to the clinical manifestations and complications of the disease (stage 2).[9] Evidence reiterates the presence of an exaggerated inflammatory response (abnormal cytokine production and neutrophil activation) and attributes the immune imbalance to the clinical manifestations of PE.[9,10] NLR, a simple marker of inflammation, is being widely assessed for its diagnostic, staging, prognostic and predictive potential in PE and associated hypertensive disorders of pregnancy.

The results of our study were similar to the study done by Serin et al that suggested maternal NLR was statistically significantly higher in PE cases than healthy pregnant females (p=0.017).[11]

Oylumlu et al also reported that a significantly higher NLR values was observed in the PE group compared to the control group (7.3±3.5 versus 3.1±1.1; p<0.001).[12]

A study done by Yavuzcan et al also reported NLR was significantly higher in the patients with PE than healthy controls.[13]

In another study by Sachan et al a significantly high neutrophil/lymphocyte ratio was observed in patients with PE compared to those with healthy pregnancies, in addition similar to our results, NLR was found to be significantly higher in the severe PE compared to the mild PE which suggests that NLR could predict the severity of PE.[14]

Kang et al suggest that NLR might be a useful laboratory marker for clinical prediction and evaluation of disease severity in PE. However, the authors also highlight the fact that available pieces of evidence are drawn from case-control studies. Therefore, prospective cohort studies are essential to accurately determine the utility of NLR, the optimal timing of analysis, and predictive cutoff values in clinical settings.[15]

In PE, neutrophils are activated as they flow through the intervillous space and are exposed to oxidized lipids secreted by the placenta. Oxidized lipids are potent activators of neutrophils, leading to expression of COX-2

which regulates the release of thromboxane, TNF and superoxide.[16]

Thus, the findings of the current study taken together with those of the previous studies have added value to the use of maternal NLR levels in the determination of PE. NLR, obtained from complete blood count, an inexpensive and routinely done test, can be used as inflammatory marker for clinical prediction and disease severity evaluation of PE.

The major limitation in our study was being a single-centre study with relatively small study population.

CONCLUSION

In conclusion, NLR was determined as significantly high in patients with mild PE compared to normotensive pregnant females, and significantly higher in those with severe PE than those with mild PE, NLR emerges as a marker for inflammatory marker for clinical prediction and disease severity evaluation of PE but further supporting cohort studies are required to determine and establish its role.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Khan JA, Ashraf A, Qureshi W, Fayaz F. Neutrophil-lymphocyte ratio as inflammatory marker for clinical prediction and disease severity evaluation of preeclampsia. Int J Reprod Contracept Obstet Gynecol 2023;12:448-51.