Original Article

Comparative Immune Profiles: Platelet-to-Lymphocyte and Neutrophil-to-Lymphocyte Ratios in Preeclampsia versus Healthy Women

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Abstract

Background: Pre-eclampsia is a hypertensive disorder linked with immune dysregulation and systemic inflammation in pregnancy. An elevated neutrophil count alongside a relatively stable lymphocyte count leads to an increased Neutrophil-to-Lymphocytic Ratio (NLR), serving as a parameter of widespread systemic inflammation. Platelet to lymphocyte ratio (PLR) is a also used as a hematological marker that reflects the balance between platelets and lymphocytes. A higher NLR and PLR may reflect increased endothelial activation and damage, contributing to the pathogenesis of preeclampsia.

Objective: The objective of the present study was to compare the Neutrophil to lymphocytic ratio (NLR as well as platelet-to-lymphocytic ratio (PLR) between women affected by preeclampsia (PE) and those with uncomplicated pregnancies.

Methods: It was a cross-sectional comparative study. Fifty-five registered preeclamptic patients were enrolled as cases along with fifty-five healthy pregnant women. Total leukocyte counts, including neutrophils and lymphocytes as well as platelet count, were calculated using an automated hematology analyzer, and the Neutrophil-to-Lymphocyte Ratio (NLR) as well as Platelet to Lymphocyte ratio were subsequently calculated.

Results: Higher value of TLC and neutrophils were recorded in pre-eclampsia. The normotensive women had higher platelet as well as lymphocyte count. NLR was significantly high in the preeclampsia contrary to PLR ratio that showed a higher value in normotensive pregnancies.

Conclusion: In conclusion, our study highlights significant alterations in the immune-inflammatory profile of patients with preeclampsia compared to controls. The observed high neutrophil-to-lymphocyte ratio (NLR) and low platelet-to-lymphocyte ratio (PLR) suggest a distinct systemic inflammatory response associated with preeclampsia.

Keywords: Preeclampsia, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

Introduction

Pre-eclampsia, is a hypertensive disorder affecting about 2-8% of pregnancies worldwide, characterized by elevated blood pressure and proteinuria after 20 weeks of gestation and is linked with notable fetal and maternal health complications and fatalities.[1] Preeclampsia is linked with immune dysregulation, endothelial dysfunction, and systemic inflammation, all of which contribute to its pathogenesis.[2] The dysfunction of the immune system plays a crucial role in the pathophysiology of preeclampsia. In a typical pregnancy, there's a modified innate immune response characterized by heightened inflammation and active complement system. This response is heightened even more in pregnancies complicated by preeclampsia.[3] Preeclampsia is

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widely regarded as a two-stage disorder, with the initial phase implicating defective trophoblast invasion and failure in the remodeling of spiral arteries, which are fundamental steps in its pathogenesis.[4] Consequently, this leads to compromised uteroplacental blood flow, resulting in hypoxia. Oxidative stress within the placenta ensues, prompting the release of various factors including proinflammatory cytokines, antiangiogenic agents, exosomes, and cell-free fetal DNA, can enter the maternal circulation.[5] These factors contribute to disrupted endothelial regulation with marked increase in permeability of the vessels. Both neutrophils and platelets can exacerbate endothelial dysfunction. Increased production of superoxide and decreased nitrite release, leading to the activation and modulation of neutrophils, are linked to widespread endothelial dysfunction in preeclampsia. Preeclampsia appears to be characterized by heightened levels of inflammation compared to uncomplicated pregnancies, with preeclamptic patients exhibiting an increase in leukocyte count, primarily driven by elevated neutrophil levels and decreased lymphocyte levels.[6,7] Neutrophils release pro-inflammatory cytokines and reactive oxygen species, while platelets release various soluble and adhesion molecules, promoting interactions with endothelial cells. This cascade of events has sparked considerable interest in the exploration of various biomarkers. It is vital to promptly identify and precisely predict preeclampsia (PE) for optimal management and better outcomes for affected women and their offspring. An elevated neutrophil count alongside a relatively stable lymphocyte count leads to an increased Neutrophil-to-Lymphocytic Ratio (NLR), serving as a parameter of widespread systemic inflammation.[7] Platelet to lymphocyte ratio (PLR) is a hematological marker that reflects the balance between platelets, which are involved in clotting and inflammation, and lymphocytes, a pivotal component of the body's immune system is a type of white blood cell essential for mounting an effective defense against pathogens. The platelet to lymphocytic ratio (PLR) as an alternative marker has arisen as a significant indicator in evaluating widespread generalized inflammation and immune response in a range of autoimmune and cardiovascular conditions.[8] A higher NLR and PLR may reflect increased endothelial activation and damage, contributing to the pathogenesis of preeclampsia. Although certain studies have proposed these ratios as a potential indicator for evaluating inflammation and immune response in preeclampsia (PE), the research outcomes remain inconclusive.[9,10,11] The objective of the present study was to compare the Neutrophil to lymphocytic ratio (NLR as well as platelet-to-lymphocytic ratio (PLR) between women affected by preeclampsia (PE) and those with uncomplicated pregnancies.

Methods

It was a cross-sectional comparative study. The place of the study was the Physiology department at Federal Postgraduate Medical Institute, Shaikh Zayed Hospital, Lahore, in collaboration with two other tertiary care hospitals in Lahore, spanning from March 2012 to April 2012, following approval from the respective Ethical Review Boards of those institutions. The study adhered to all ethical standards set by the Institutional Ethical Review and complied with the principles outlined in the 1975 Helsinki Declaration, which was revised in 2000. All the participants were briefed about the study and included in the study after their consent and written informed consent. To calculate the sample size, the formula for two population means, provided by the World Health Organization (WHO) calculator was used[12] and fifty-five registered preeclamptic patients were enrolled as cases, meeting criteria of a more than 140 mmHg of systolic and more than 90mmHg of diastolic blood pressure on multiple occasions, six hours apart, along with proteinuria of a minimum 300 mg in urine in 24-hour. Fifty-five healthy pregnant women with normal blood pressure, paired based on age and gestational age, with normal Body Mass Index, were incorporated as controls through a convenience sampling technique. Subjects suffering from chronic diseases such as diabetes mellitus, pregestational hypertension, renal disease, multi-fetal pregnancy, liver disease, history of smoking, or previous history of preeclampsia were omitted from the study. Blood pressure measurements were documented, maternal venous blood samples were collected in EDTA-coated vacutainers. Total leukocyte counts, including neutrophils and lymphocytes as well as platelet count, were calculated using an automated hematology analyzer, and the Neutrophil-to-Lymphocyte Ratio (NLR) as well as Platelet to Lymphocyte ratio were subsequently calculated.

SPSS 16 was used to analyze the Data. Shapiro wilk test of normality was applied to check the distribution of the data. Mean ± SD was given for all those parameters that showed normal distribution. Independent samples T test was used to compare the values between preeclamptic and normotensive pregnancies. A p value < 0.05 was considered statistically significant.

Results

Out of the total 110 patients, 55 presented with pree-

Table I: *Demographic and medical characteristics of healthy and preeclamptic pregnancies*

Variable	Group		p Value
	Normotensive n = 55	Preeclampsia n = 55	
Maternal age (years)	25.83± 4.8	27.32 ± 4.3	<0.001*
Gestational age(weeks)	37.8 ± 1.36	36.51 ± 2.0	0.03
BMI	22.80 ± 3.0	23.76 ±1.2	<0.001*
Systolic blood pressure(mmHg)	111.27 ± 7.4	147.81 ± 8.0	<0.001*
Diastolic blood pressure(mmHg)	72.00 ± 6.2	99.63 ± 5.6	<0.001*

n = number of study participants, p value < 0.05 considered significant shown with hysteric, Independent samples t test applied to calculate p value.*

clampsia while the remaining 55 exhibited normal healthy pregnancies. The maternal age as well as gestational age of the participants at the time of sample collection was not different statistically as shown in Table I. Hematological parameters including Total leukocyte count (TLC), Neutrophil count, Lymphocyte count and platelet count demonstrated a notable variance in outcomes between the case group and controls with higher value of TLC, neutrophils, and NLR in preeclampsia (Table II). The normotensive women had higher platelet as well as lymphocyte count. NLR was significantly high in the preeclampsia contrary to PLR ratio that showed a higher value in normotensive pregnancies (Figure I).

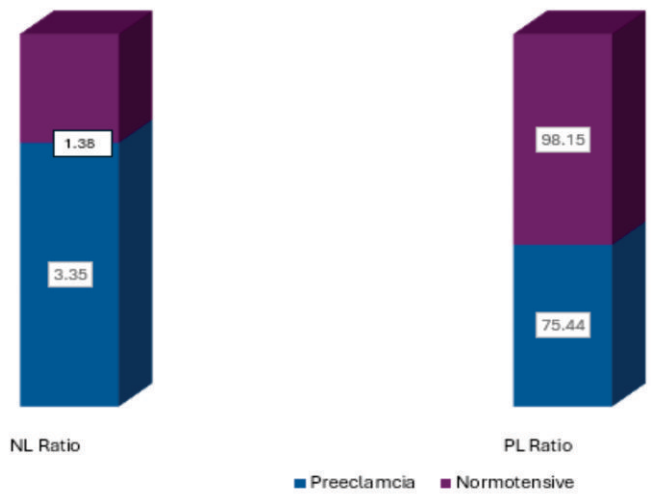

Figure I: *NL Ratio and PL Ratio in preeclampsia and normotensive pregnancies.*

Table II: *Hematological characteristics of normal and preeclamptic pregnancies*

Variable	Group		p Value*
	Normotensive	Preeclampsia	
Total Leukocyte count	7072 ± 1620	9890 ± 1458	< 0.001
Neutrophil count×10^3µL	5.32 ± 0.36	6.88 ± 0.60	< 0.001
Lymphocyte count×10^3cu.mm	3.88 ± 0.40	2.14 ± 0.45	< 0.001
Platelet count×10^3cu.mm	377 ± 34.0	159.22±36.7	< 0.001

p value < 0.05 considered significant shown with hysteric, Independent samples t test used to calculate p value.*

NL Ratio: Neutrophil to lymphocytic ratio, PL Ratio: Platelet to lymphocytic ratio, a p value of < 0.05 considered significant, calculated by independent samples t test.

Discussion

The findings of our current study highlight a significant increase in total leukocyte number and neutrophil-to-lymphocytic ratio (NLR) among patients of preeclampsia compared to those with healthy pregnancies. The findings align with several studies reinforcing the significance of persistent and heightened systemic inflammation in the development of endothelial dysfunction in preeclampsia with similar alterations in hematological parameters.[6,7] Preeclampsia's etiology is multifaceted, with the most prevalent theory revolving around inadequate placental development, resulting in hypoxia and the release of proinflammatory cytokines. Additionally, there's evidence indicating immune maladaptation in preeclampsia. High total leukocyte count and elevated neutrophil levels play pivotal role in the development of preeclampsia, reflecting underlying systemic inflammation and endothelial dysfunction.[13] An elevated neutrophil count alongside a relatively stable lymphocyte count leads to an increased Neutrophil-to-Lymphocytic Ratio (NLR), serving as a parameter of widespread systemic inflammation. In line with our research, Oylumlu et al. illustrated that elevated value of the neutrophil-to-lymphocytic ratio (NLR) was independently linked with patients of preeclampsia (PE) compared to healthy pregnancies.[14]

Neutrophils, as key mediators of the inflammatory response, contribute to the release of pro-inflammatory mediators and reactive oxygen species, accelerating endothelial injury and vasoconstriction.[15] This inflammatory cascade leads to impaired placental perfusion, endothelial dysfunction, and the characteristic hypertension and proteinuria seen in preeclampsia. Additio-

nally, neutrophils may exacerbate oxidative stress and damage to vascular endothelium, further perpetuating the pathophysiological processes underlying this hypertensive disorder of pregnancy.

Additionally, we observed a notable decrease in platelet count in individuals with pre-eclampsia and this observation aligns with the well-established association between PE and platelet dysfunction.[16] In preeclampsia, low platelet count, or thrombocytopenia, can result from several interconnected mechanisms. One primary cause is endothelial dysfunction and microangiopathy, leading to platelet activation, consumption, and subsequent sequestration within damaged vessels.[17] Additionally, abnormal placental development in preeclampsia can trigger an increase in the levels of anti-angiogenic factors like soluble fms-like tyrosine kinase-1 (sFlt-1), which contribute to platelet aggregation and consumption. Moreover, the systemic inflammation characteristic of preeclampsia can lead to increased platelet destruction and impaired production in the bone marrow.[18] Ultimately, thrombocytopenia in preeclampsia contributes to the risk of coagulopathy, hemorrhage, and adverse maternal and fetal outcomes. However, it is crucial to pay attention to the presence of studies with contrasting findings. Some investigations have reported no significant differences in total leukocyte count, NLR, or platelet count between preeclamptic and normotensive pregnancies.[19] These conflicting results may be attributed to variations in study populations, sample sizes, diagnostic criteria for preeclampsia, and methodologies used for hematological assessments. The current study reported a lower platelet to lymphocyte ratio (PLR) in pre-eclampsia in accordance with previous research,[20] shedding light on potential biomarkers and underlying mechanisms of this complex disorder. Platelets and lymphocytes are integral components of the immune system, and alterations in their ratio may reflect systemic inflammation and immune dysregulation, both of which are implicated in the pathophysiology of preeclampsia. The elevated PLR observed in preeclampsia suggests a possible imbalance between pro-inflammatory and anti-inflammatory responses.[21] Platelets play a crucial role not only in hemostasis but also in inflammatory processes, where they release various mediators that can exacerbate endothelial dysfunction and promote vascular inflammation. Meanwhile, lymphocytes are key regulators of immune responses, and alterations in their levels could signify immune system dysregulation, further contributing to the inflammatory milieu observed in preeclampsia.[22]

Activated platelets release a variety of soluble and adhesion molecules that initiate interactions among platelets, leukocytes, and endothelial cells. Previous data indicate a significant contribution of platelets to the pathogenesis of preeclampsia.[23] Elevated ratio of Neutrophil to Lymphocytes as well as Platelet to Lymphocyte suggest a disturbance between inflammatory (neutrophils and platelets) and anti-inflammatory (lymphocytes) components of the immune system. This imbalance may contribute to the inflammatory cascade observed in preeclampsia, leading to endothelial dysfunction and hypertension.[24] The implications of a higher PLR in preeclampsia help in understanding the relationship between PLR and preeclampsia could potentially lead to the progression of new treatment approaches targeting immune dysregulation and inflammation in affected individuals. The identification of a higher PLR in preeclampsia highlights the intricate interplay between inflammation, immune dysregulation, and vascular dysfunction in the pathogenesis of this condition. Furthermore, while this study adds knowledge to the existing literature and supports the fact that there is a link between altered hematological parameters and preeclampsia, it is imperative to acknowledge the necessity for additional research to clarify the underlying mechanisms and clinical implications of these hematological changes. Longitudinal studies with larger sample sizes and multicenter collaborations may provide more comprehensive insights into the hematological alterations associated with pre-eclampsia and their implications for maternal and fetal health outcomes.

Conclusion

In conclusion, our study highlights significant alterations in the immune-inflammatory profile of patients with preeclampsia compared to controls. The observed high neutrophil-to-lymphocyte ratio (NLR) and low platelet-to-lymphocyte ratio (PLR) suggest a distinct systemic inflammatory response associated with preeclampsia. The alteration in neutrophil-to-lymphocyte ratio (NLR) and low platelet-to-lymphocyte ratio (PLR) may appear earlier in the course of disease far before the classic cascade of PE begins. Hence these findings underscore the potential utility of NLR and PLR as biomarkers for the early identification and monitoring of preeclampsia. This will improve both perinatal morbidity and mortality. Further research is warranted to elucidate the under-

lying mechanisms driving these immune alterations and their implications for the pathogenesis and management of preeclampsia.

Conflict of Interest: None

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Ethical Consideration: The study was approved by the ethical review board. Informed written consent was obtained from the participants, and the confidentiality of their data was clearly explained.

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Authors Contribution:

All the authors contributed equally in accordance with ICMJE guidelines and are accountable for the integrity of the study.

MR: Study design and concept, Acquisition of data and final approval

MZ: Data Collection, analysis and final revision

BI: Data Collection, statistical analysis and final revision

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