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The performance of various serum parameters in blood during the first trimester in the early detection of pre-eclampsia

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ABSTRACT

Aims: The aim of this study is to examine the alterations in various serum parameters within the circulatory system throughout the first trimester and assess their efficacy in identifying pre-eclampsia at an early stage.

Methods: This retrospective analysis undertook an examination of the medical records pertaining to 225 pregnancies that met the eligibility criteria at a tertiary referral center, spanning the years 2018 to 2021. Furthermore, an examination of laboratory parameters during the first trimester was performed, which included neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune inflammation index, systemic inflammation response index, pan-immune inflammation value, AST-to-platelet ratio index, delta neutrophil index, and prognostic nutritional index (PNI). A receiver operating characteristic curve analysis was performed to determine the optimal cut-off values for inflammatory and nutritional biomarkers to predict early- onset pre-eclampsia.

Results: The group of individuals with early-onset pre-eclampsia displayed notably elevated levels of neutrophil, lymphocyte, PCT, MPV, ALT, and creatinine, while displaying significantly reduced levels of albumin, bilirubin, PLR, MLR, and PNI ($p<0.05$, for all). The statistical significance of the area under the curve for PNI, albumin, PLR, MLR, and bilirubin values was observed to be greater than 0.5 ($p<0.05$, for all).

Conclusion: This article is the first to examine the efficacy of the first trimester PNI value in early detection of pre-eclampsia patients. According to this study, PNI, albumin, PLR, MLR, and bilirubin show potential as useful indicators for predicting the likelihood of developing pre-eclampsia at an early stage in the first trimester.

Keywords: Serum markers, pregnancy, first trimester, high-risk, pre-eclampsia

INTRODUCTION

Pre-eclampsia (PE) is a complex, heterogeneous pregnancy-related disease that occurs as a disruption of the mother's organs and systems. It is characterized by elevated blood pressure levels (≥140/90 mmHg) and the presence of protein in the urine (≥300 mg/L per 24 hours) occurring after the 20th week of gestation.[1] PE is a significant contributor to maternal and perinatal mortality on a global scale. It affects approximately 3% to 10% of all pregnancies. PE can be categorized into two groups based on the time it begins: early-onset preeclampsia (EOPE, <34 weeks) and late-onset preeclampsia (LOPE, ≥34 weeks).[1] PE is thought to typically manifest in the initial stages of pregnancy, particularly during the placental phase. However, the underlying pathophysiological alterations become evident in the latter portion of pregnancy.[2] Despite numerous proposed pathogenic theories of PE, the precise cause remains unknown, and the management of this condition remains a significant challenge that necessitates further investigation. Possible factors involved in the pathogenesis of PE during the first trimester include inadequate trophoblastic invasion and secretion of pro-inflammatory cytokines and angiogenic factors. These alterations result in impaired endothelial function, activation of leukocytes, and increased concentrations of inflammatory markers.[3] The activation of various major leukocytes, such as neutrophils, lymphocytes, and monocytes, occurs as a result of the secretion of lipids from the placenta. Recent research has established a strong association between preeclampsia and immune dysfunction within the inflammatory disease classification. Activated leukocytes accumulate in the intimal space of the maternal vascular tissue, resulting in inflammation of the vascular smooth muscle in preeclampsia patients. This ultimately leads to vasoconstriction and vascular dysfunction.[4] Pregnant women frequently experience malnutrition as a comorbidity, which is associated with unfavorable outcomes.[5] Nevertheless, the assessment of nutritional status is a multifaceted and impartial process. Evaluating the nutritional status solely

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based on a single nutritional index is both unilateral and unreasonable. Several studies have identified a correlation between nutritional status and patients with PE.[6]

After the diagnosis of PE, the only available treatment option is delivery. Nevertheless, research has demonstrated that initiating a dosage of 150 mg of aspirin prior to week 16 can effectively avert nearly 50% of cases of EOPE. Due to this rationale, numerous studies have been dedicated to the identification of individuals who are susceptible to PE during the initial phases of pregnancy.[7] Preeclampsia is a complex hypertensive disorder that occurs during pregnancy and is caused by multiple factors. The exact mechanisms behind this condition are not yet completely understood. Although the standard course of pregnancy is associated with oxidative stress, factors such as vascular endothelial damage, placental ischemia, oxidative damage, coagulation anomalies, inflammation are predisposing factors to preeclampsia.[8] In previous studies, biomarkers of oxidative stress (Ischemia-modified albumin (IMA), uric acid (UA), and malondialdehyde (MDA))[9] and routine hemogram parameters (neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume, platelet count)[10] has been found to be associated with the pathogenesis of preeclampsia. For this reason, it is predicted that some biomarkers may be indicators of developing preeclampsia and can be used for timely diagnosis.[9] Numerous studies have been conducted to investigate diverse biochemical markers in order to achieve this objective. Therefore, the aim of our study was to investigates the clinical indicators of nutrition and inflammation in the bloodstream of pregnant women in their first trimester, and explores their potential association with the risk of EOPE.

METHODS

The study conducted at Etlik Zübeyde Hanım Maternity Hospital from January 2018 to January 2021 was a single-center case-control study. The scope of our study encompassed a retrospective examination of the medical records of 225 pregnant women who met the eligibility criteria. The study population consisted of patients who had been diagnosed with EOPE. The EOPE group consisted of patients who were diagnosed with PE prior to the 34th week of gestation. The diagnosis of PE was established when there was a blood pressure elevation of 140/90 mmHg on two separate occasions, with a time interval of 4 hours between each measurement. Additionally, proteinuria was defined as a proteinuria level of 300 mg/dl in 24-hour urine or a proteinuria level of +2 as determined by the dipstick test in spot urine.[11] The control group consisted of healthy patients who had no PE and no systemic diseases that could possibly affect the parameters examined and who were regularly treated in our prenatal clinic. Approval to conduct the study was obtained from the Health Sciences University Etlik Zübeyde Hanım Maternity Hospital Local Ethics Committee (Date: 28.02.2024, Decision No: 02) and was conducted following the guidelines of the Helsinki Declaration. Exclusion criteria encompassed patients lacking available first trimester findings for assessment, as well as individuals suffering from chronic systemic illness that could potentially impact any variable examined in the current study. As a result, individuals who were diagnosed with HELLP syndrome, chronic hypertension, diabetes mellitus, hepatic and renal disease, collagen vascular and coronary artery disease, thyroid disorders, and a reduced number of patients with rupture of membranes were not included in the ensuing evaluation. The exclusion criteria included patients who had undergone more than one pregnancy. The extraction of patient data was performed by utilizing healthcare documents and the medical center's data. This research specifically focused on pregnant women who had undergone all necessary antenatal assessments and gave birth at our clinic.

In their the first trimester health checks examination, which took place within the gestational period of 8 to 14 weeks, laboratory values were measured in a random manner. The study incorporated comprehensive data on demographics and perinatal outcomes for statistical examination. The variables to be included are age, body-mass index (BMI), gravida, parity, dilatation and curettage (D/C), abortus, living children, diagnosis time of PE, use of antihypertensive (anti-HT) drugs, application of betamethasone and MgSO4, birth age, birth weight, birth type, APGAR score at 1st and 5th minutes, hospitalization in the neonatal intensive care unit (NICU), fetal gender, and laboratory tests including hemoglobin, neutrophils, monocytes, lymphocytes, platelets, albumin, white blood cells (WBC), plateletcrit (PCT), mean platelet volume (MPV), bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), urea, creatinine, 24-hour urine protein, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune inflammation index (SII), systemic inflammation response index (SIRI), pan-immune inflammation value (PIV), AST-to-platelet ratio index (APRI), delta neutrophil index (DNI), and prognostic nutritional index (PNI).

The inflammatory and nutritional biomarkers were calculated using the following formulas: NLR represents the ratio of absolute neutrophil count (ANC) to absolute lymphocyte count (ALC); PLR represents the ratio of absolute platelet count (APC) to ALC; MLR represents the ratio of absolute monocyte count (AMC) to ALC; SII=APCxANC/ALC; SIRI=AMCxANC/ALC; PIV=APCxAMC/ALC; APRI=(AST/ normal upper limit of AST/patient's platelet count x100; PNI=10 x albumin+0.005 x total lymphocyte count. DNI was recorded as the value obtained from complete blood count analysis.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) v29.0 software (IBM® SPSS® Statistics, Armonk, New York, USA) was used for the statistical analysis. The suitability of numerical data for normal distribution was analyzed according to the Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical data were given as median (interquartile range (IQR) or min-max) or mean±SD. Categorical variables were presented as numbers (percentage) and the chi-square test was used. This study consisted of two independent groups. Student's t-test was used to compare normally distributed data and data were

presented as mean±SD. The Mann-Whitney U test was used to analyze data that did not have a normal distribution, and data were presented as median (25^{th}-75^{th} percentile). Due to the significant difference between groups in age and BMI variables, multivariate analysis of variance (MANOVA) was performed between groups with significant markers. The area under the receiver operating characteristic (ROC) curve was used for cut-off values, sensitivity, and specificity. The relationship between the variables was investigated with Pearson correlation analysis. Results with p<0.05 were accepted as significant.

RESULTS

Within the sample size of 225 individuals, it was observed that 89 participants (39.55%) were assigned to the EOPE group (group 1), while 136 participants (60.45%) were assigned to the control group (group 2). Table 1 displays the demographic, obstetric, and clinical details and results of the groups. The maternal age and BMI values of group 1 were found to be significantly higher in comparison to group 2 (p<0.001). Gravida, parity, abortus, D/C, and living children were similar in both groups (p>0.05, for all). The group 1, 24-hour urine protein was found to be 359 (87) mg, the age at onset of PE was 190 (68) days and the rates of antihypertensive (anti-HT) drug use, betamethasone and MgSO4 application were significantly higher than the group 2 (p<0.001, for all). The rates of cesarean section and hospitalization in the NICU showed significant differences between the groups, with the EOPE group experiencing an increase in these rates (p<0.001, for all). Additionally, gestational age at birth, birth weight, and the 1st and 5th minute APGAR scores were exhibited statistically significant lower in group 1 than in group 2 (p<0.001, for all). There was no differences between the groups regard to fetal gender (p>0.05) (Table 1).

The comparison of blood-based clinical biomarkers of nutrition and inflammation between groups are shown in Table 2. The EOPE group exhibited significantly higher values of neutrophil, lymphocyte, PCT, MPV, ALT, and creatinine, while demonstrating significantly lower values of albumin, bilirubin, PLR, MLR, and PNI (p<0.05, for all). Both groups exhibit similar values for various markers, including hemoglobin, platelets, WBC, DNI, monocyte, AST, urea, NLR, SII, SIRI, PIV, and APRI.

ROC curve analysis was used to assess key blood-based clinical biomarkers of nutrition and inflammation. Only the area under the curve for PNI, albumin, PLR, MLR and bilirubin values exceeded 0.5 and were found to be statistically significant (p<0.05, for all) (Table 3). The cut-off value for PNI was 34.00 (p<0.001), with a sensitivity of 80.3% and a specificity of 58.4%, for PLR the cut-off value was 138.65 (p= 0.025), with a sensitivity of 68.2% and a specificity of 50.6%, for MLR the cut-off value is 0.20 (p<0.001) with a sensitivity of 69.7% and a specificity of 50.6%, for albumin the cut-off value is 3.45 (p<0.001) with a sensitivity of 71.2% and a specificity of 67.4%, and for bilirubin the cut-off value is 0.29 with a sensitivity of 61.4% and a specificity of 59.5% (p=0.023). The ROC curve for PNI, albumin, PLR, MLR and bilirubin is shown in Figure.

Table 1. Demographic, obstetric and clinical characteristics of the groups

Variable(s)	Early-onset preeclampsia group	Control group	p-value
Participant (n, %)	89 (39.55)	136 (60.45)	n/a
Age (years, median, IQR)	32 (10)	27 (8)	<0.001[a]
BMI (kg/m^2, median, IQR)	34 (9)	28 (4)	<0.001[a]
Gravida (n, median, IQR)	2 (1)	2 (1)	0.708[a]
Parity (n, median, IQR)	1 (2)	1 (2)	0.769[a]
Abortus (n, median, IQR)	0 (0)	0 (1)	0.280[a]
D/C (n, median, IQR)	0 (0)	0 (0)	0.589[a]
Living children (n, median, IQR)	1 (2)	1 (2)	0.891[a]
Preeclampsia diagnosis time (day, median, IQR)	190 (68)	-	n/a
24-hour urine protein (mg, median, IQR)	359 (87)	-	n/a
Anti-hypertensive drug (n, %)			<0.001[b]
No	0 (0)	136 (100)	
Yes	89 (100)	0 (0)	
Betamethasone (n, %)			<0.001[b]
No	38 (42.7)	136 (100)	
Yes	51 (57.3)	0 (0)	
$MgSO_4$ (n, %)			<0.001[b]
No	55 (61.8)	136 (100)	
Yes	34 (38.2)	0 (0)	
Birth age (day, median, IQR)	256 (22)	269 (10)	<0.001[a]
Birth weight (g, median, IQR)	2900 (990)	3145 (536)	<0.001[a]
Birth type (n, %)			<0.001[b]
Vaginal	17 (19.1)	128 (94.1)	
Cesarean	72 (80.9)	8 (5.9)	
Apgar 1 (median, min-max)	9 (5-9)	9 (9-9)	<0.001[a]
Apgar 5 (median, min-max)	10 (7-10)	10 (10-10)	<0.001[a]
Gender (n, %)			0.819[b]
Female	47 (52.8)	74 (54.6)	
Male	42 (47.2)	62 (45.4)	
NICU (n, %)			<0.001[b]
No	82 (92.1)	136 (100)	
Yes	7 (7.9)	0 (0)	

a=Mann-Whitney U test, b=Chi-square test, IQR: Inter quantile range, BMI: Body-mass index, D/C: Dilatation and curettage, $MgSO_4$: Magnesium sulfate, NICU: Neonatal intensive care unit

Table 2. Comparison of blood-based clinical biomarkers of nutrition and inflammation between groups

Variable(s)	Early-onset preeclampsia group	Control group	p-value
Participant (n,%)	89 (39.55)	136 (60.45)	n/a
Hemoglobin (g/dL, mean±SD)	12.29±1.22	12.54±1.15	0.060[a]
Platelets (10^3/mm^3, median, IQR)	276.0 (81.5)	259.0 (79.0)	0.086[b]
PCT (µg/L, mean±SD)	0.23±0.47	0.21±0.44	<0.001[a]
WBC (10^3/mm^3, mean±SD)	9.1164±2.4637	8.787±8.2034	0.710[a]
Neutrophil (10^3/mm^3, mean±SD)	6.4270±2.1040	5.7975±1.6677	0.007[a]
Lymphocyte (10^3/mm^3, median, IQR)	1.88 (0.83)	1.61 (0.62)	<0.001[b]
Albumin (g/dL, median, IQR)	3.3 (0.3)	3.6 (0.3)	<0.001[b]
Monocyte (10^3/mm^3, median, IQR)	0.40 (0.15)	0.39 (0.16)	0.847[b]
DNI (Median, IQR)	-2.9 (4.0)	-3.2 (4.0)	1.000[b]
MPV (fl, median, IQR)	8.1 (1.5)	7.8 (0.8)	0.014[b]
Bilirubin (mg/dL, median, IQR)	0.30 (0.18)	0.38 (0.32)	0.021[b]
AST (IU/L, median, IQR)	16.0 (5.0)	15.0 (4.0)	0.141[b]
ALT (IU/L, median, IQR)	14.0 (9.0)	12.0(5.0)	0.041[b]
Urea (mg/dL, median, IQR)	8.0 (4.0)	8.0 (3.0)	0.610[b]
Creatinine (mg/dL, median, IQR)	0.50 (0.10)	0.40 (0.10)	0.025[b]
NLR (Median, IQR)	3.13 (1.54)	3.28 (1.33)	0.061[b]
PLR (Median, IQR)	138.49 (64.84)	160.62 (65.48)	0.018[b]
MLR (Median, IQR)	0.20 (0.09)	0.24 (0.10)	<0.001[b]
SII (Median, IQR)	930.35 (538.62)	907.51 (448.32)	0.955[b]
SIRI (Median, IQR)	1.25 (1.0)	1.37(0.88)	0.384[b]
PIV (Median, IQR)	59.31 (41.20)	62.01 (33.95)	0.121[b]
APRI (Median, IQR)	170.74 (94.72)	171.21 (66.52)	0.981[b]
PNI (Median, IQR)	33.01 (3.01)	36.00 (3.00)	<0.001[b]

[a]=Indepented t test [b]=Mann Whitney U test, SD: Standart devation, IQR: Inter quantile range, PCT: Plateletcrit, WBC: White blood cells, DNI: Delta neutrophil index, MPV: Mean platelet volume, AST: Aspartate transaminase, ALT: Alanine transaminase, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, PIV: Pan-immune inflammation value, APRI: AST-to-platelet ratio index, PNI: Prognostic nutritional index

Given the considerable differences in age and BMI variables between the groups, a multivariate analysis was performed for the significant markers PNI, albumin, PLR, MLR and bilirubin. According to the findings presented in Table 4, there was no significant impact of age and BMI on biomarker outcomes, specifically PNI, albumin, and MLR, across the groups. The adjusted model yielded R^2 values of 0.149 for PNI (aR^2=0.137, p<0.001), 0.149 for albumin (aR^2=0.137, p<0.001), and 0.016 for bilirubin (aR^2=.003, p=0.313). Additionally, R^2 values of 0.030 (aR^2=.017, p=0.081) were calculated for PLR, and 0.029 (aR^2=.041) for MLR.

Table 3. ROC analyses for significant biomarkers

Test result variable(s)	Area	SD error	Asymptotic significance	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Neutrophil (10^3/mm^3)	.393	.039	.007	.316	.470
Lymphocyte (10^3/mm^3)	.345	.038	<0.001	.270	.419
PCT (µg/L)	.365	.038	.001	.289	.440
MPV (FL)	.399	.042	.011	.318	.481
Albumin (g/dL)	.749	.036	<0.001	.679	.819
Bilirubin (mg/dL)	.590	.038	.023	.515	.665
ALT (IU/L)	.421	.040	.047	.343	.500
Creatinine (mg/dL)	.422	.039	.048	.346	.497
PLR	.589	.040	.025	.512	.667
MLR	.643	.038	<0.001	.568	.718
PNI	.736	.037	<0.001	.664	.807

ROC: Receiver operating characteristic curve, SD: Standart devation, PCT: Plateletcrit, MPV: Mean platelet volume, ALT: Alanine transaminase, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PNI: Prognostic nutritional index

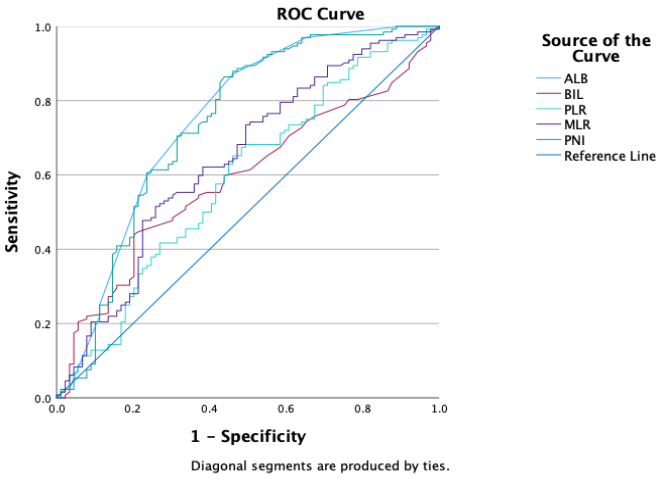

Figure. ROC curves for PNI, Albumin, PLR, MLR and Bilirubin
ROC: Receiver operating characteristic curve, ALB: Albumin, BIL: Bilirubin, PLR: platelet-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, PNI: prognostic nutritional index

DISCUSSION

Our study stands out by focusing on the NLR, PLR, MLR, SII, SIRI, PIV, APRI, and PNI as potential prognostic indicators of PE. We specifically use data obtained exclusively from blood samples. The findings of our study demonstrated significant increases in neutrophil, lymphocyte, PCT, MPV, ALT, and creatinine values, while remarkable decreases in albumin, bilirubin, PLR, MLR, and PNI in the EOPE group, unlike the control group. However, hemoglobin, platelets, WBC, DNI, monocyte, AST, urea, NLR, SII, SIRI, PIV and APRI values were similar in the both groups. Notably, PLR, MLR, PNI, albümin, and bilirubin emerged as reliable indicators of EOPE, with defined cutoff values of 138.65, 0.20, 34.00, 3.45, and 0.29, respectively. These findings emphasize the potential for these nutrition and inflammation-related indices to be useful in

Table 4. Multivariate analysis of parameters

Source	Dependent variable	Type III sum of squares	DF	Mean square	F	Significance	Partial eta-squared
Corrected model	PNI	198.524	3	66.175	12.672	<.001	.149
	Albumin	1.988	3	.663	12.691	<.001	.149
	Bilirubin	.215	3	.072	1.194	.313	.016
	PLR	21785.345	3	7261.782	2.276	.081	.030
	MLR	.154	3	.051	3.068	.029	.041
Age	PNI	3.518	1	3.518	.674	.413	.003
	Albumin	.035	1	.035	.675	.412	.003
	Bilirubin	.014	1	.014	.238	.626	.001
	PLR	7005.528	1	7005.528	2.195	.140	.010
	MLR	.042	1	.042	2.537	.113	.012
BMI	PNI	8.973	1	8.973	1.718	.191	.008
	Albumin	.090	1	.090	1.716	.192	.008
	Bilirubin	.010	1	.010	.172	.679	.001
	PLR	189.219	1	189.219	.059	.808	.000
	MLR	.024	1	.024	1.433	.233	.007

PNI: Prognostic nutritional index, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, BMI: Body-mass index

predicting the EOPE in a clinical setting. The PLR, MLR, and PNI indices, which incorporate measurements of albümin, monocyte, platelet, and lymphocyte counts, are utilized as markers for assessing the nutritional and inflammatory status of the body. Only the MLR, PNI, and albumin parameters were found to predict EOPE in the first trimester in the multivariate model. In order to assess our findings, we carried out a comprehensive review of the existing literature. The correlation between the existence of risk factors in patients and the higher occurrence of PE is possible; nevertheless, the advancement of the condition is not consistently foreseeable.[12] The anticipation of PE, specifically during the first trimester, is a subject of considerable clinical significance owing to its capacity to profoundly influence patient care and maternal-fetal results.[13]

Early trophoblast development in normal pregnancies necessitates a hypoxic intrauterine environment. Within this framework, diverse biomarkers of oxidative stress were analyzed in the mother's serum to indicate the oxidative stress linked to placental development. One of the biomarkers associated with oxidative stress is IMA.[14] According to the literature, there is a significant increase in the average serum IMA value during pregnancy.[15] In a study conducted in this context, although serum IMA levels were found to be higher in patients with preeclampsia than in healthy pregnancies, no significant correlation was found in terms of preeclampsia severity.[8]

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor proteins that regulate gene expression. PPARs have been reported to play a significant role in the (dys-) regulation of blood pressure. PPAR isoforms may be expressed in the amnion, decidua, and villous placenta, but are mainly represented in cytotrophoblasts and syncytiotrophoblasts in the first trimester of the placenta, signifying their exclusive contributions to trophoblast differentiation and functions of the placenta.[16] So far, numerous review articles have been published regarding the function of PPARs in trophoblast differentiation and the promotion of a healthy placental development.[17–19] In this context, there are many studies investigating the role of PPAR in preeclampsia. Different study groups reached contradictory conclusions in terms of PPAR expression in preeclamptic placentae. The review by Iason et al.[20] highlights the critical role of PPARs in preeclampsia.

Extensive research has been conducted on the predictive capabilities of NLR, PLR, and MLR in various domains, including cardiovascular diseases, neurological and psychiatric disorders, as well as vascular and oncological surgical procedures. PE is one of these areas.[21] However, research on the inflammatory indices PLR, NLR, and MLR in PE did not reach a unanimous agreement.[21,22] As an illustration, there exist studies that demonstrate the impact of NLR[23] or not significantly affected,[21] PLR is affected[23] or not significantly affected[21] and MLR is affected[23] or not significantly affected[24] in PE cases. Most studies show that there is a clear effect, indicating that inflammatory parameters (MLR and NLR) increase in preeclampsia.[23,25,26] However, there are also studies that show a significant decrease in these indices. According to Cui et al.,[27] it was proposed that preeclampsia patients exhibited lower inflammation indices in comparison to the control group, which can be attributed to an elevation in lymphocyte count. In the present study, it was observed that patients with PE exhibited significantly lower values of PLR and MLR in comparison to the control group. Additionally, the NLR was found to be low, although it did not reach statistical significance. The observed outcomes are hypothesized to be attributed to the augmentation in

lymphocyte count. Therefore, our research corroborates the findings of Cui et al.'s study.[27]

The DNI index, as proposed by Pyo et al.,[28] is a novel measure that quantifies the percentage of immature granulocytes present in the bloodstream. Pyo et al. demonstrated that the augmentation of immature granulocytes in peripheral blood holds significant prognostic and diagnostic value in the context of infections and sepsis. The findings of Laresgoiti-Servitje et al.[3] indicate a potential correlation between the pathophysiology of PE and DNI. Cho et al.[29] observed an elevation in DNI levels among individuals with severe PE in comparison to those with PE and normotensive individuals. However, Ozkan et al.'s[30] findings indicated that the DNI value alone may not be adequate for assessing the risk of developing gestational hypertension and preeclampsia, as well as predicting the severity of preeclampsia. In the present study, it was observed that while the DNI values exhibited an increase within the EOPE group, these increases did not reach statistical significance.

The primary transaminase released into the peripheral circulation in cases of liver dysfunction caused by PE is AST, which is also linked to periportal necrosis.[31] In liver fibrosis, the APRI serves as a non-invasive measure for assessing inflammation. According to several studies,[32,33] there is evidence suggesting that the APRI level is a more reliable predictor of HELLP syndrome compared to AST alone. Our study revealed that the EOPE group exhibited elevated levels of AST and ALT. However, only a notable rise in ALT value was observed, whereas APRI levels were similar to those of the control group.

The parameters PIV, SII, and SIRI reflect the inflammatory status of the body by encompassing counts of neutrophils, monocytes, platelets, and lymphocytes. Given the characteristic features of PE, namely dysfunction of the endothelial system and increased inflammation-related activity, the augmentation of parameters related to inflammation presents itself as a feasible approach for prognosticating the probability of PE onset. In their study, Seyhanli et al.[25] demonstrated that there was an increase in SII levels in the severe and mild PE individuals. However, it was found that SII did not exhibit statistical significance as a predictor of PE. Conversely, the mild PE group exhibited significant increases in SIRI and PIV indices when compared to the control group. There was no statistically significant difference observed in the levels of SII between the PE and control groups in the research carried out by Maziashvili et al.[34] The results of our study indicate that there was no statistically significant increase in the SII, SIRI, and PIV indices between the EOPE group and the control group. In recent times, these parameters have gained significant popularity due to their affordability and the ease with which they can be computed using standard blood tests. The literature pertaining to this subject is highly intricate. It is plausible that the reduced number of components in these parameters renders them susceptible to the influence of patients' concurrent health conditions.

The pathophysiology of PE is believed to encompass atypical formation of placental vasculature, characterized by impaired deep placentation and absence of spiral artery transformation.[35] Nutrition and the release of inflammatory factors have been proposed to have a significant impact on placental endothelial function and oxidative stress.[36] Malnutrition significantly impacts placental endothelial function, oxidative stress, and the expression of angiogenic factors, as indicated by the literature.[37] Moreover, there is a correlation between malnutrition and negative outcomes such as fetal growth restriction, low birth weight, and preterm delivery.[38] The utilization of the PNI score as a metric for assessing the nutritional status of individuals has been found to have a significant correlation with the prognosis of patients diagnosed with gynecological cancer. The studies conducted by Zheng Feng et al.[39] and Naoko Komura et al.[40] demonstrated that a reduced PNI score prior to treatment does not serve as a reliable prognostic indicator for individuals diagnosed with ovarian cancer. The PNI score, derived from the measurement of serum albumin concentration and total lymphocyte count in the peripheral blood, has the potential to serve as an indicator of an individual's nutritional status.[41] The investigation conducted by Wei et al.[42] aimed to assess the predictive value of the PNI score in identifying adverse events that may arise during hospitalization prior to the termination of pregnancy in patients diagnosed with PE. However, a comparison was made between the low PNI group and the high PNI group. It has been demonstrated that a low PNI score is linked to poorer clinical outcomes in patients with PE, including higher rates of admission to the intensive care unit and the occurrence of adverse events such as HELLP syndrome, placental abruption, and heart failure during hospitalization. In addition, in this study, it was found that the albumin level in the group with low PNI was significantly lower than in the group with high PNI. In our investigation, akin to the present study, we observed a notable decrease in PNI and albumin levels within the cohort that experienced PE in comparison to the control group. Furthermore, based on the findings of the multivariate analysis of variance, it was determined that there was no significant impact of age and BMI on PNI and albumin levels across the groups. The PNI exhibited a significant cut-off value of 34.00, demonstrating a sensitivity of 80.3% and specificity of 58.4%. A cut-off value of 3.45 was determined for albumin, exhibiting a sensitivity of 71.2% and specificity of 67.4%. These outcomes could have important consequences for clinical practice, especially in predicting EOPE.

Limitations

We must recognize that our study is retrospective and carried out at a single institution, with a relatively small sample size. However, the advantage of our study lies in its ability to eliminate device-related variability by analyzing data exclusively from a single central laboratory in a tertiary care center. Furthermore, the PNI exhibited a statistically significant reduction, particularly within the EOPE group, and its sensitivity was also determined to be elevated. This article is the first to examine the efficacy of the first trimester PNI value in early detection of PE patients. It is imperative to conduct future studies involving larger patient cohorts in order to enhance the dependability of these parameters. This subject necessitates the implementation of prospective studies

and randomized controlled trials. In this regard, we believe that it provides a substantial contribution to the existing body of the literature. However, it is crucial to recognize that the simplicity and cost-effectiveness of these parameters, which can be obtained from routine blood tests, offer significant advantages in the realm of clinical practice.

CONCLUSION

The present research emphasizes the potential efficacy of PNI, albumin, and MLR as predictive measures for assessing the likelihood of EOPE in the first trimester. The aforementioned parameters have the potential to enhance monitoring, enable early detection and intervention, and consequently potentially mitigate complications related to PE. This study represents the inaugural investigation into the effectiveness of the first trimester PNI value in the timely identification of patients with EOPE.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethics Committee of Etlik Zübeyde Hanım Maternity Hospital (Date: 28.02.2024, Decision No: 02).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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