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ORIGINAL RESEARCH

Are NLR, PLR, and Elevated Uric Acid Levels Predictive of Preeclampsia?

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ABSTRACT

Background: It is estimated that 2 to 8% of pregnancies are complicated by gestational hypertension and preeclampsia, the latter being considered a major cardiovascular emergency due to its possible progression to severe eclampsia and HELLP syndrome. New inflammatory biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), may predict the progression of gestational hypertension. **Aim of the study:** The aim of this study was to assess whether NLR, PLR, and uric acid play a role in predicting preeclampsia and its severe forms. **Methods:** This prospective, single-center cohort study, conducted between January 1, 2020 and December 31, 2022, included 107 pregnant women with gestational hypertension, preeclampsia and its severe forms, HELLP syndrome and eclampsia. Patients were divided into two groups: the first group included 88 patients with gestational hypertension (GH group), and the second group included 19 patients with preeclampsia and its severe forms (PE group). We compared demographic, clinical and biochemistry data between the two groups. **Results:** PLR was significantly lower in women with preeclampsia (85.47 ± 7.91 vs. 115.90 ± 4.63, p = 0.005). The mean serum uric acid level in the PE group was significantly higher than in the GH group (6.71 ± 0.44 mg/dL vs. 4.59 ± 0.12 mg/dL, p <0.0001). **Conclusion:** In this study, low-cost biomarkers PLR and serum uric acid were associated with a higher risk of PE and its severe forms and may be used to predict the progression of gestational hypertension.

Keywords: gestational hypertension, preeclampsia, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

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INTRODUCTION

It is estimated that 2 to 8% of pregnancies are complicated by gestational hypertension and preeclampsia, with an important impact on the fetuses as well as on maternal health.[1] Preeclampsia is regarded as a major cardiovascular emergency due to its possible progression to severe eclampsia and HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome, two life-threatening conditions. De novo onset of these disorders appears usually after 20 weeks of gestation, and they are thought to be among the major causes of maternal and perinatal mortality worldwide.[2]

Gestational hypertension is defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg appearing for the first time after 20 weeks of pregnancy, in the absence of proteinuria. It is estimated that in 25% of cases, gestational hypertension will lead

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to preeclampsia, most of the time without affecting fetal growth.[3]

Preeclampsia is a pregnancy disorder defined as new-onset hypertension (high systolic and diastolic blood pressure exceeding the threshold 140/90 mmHg, occurring at least two times in a 4-hour time interval, in a woman without hypertension history) after 20 weeks of pregnancy.[4] In addition, preeclampsia can evolve into severe acute complications of pregnancy, such as eclampsia and HELLP syndrome, which are associated with increased maternal and neonatal morbidity and mortality.

Eclampsia is characterized by the presence of the following symptoms: at least one generalized, tonic-clonic seizure in a pregnant woman with gestational hypertension without another identified cause, extreme agitation, and unconsciousness.[5] Before the seizure, the pregnant woman often experiences severe headache, loss of vision or diplopia, nausea and vomiting, epigastric pain, and swelling of the face and hands.[6]

HELLP syndrome refers to the triad of hemolysis (LDH >600 U/L, serum bilirubin ≥1.2 mg/100 mL), increased liver enzymes (aspartate aminotransferase ≥70 IU/L) and low platelet count ($<100 \times 10^9$/L). The most common symptoms include pain in the epigastrium or the right upper abdominal quadrant, nausea, and vomiting.[7] Incomplete forms of HELLP syndrome are characterized by one or two elements of the HELLP triad.[8]

In pregnant women with preeclampsia, the white blood cell (WBC) count is higher than in women with normal pregnancy and is associated with a higher neutrophil count,[9] which translates into hyperactivation of immunologic and inflammatory responses, leading to endothelial dysfunction. The role of neutrophils and lymphocytes in the pathogenesis of preeclampsia has been studied intensely lately.[10] New inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), seem to be important predictors of the prognosis of the disease[11] and are increasingly used to predict hypertensive disorders in pregnancy.

Data from the literature show that increased serum uric acid levels can induce oxidative stress and endothelial and mitochondrial dysfunction, through which hyperuricemia might be involved in the development of preeclampsia.[12]

The aim of this study was to investigate whether serum inflammatory markers, such as NLR, PLR, and serum uric acid, can be useful in predicting the occurrence of preeclampsia and its severe complications in pregnant women with gestational hypertension.

MATERIAL AND METHODS

STUDY DESIGN AND PATIENT GROUPS

This prospective, single-center cohort study conducted between January 1, 2020 and December 31, 2022 included 107 pregnant women with gestational hypertension, preeclampsia, and its severe forms, HELLP syndrome and eclampsia, admitted to the "Elena Doamna" Clinical Hospital of Obstetric and Gynecology, Iași, Romania. The patients were divided, according to diagnostic criteria, into two groups: group 1 (GE) consisted of 88 patients with gestational hypertension, and group 2 (PE) consisted of 19 patients with preeclampsia and its severe forms. Of the 19 patients in the PE group, 14 were diagnosed with preeclampsia, 3 with incomplete HELLP syndrome, and 2 with eclampsia.

Exclusion criteria were: fever, chronic systemic disease during pregnancy, such as nephropathy, renal or hepatic dysfunction, active infections, or autoimmune disease, chorioamnionitis, previous pregnancy with preeclampsia, cholestasis of pregnancy, inflammatory bowel diseases, thyroid disorders, type B or C hepatitis, human immunodeficiency virus infection, syphilis infection, fetal anomalies, or the use of any anti-inflamatory medication, such as corticosteroids, prior to admission.

CLINICAL PARAMETERS

The following demographic parameters, medical history, and clinical information were recorded: age, body mass index (BMI), comorbidities, symptoms, pregnancy risk factors and current medication. Blood samples for laboratory analyses (complete blood count and biochemical analysis) were collected at the time of diagnosis for the PE group and between gestational weeks 20 and 34 for the GH group. Before initiating any medical treatment, such as magnesium sulphate or antenatal corticosteroids, blood samples for complete blood count and urine samples were taken at admission to the emergency department. Venous blood samples were drawn into EDTA samples tubes (5 mL). The processing of all samples was done within 2 h after venipuncture. The presence of proteinuria was evaluated using spot urine tests, and 24-h proteinuria was assesed using a MAN BTS350 semi-automalic analyzer from the urine collected for 24 h. For complete blood count we used a RAYTO 7600 Auto Hematology Analyzer, and biochemical analyses (serum uric acid, liver enzimes, creatinine and urea) were carried out using a MINDRAY BS-200 clinical analyzer.

TABLE 1. Demographic characteristics and personal pathological antecedents of the study population

Variable	GH group (n = 88)	PE group (n = 19)	95% CI	p value
Age <18 and >35	0.31 ± 0.05	0.21 ± 0.10	-0.13 to 0.33	0.41
BMI (kg/m²)	27.86 ± 0.60	27.21 ± 1.30	-2.19 to 3.49	0.65
Smoking	0.19 ± 0.04	0.21 ± 0.10	-0.22 to 0.18	0.86
Caffeine	0.31 ± 0.05	0.21 ± 0.10	-0.13 to 0.32	0.38
Hematological disease	0.06 ± 0.02	0.05 ± 0.05	-0.11 to 0.12	0.94
Hypertension history	0.28 ± 0.05	0.21 ± 0.09	-0.15 to 0.29	0.50
Diabetes mellitus history	0.06 ± 0.02	0.11 ± 0.07	-0.21 to 0.11	0.53

Results are expressed as mean ± standard deviation. The comparison between groups was performed using the t-test.

STATISTICAL ANALYSIS

All statistical analyses were performed using Prism 5.0 software (GraphPad, San Diego, CA, USA). Data are presented as mean ± standard deviation (SD) for continuous variables and number of subjects (n) and percentage (%) for categorical variables. The two groups were compared using the two-sample t-test, and categorical variables were compared using the chi-squared test. The significance level was set at $p < 0.05$.

ETHICS

The study was carried out in accordance with the principle stated in the Declaration of Helsinki and was approved by the ethics committee of the "Elena Doamna" Clinical Hospital of Obstetric and Gynecology, Iași, Romania.

RESULTS

BASELINE CHARACTERISTICS

A total of 107 women participated in this prospective study; 88 had gestational hypertension and 19 had preeclampsia and its severe forms. Baseline patient characteristics are presented in Table 1. There were no statistically significant differences between the groups regarding the proportion of patients under the age of 18 and over the age of 35 years (0.31 ± 0.05 in the PE group vs. 0.21 ± 0.10 in the GH group; p = 0.41). Furthermore, no significant differences were observed between the two groups regarding BMI, smoking status, history of hypertension, and the presence of diabetes or hematological diseases.

BIOCHEMICAL PARAMETERS AND COMPLETE BLOOD COUNT

Aspartate aminotransferase (AST) (42.95 ± 7.28 IU/L in the PE group vs. 20.83 ± 1.20 IU/L in the GH group) and alanine transaminase (ALT) (43.37 ± 10.66 IU/L in the PE group vs. 17.30 ± 1.70 IU/L in the GH group) levels were significantly higher in the PE group (both $p < 0.001$). Creatinine (0.99 ± 0.07 mg/dL in the PE group vs. 0.73 ± 0.02 mg/dL in the GH group, $p < 0.0001$) and urea (30.04 ± 2.87 mg/dL in the PE group vs. 19.62 ± 0.70 mg/dL in the GH group, $p < 0.001$) levels were also significantly higher in the PE group.

Although the WBC count was higher in the PE group, the threshold of statistical significance was not reached (p = 0.06). No significant differences were observed between the two groups regarding the value of hemoglobin (Hb) and hematocrit (Hct), or the absolute number of lymphocytes. The platelet count (PLT) was significantly lower in the PE group (234.2 ± 19.59 × 103 cells/μL in the PE group vs. 275.30 ± 79.97 × 103 cells/μL in the GH group, p = 0.003), while the neutrophil count was significantly higher in the PE group (10.24 ± 0.41 × 103 cells/μL in the PE group vs. 8.46 ± 0.23 × 103 cells/μL in the GH group, p = 0.001) (Table 2).

SERUM URIC ACID AND INFLAMMATORY MARKERS IN PREECLAMPSIA

The results regarding serum uric acid levels, NLR, and PLR are presented in Figure 1. There was no statistical difference regarding NLR between the two study groups (3.51 ± 0.12 in the PE group vs. 3.76 ± 0.26 in the GH group, p = 0.40). However, PLR was significantly lower in the PE group (85.47 ± 7.91 in the PE group vs. 115.90 ± 4.63 in the GH group, p = 0.005), and serum uric acid levels were significantly higher in the PE group (6.71 ± 0.44 mg/dL

TABLE 2. Comparison of the study groups in terms of liver function, renal function, and complete blood count

Variable		GH group (n = 88)	PE group (n = 19)	p value
Liver function	AST (U/L)	20.83 ± 1.21	42.95 ± 7.28	<0.0001
	ALT (U/L)	17.30 ± 1.71	43.37 ± 10.66	<0.0001
Renal function	Creatinine (mg/dL)	0.73 ± 0.02	0.99 ± 0.07	<0.0001
	Urea (mg/dL)	19.62 ± 0.70	30.04 ± 2.87	<0.0001
Complete blood count	White blood cells (× 10^4/µL)	11.06 ± 0.32	12.45 ± 0.65	0.07
	Hb (g/dL)	11.78 ± 0.15	11.90 ± 0.32	0.74
	Hct (%)	34.56 ± 0.38	35.38 ± 0.88	0.37
	Platelets (× 104/µL)	275.50 ± 7.99	234.20 ± 19.59	0.04
	Neutrophils (× 104/µL)	8.46 ± 0.23	10.24 ± 0.42	0.001
	Lymphocytes (× 104/µL)	2.58 ± 0.09	3.01± 0.28	0.07

Results are expressed as mean ± standard deviation. The comparison between groups was performed using the t-test. AST, aspartate aminotransferase; ALT, alanine transaminase

in the PE group vs. 4.59 ± 0.12 mg/dL in the GH group, p <0.0001).

DISCUSSION

The main findings of our study suggest that low-cost inflammatory markers, such as PLR and serum uric acid level, can predict the occurrence of preeclampsia, eclampsia, and HELLP syndrome in pregnant women with gestational hypertension. PLR was significantly lower in women with preeclampsia, while serum uric acid levels were significantly higher. Although no significant differences were observed, NLR was higher in women with preeclampsia, underlining the importance of inflammation in the development of hypertension complications in pregnant women. The state of hypoxia induced by inadequate perfusion of the placenta will cause inflammation, leading to the release of pro-inflammatory cytokines, anti-angiogenic factors, and chemokines, as well as the activation of neutrophils and monocytes.[13] Neutrophils are

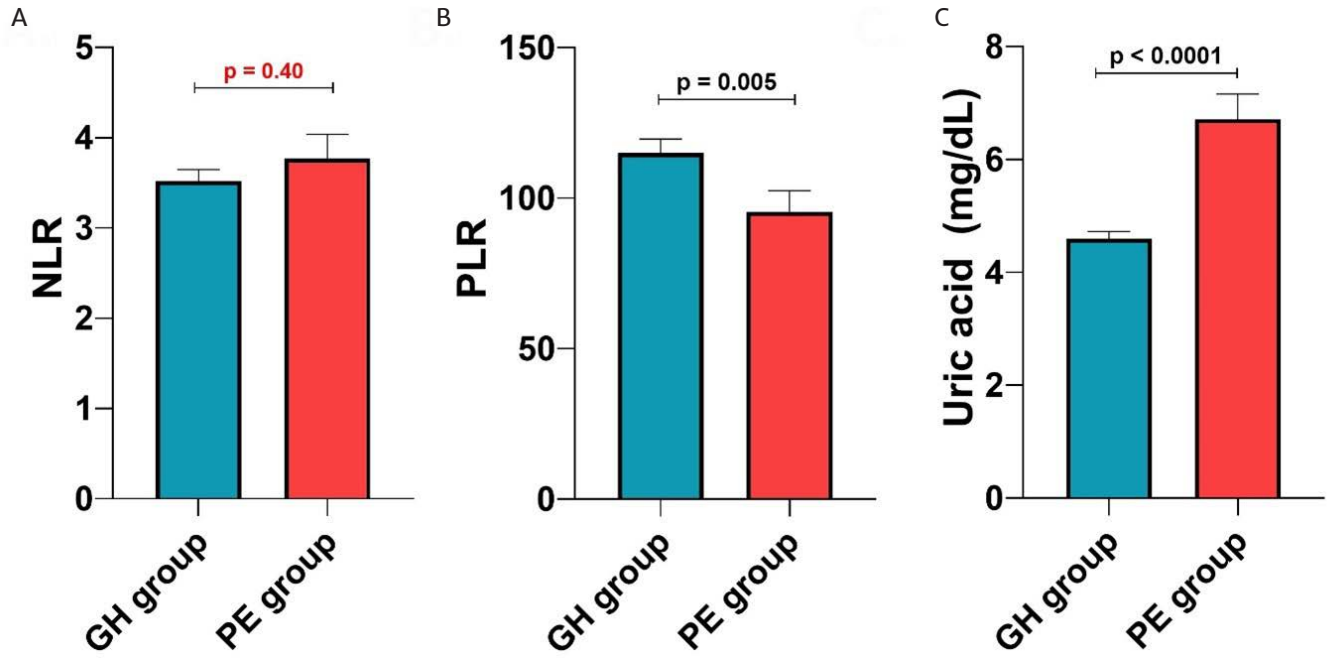

FIGURE 1. **A** – NLR in GH vs. PE groups; **B** – PLR in GH vs. PE groups; **C** – Serum uric acid level in GH vs. PE groups. Results are expressed as mean ± standard deviation. The comparison between groups was performed using the t-test.

a key factor in preeclampsia. When neutrophils are activated, they infiltrate the maternal vascular tissue causing systemic vascular inflammation. This condition will lead to the development of hypertension, endothelial dysfunction, thrombocyte activation, vasoconstriction, and ischemia.[14,15]

Although NLR, PLR, and serum uric acid were widely studied in hypertensive disorders of pregnancy, to the best of our knowledge, this is the first study to assess these markers in late pregnancy with preeclampsia and its severe forms, eclampsia, and HELLP syndrome compared to gestational hypertension.

Maziashvili *et al.* showed that systemic inflammatory response markers may be able to predict the development of preeclampsia.[16] Ozkan *et al.* reported that NLR, PLR, the delta neutrophil index (DNI) and platelet distribution width (PDW) have no clinical importance in predicting the severity of preeclampsia and assessing the risk of developing gestational hypertension and preeclampsia.[17] Kang *et al.* sugested that NLR is higher in preeclampsia, especially in its severe forms. NLR might be an effective laboratory marker for clinical prediction and disease severity evaluation in preeclampsia.[18] Sisti *et al.* demonstrated that NLR was higher and PLR was lower in women with HELLP syndrome and suggested that these markers should be incorporated into the diagnostic algorithm of HELLP syndrome.[19] Wang *et al.* reported that total neutrophil, lymphocyte, and monocyte counts, as well as NLR and monocyte-to-lymphocyte ratio (MLR) values were significantly different in patients with preeclampsia compared to the control group.[20] In a study published by Zheng *et al.*, NLR had unsatisfactory specificity but acceptable sensitivity for the diagnosis of preeclampsia.[21] Another study reported that the inflammatory markers NLR, PLR, red cell distribution width (RDW), and mean platelet volume (MPV) were higher in women with preeclampsia.[22] Mannaerts *et al.* showed that at the ending of pregnancy, NLR and MPV were higher and PLR was lower in women with preeclampia compared to controls, which reinforces the current knowledge on the pathogenesis of this pregnancy complication.[23] Yücel *et al.* reported that there were no significant differences in NLR between women with and without preeclampsia ($p = 0.42$). PLR and PCT were lower in the patients with serious preeclampsia ($p = 0.007$ and $p < 0.001$, respectively).[15] However, Serin *et al.* demonstrated that NLR was significantly higher in women with severe preeclampsia than in those with mild preeclampsia ($p = 0.03$).[24]

One of the biochemical markers studied in preeclampsia is serum uric acid, its increased level being associated with renal function impairment and oxidative stress as a consequence of placental ischemia and reduced maternal glomerular filtration rate.[25] Uric acid is a key factor leading to the pathogenesis of preeclampsia. Pasyar *et al.* demonstrated that serum uric acid levels are significantly increased in preeclamptic pregnancies compared to normal pregnancies, and the level of uric acid may have diagnostic relevance in the occurrence of preeclampsia.[26] Bellos *et al.* showed that hyperuricemia predicted severe preeclampsia, eclampsia, and hemolysis.[27] Another study reported that elevated serum uric acid in Chinese Han women with gestational hypertension increased the risk of progression to preeclampsia and the delivery of small-for-gestational-age infants.[28] Ryu *et al.* suggested that in women with preeclampsia, serum uric acid level is an important parameter for predicting low birth weight.[29] Moreno Santillan *et al.* reported that serum uric acid levels ≥6 mg/dL in women with severe preeclampsia may be a significant biomarker for preeclampsia and related with the presence of adverse fetal and maternal effects.[30] In this study, serum uric acid level was not adjusted according to gestational age.

The results of our study suggest that a PLR of <85.47 and a serum uric acid level of >671 ± 0.44 mg/dL can be used as diagnostic markers in preeclampsia.

LIMITATIONS

The main limitation of our study was the relatively small sample. Being a single-center study and taking into consideration the incidence of gestational hypertension and preeclampsia (2 to 8%), a small number of patients was expected.

CONCLUSIONS

The present study found that increased serum uric acid levels are associated with severe forms of hypertension, such as preeclampia, in pregnant women. PLR was significantly lower in women with preeclampsia and its severe forms compared to women with gestational hypertension. During the prenatal follow-up, the measurement of low-cost inflammatory markers, such as PLR and serum uric acid, are valuable intruments for predicting preeclampsia in pregnant women with hypertension and could lead to a better prevention of preeclampsia and its severe forms in patients at risk.

In the future, prospective multicenter research trials with large numbers of patients are required to accurately establish the usefulness of these inflammatory markers as predictors for preeclampsia.

CONFLICT OF INTEREST

Nothing to declare.

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