

# Evaluation of Platelet Large Cell Ratio (PLCR) Results in Patients with Preeclampsia and HELLP

✉ Berna Şermin Kılıç, ✉ Nil Atakul

Department of Obstetrics and Gynecology, Istanbul Training and Research Hospital, Istanbul, Turkey

## Abstract

**BACKGROUND/AIMS:** Preeclampsia is a multi-systemic syndrome that often occurs after the 20<sup>th</sup> week of pregnancy. It is one of the main causes of maternal morbidity and mortality in the obstetric population. There is still a debate about whether hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) is a form of severe preeclampsia or a separate disease. We aimed to find a relationship between platelet large cell ratio (PLCR) and preeclampsia in our study, and try to assess whether this parameter could be used as marker for early diagnosis.

**MATERIALS AND METHODS:** This retrospective cohort study included 86 preeclampsia and 50 normotensive patients who were admitted to Istanbul Training and Research Hospital between January 2018 and December 2019. Complete blood count values from preeclampsia and normotensive pregnancies were measured using an automated hematological analyzer (XN 3000, Sysmex Corp., Kobe, Japan) at their first entry to the emergency service department. The PLCR value was calculated using data from full blood count analysis. Hemogram and biochemistry results were compared in the preeclampsia and control groups from the patient records.

**RESULTS:** No statistically significant difference was found among the body mass index (BMI), PLCR, hemoglobin (Hg), hematocrit (Hct) and platelet values of the preeclampsia and control group pregnant women. The PLCR values showed a statistically significant positive correlation with alanine transaminase, aspartate aminotransferase, urea, and lactate dehydrogenase values ( $p < 0.05$ ) in the preeclampsia patients. The PLCR value showed the highest statistically significant negative correlation with the platelet count and a positive correlation with the creatinine level ( $p < 0.01$ ).

**CONCLUSION:** Our study supports the belief that HELLP syndrome develops with different mechanisms and adaptive responses from preeclampsia, the underlying enhanced inflammatory response has been demonstrated. Our findings support the belief that anti-inflammatory treatment method could be applied along with appropriate preventive and therapeutic options in those patients with HELLP syndrome.

**Keywords:** Blood platelets, pre-eclampsia, pregnancy

## INTRODUCTION

Preeclampsia is a multi-systemic, pregnancy-specific syndrome characterized by hypertension and proteinuria, which often occurs after the 20<sup>th</sup> week of pregnancy.<sup>1</sup> Preeclampsia is one of the most important health problems which cause maternal morbidity and mortality. It occurs in 3%–8% of pregnancies.<sup>2</sup> Although the exact pathogenesis of preeclampsia is unknown, placental

vascular inadequate perfusion, maternal endothelium damage and increased vascular permeability are thought to contribute to the pathophysiology of this disease.<sup>3</sup> Preeclampsia, which can be described as a common inflammatory process that develops due to endothelial damage; platelets that come into contact with the damaged endothelium activate the coagulation system, which leads to both an increase in consumption and bone marrow production of platelets. Increased thrombopoiesis produces larger and younger

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**ORCID IDs of the authors:** B.Ş.K. 0000-0002-0103-0709; N.A. 0000-0003-3874-8797.



**Address for Correspondence:** Berna Şermin Kılıç

**E-mail:** berna\_doctor@hotmail.com

**ORCID ID:** orcid.org/0000-0002-0103-0709

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platelets rather than older platelets, and these platelets are more enzymatic and metabolically active.<sup>4</sup> As a result, the bone marrow releases larger young platelets resulting in increased platelet indexes such as average platelet volume (MPV), platelet distribution width (PDW) and PLCR. Hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome is a serious complication of pregnancy with hemolysis, high liver enzymes and low platelets. It occurs in 0.2%–0.6% of all pregnancies. HELLP occurs in 10%–20% of severe preeclampsia and often leads to negative maternal and perinatal consequences.<sup>5</sup>

There is still a debate about whether HELLP is a form of severe preeclampsia or a separate disease. Laboratory findings and clinical presentations differ in preeclampsia and HELLP syndrome. Preeclampsia is associated with an increase in platelet function. Thus, platelets contribute to the formation of micro-thrombosis in the placenta and exacerbate vascular dysfunction seen in preeclampsia. Therefore, platelet activation markers may be more sensitive to an early suspicion of potential preeclampsia than the number of platelets, which can vary during normal pregnancy as a result of preeclampsia.<sup>6</sup>

Various studies have shown that platelets are decreased significantly in women with preeclampsia, and MPV is increased significantly.<sup>7</sup> The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are inflammatory markers used to predict the diagnosis and severity of preeclampsia.<sup>8</sup>

PLCR values are novel parameters that have recently been studied in patients with preeclampsia. In a study involving 219 patients with preeclampsia,<sup>9</sup> PLCR values were found to be higher in those patients with severe preeclampsia compared to patients with mild preeclampsia, and they stated that thrombocyte markers could be used to predict the prognosis of preeclampsia.

PLCR is an indicator of larger platelets (>12 fL) shown as a percentage. The normal percentage range is 15%–35%. It is also used to monitor platelet activity.<sup>10</sup>

In our study, we aimed to determine the prognostic and diagnostic importance of PLCR, a systemic inflammatory response marker easily detected in peripheral blood, in preeclampsia and HELLP syndrome.

## MATERIALS AND METHODS

Eighty-six preeclampsia and 50 normotensive pregnant patients were admitted to Istanbul Training and Research Hospital Obstetrics and Gynecology Emergency Department between January 2018 and December 2019 and these inpatients were examined retrospectively.

Those patients with blood pressure, measured at least twice with an interval of six hours, above or equal to 140 mmHg in systolic and 90 mmHg in diastolic, and with 300 mg or more of proteinuria in 24-hour urine were included in the mild preeclampsia group. Blood pressure (above 160/110 mmHg), Oliguria (less than 400 mL in 24 hours), headache, visual impairment, pain in the epigastric and upper right quadrant, pulmonary edema, cyanosis, more than 3 gr/24-hour urine or 3+ proteinuria in spot urine sample, thrombocytopenia (<100,000/mm<sup>3</sup>), and patients with impaired liver function were included in the severe preeclampsia group. HELLP syndrome was defined as hemolysis, high liver enzymes and low platelets.

The small for gestational age (SGA) is defined as a birth weight below the 10th percentile for the gestational week.

Those patients with hypertension <20 gestational weeks (GWs) or before pregnancy, kidney disease, diabetes mellitus, cardiovascular, neurological disease, a history of drug use, the presence of any infection, fetal anomaly, in utero fetal death, hematological or immunological diseases were excluded from this study.

Those patients with HELLP, eclampsia, associated coagulopathy, bleeding, acute renal failure, hepatic insufficiency, unregulated hypertension, pulmonary hypertension, pulmonary edema, hemodynamic instability, or the need for mechanical ventilation were followed up in the intensive care unit for close monitoring.

Blood samples were taken from preeclampsia and normotensive patients at the first entrance to the emergency room and analyzed with an automated hematologic analyzer (XN 3000, Sysmex Corp., Kobe, Japan). PLCR was calculated using data from the complete blood count analysis. The hemogram and biochemistry results were examined retrospectively in the preeclampsia and control group from the patient records. The mean PLCR values of the two patient groups were compared.

## Statistical analysis

The R-version for statistical analysis 2.15.3 program (R Core Team, 2013) was used. The normal distribution conformity of quantitative data was evaluated by the Shapiro–Wilk test and graphical examination. Independent samples t-test was used in comparisons between two groups of quantitative variables with normal distribution, and Mann–Whitney U test was used in comparisons between two groups of quantitative variables which did not show normal distribution. Pearson correlation analysis was used to determine the level of relationship between the quantitative variables of the preeclampsia and control group pregnant women. Statistical significance was considered as  $p < 0.05$ . The statistical analysis of the PLCR values of the preeclampsia women who were admitted to the intensive care unit or had SGA fetuses was performed using the Chi-square test.

Permission and approval of Istanbul Training and Research Hospital Ethics Committee were obtained for our study (decision no: 2072, date: 06/12/2019). Since our study was retrospective, written consent could not be obtained from the patients.

## Results

In our study, 86 preeclampsia and 50 normotensive pregnant patients were analyzed. Of the 86 preeclampsia patients, 44 patients were admitted to the intensive care unit and 42 patients were followed up in cesarean section or normal labor postpartum delivery rooms. SGA fetus was detected in 26 (30%) of the preeclampsia pregnancies.

As shown in Table 1, the age of the preeclampsia patients was statistically higher than the normotensive patients ( $p < 0.05$ ). There was no statistically significant difference found between the Body Mass Index (BMI), PLCR, hemoglobin (Hgb), hematocrit (Hct), or platelet values of the preeclampsia and normotensive patients. The gestational week of the preeclampsia patients was statistically lower than the control group ( $p < 0.05$ ). The urea, creatinine, alanine transaminase (ALT) and aspartate transaminase (AST) values of the preeclampsia patients were statistically significantly higher ( $p < 0.05$ ) than the control group.

Table 2 shows the correlation of the preeclampsia patients' laboratory and clinical data with each other. The GW and BMI values did not show a statistically significant correlation with any laboratory values. The platelet values show a statistically significant high positive correlation with PLCR, ALT, AST, and lactate dehydrogenase (LDH) values ( $p < 0.01$ ). The ALT values show a statistically significant high positive correlation with AST, urea, and LDH values ( $p < 0.01$ ). The AST values show a statistically significant high positive correlation with ALT, urea, and LDH values ( $p < 0.01$ ).

The PLCR values show a statistically significant high positive correlation with ALT, AST, urea, and LDH values ( $p < 0.05$ ). The PLCR value showed the highest statistically significant correlation with platelet count negatively and with creatinine level positively ( $p < 0.01$ ).

The PLCR values of the preeclampsia patients admitted to the intensive care unit were not statistically significantly different from those patients monitored in postpartum delivery room ( $p = 0.444$ ).

There was no statistically significant difference found in the PLCR values between the preeclampsia patients with SGA fetus or the women with appropriate for gestational age (AGA) fetuses using chi-square analysis ( $p = 0.162$ ).

## DISCUSSION

Preeclampsia pathogenesis consists of two consecutive stages. In the first stage, genetic factors, immunological maladaptation or primary trophoblast defect primarily cause placentation problems. In the second stage, abnormal cytokine released from the placenta, oxidative stress and the release of free radicals, the stimulation of leucocytes and macrophages, the activation of the complement system and apoptosis and the release of micro-particles into the maternal circulation cause widespread endothelial damage. Widespread endothelium damage also leads to the emergence of the maternal presentation of preeclampsia. Vascular damage is caused by the interaction of macrophages, T-lymphocytes, activated complement and the coagulation system and platelets.<sup>11</sup>

In HELLP syndrome, the inflammatory reaction is more severe, and the inflammation mostly attacks the liver and clotting system. Clinical symptoms usually appear before laboratory findings. However, in some cases, HELLP syndrome may present with viral syndrome-like symptoms or weakness.<sup>12</sup>

HELLP syndrome, considered a complication of preeclampsia, is characterized by pronounced endothelial cell damage to the liver. Hepatic ischemia can cause inflammation, subcapsular hematomas and intraparenchymal hemorrhage. Liver rupture is a rare but serious and life-threatening complication.<sup>13</sup>

Hemolysis in microangiopathic blood dissemination, one of the most important features of the disease, reflects the damage of the vascular endothelium. The decreased number of platelets in HELLP syndrome indicates increased consumption. Platelets are activated and adhere to the damaged vessel endothelium, resulting in an increased platelet turnover with a shorter half-life. The diagnosis of hemolysis is supported by the high concentration of LDH and the presence of non-conjugate bilirubin. The elevation of liver enzymes may reflect a hemolytic process due to liver involvement. The elevation of AST and ALT levels is

mostly due to liver damage. Thrombocytopenia (platelet  $< 100,000/\text{mL}$ ) is definitely seen in HELLP.<sup>13</sup>

Maternal manifestations of HELLP syndrome can be explained by systemic inflammatory reaction including; hypertension, proteinuria, intravascular coagulation, low platelet count, and hemolysis endothelial cell dysfunction.<sup>14</sup> In our study, we found that PLCR values did not differ between the preeclampsia and normotensive patients (Table 1) and correlated with the HELLP syndrome criteria (Table 2). We did not find any correlation between PLCR values in preeclampsia patients and with those patients who had SGA fetuses or with patients who were admitted to the intensive care unit, showing preeclampsia severity. Although an inflammatory process plays a role SGA fetus, it occurs due to chronic vascular insufficiency. We conclude that the significant difference of PLCR values in HELLP syndrome may be explained by the acute nature of the disease.

Our findings suggest that HELLP has a different etiopathogenesis than preeclampsia. Our study also supports the belief that HELLP syndrome is mainly an inflammatory process.

In another report,<sup>15</sup> supporting our study, plasma levels of Interleukin-6 (IL-6) and IL-1Ra were found to be increased significantly during HELLP compared to preeclampsia and normotensive pregnancies. During HELLP acute flare, median GSTA1-1 levels were found to be significantly higher than preeclampsia and normal pregnancies.<sup>15</sup> Those studies have concluded that these findings are associated with a more intense inflammation of HELLP syndrome. In addition, prednisone therapy in patients during HELLP syndrome has been shown to decrease the increase in plasma levels of cytokine IL-6.<sup>15</sup> Corticosteroids have been reported to have an endothelial stabilizing effect in patients with HELLP syndrome. With gene expression measurement (HELLP - healthy), it has been showed that there was an up-regulation of IL-10, IL-6 receptor and TGF- $\beta$ 3 in HELLP placentas.<sup>16</sup>

**Table 1. Analysis of preeclampsia and control pregnant patient data**

|                          | Preeclampsia (n=86) | Control (n=50) | p-value     |
|--------------------------|---------------------|----------------|-------------|
| Age (years)              | 31.2                | 27.3           | <b>0.01</b> |
| BMI (kg/m <sup>2</sup> ) | 28.8                | 30.4           | 0.08        |
| PLCR                     | 32.1                | 33.9           | 0.13        |
| GH (weeks)               | 34.8                | 36.3           | <b>0.01</b> |
| Hg (g/dL)                | 11.2                | 11.5           | 0.428       |
| HCT (%)                  | 33.9                | 35.3           | 0.96        |
| PLT (k/L)                | 213                 | 225            | 0.48        |
| Urea                     | 66                  | 11             | <b>0.01</b> |
| Creatinine               | 77                  | 0.8            | <b>0.01</b> |
| ALT (IU/L)               | 64.9                | 17.2           | <b>0.01</b> |
| AST (IU/L)               | 83.6                | 12.3           | <b>0.01</b> |
| LDH (U/L)                | 389                 |                |             |
| Uric acid                | 5.3                 |                |             |

Significant p-values are shown in bold.

GH: gestational week, BMI: body mass index, PLCR: platelet large cell ratio, PLT: platelet, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, n: number.

**Table 2. Correlation of clinical and laboratory data of preeclampsia patients**

| GH (weeks)               | 1     | 2      | 3       | 4      | 5      | 6      | 7      | 8      | 9      |
|--------------------------|-------|--------|---------|--------|--------|--------|--------|--------|--------|
| BMI (kg/m <sup>2</sup> ) | 0.17  |        |         |        |        |        |        |        |        |
| PLT (K/L)                | -0.15 | 0.27   |         |        |        |        |        |        |        |
| PLCR                     | 0.25  | -0.28* | -0.46** |        |        |        |        |        |        |
| ALT (IU/L)               | -0.04 | -0.09  | -0.46** | 0.33*  |        |        |        |        |        |
| AST (IU/L)               | -0.05 | -0.16  | -0.49** | 0.33*  | 0.92** |        |        |        |        |
| UREA (mg/dL)             | 0.06  | 0.09   | -0.29   | 0.33*  | 0.51** | 0.54** |        |        |        |
| LDH (U/L)                | 0.03  | -0.16  | -0.47** | 0.32*  | 0.82** | 0.93** | 0.56** |        |        |
| Creatinine (mg/dL)       | 0.05  | -0.11  | -0.25   | 0.47** | 0.35*  | 0.42** | 0.67** | 0.50** |        |
| Uric Acid (mg/dL)        | 0.08  | 0.26   | -0.01   | 0.19   | 0.10   | 0.04   | 0.49** | 0.07   | 0.48** |

\*Statistically significant correlation (0.05 level) (2-tailed), \*\*statistically significant correlation (0.01 level) (2-tailed).

GH: gestational week, BMI: body mass index, PLCR: platelet large cell ratio, PLT: platelet, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase.

Although the cause of tissue damage in HELLP syndrome is multifactorial. It can be said that factors from aberrant inflammatory response to abnormal placentation have an important role.

HELLP is seen as a more severe variant of preeclampsia. However, several studies<sup>17</sup> suggest that this may be a separate disease: differences in placental gene expression and maternal polymorphic alleles related to inflammatory responses confirm this hypothesis.

In our study, we found the highest statistically significant correlation of PLCR values with platelet count and creatinine level. We assume that platelet count and creatinine levels are the most important laboratory parameters in the progression of preeclampsia to HELLP syndrome.

Our study supports the belief that HELLP syndrome develops with different mechanisms and adaptive responses from preeclampsia, and the underlying increased inflammatory response was shown in our study. Our findings also support the belief that anti-inflammatory treatment methods might be applied with appropriate preventive and therapeutic options, especially in patients with HELLP syndrome.

## CONCLUSION

We are the first to show that complete blood parameters are simple, inexpensive and rapidly achievable tests in daily practice and they could be used to determine the risk of progression to HELLP syndrome in patients with preeclampsia. Our results support the hypothesis that the innate immune system contributes to maternal susceptibility to HELLP syndrome. Therefore, the identification of the components of the maternal innate inflammatory system that predispose patients to hypertensive disorders of pregnancy merits further investigation.

Although there are only a limited number of studies examining PLCR values in preeclampsia patients, a limitation of our study is the lack of exclusion of other inflammatory conditions which might cause higher or lower PLCR values in some patients. However, due to the large sample size of our study, we assume that this effect is negligible.

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## MAIN POINTS

- PLCR values can be used to determine the risk of progression to HELLP syndrome.
- Enhanced inflammatory response has been demonstrated in HELLP syndrome.
- Anti-inflammatory treatment methods can be a therapeutic option in those patients with HELLP syndrome.

## ETHICS

**Ethics Committee Approval:** İstanbul Training and Research Hospital Ethics Committee approved this study (decision no: 2072, date: 06/12/2019).

**Informed Consent:** Since this study was retrospective, written consent could not be obtained from the patients.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: B.Ş.K., Design: B.Ş.K., Supervision: B.Ş.K., Data Collection and/or Processing: B.Ş.K., N.A., Analysis and/or Interpretation: N.A., Literature Search: N.A., Writing: B.Ş.K, Critical Review: B.Ş.K.

## DISCLOSURES

**Conflict of Interest:** No conflict of interest was declared by the authors.

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