



Comparison of Inflammation Scores of Patients Diagnosed with Hyperemesis Gravidarum who Applied to the Emergency Clinic and Were Hospitalized with Pregnant Women with a Normal Course

Acil Polikliniğine Başvuran ve Hospitalize Edilen Hiperemesis Gravidarum Tanılı Hastaların İnflamasyon Skorlarının Normal Seyirli Gebelerle Karşılaştırılması

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Abstract

Aim: We aimed to compare systemic inflammatory markers ((NLR (neutrophil/lymphocyte ratio), PLR (platelet/lymphocyte ratio), MLR (monocyte/lymphocyte ratio), SII (systemic immune-inflammation index) and SIRI (systemic inflammation response index)) in patients diagnosed with HEG with normal pregnant women in the first trimester.

Material and Method: Our research is a retrospective diagnostic study. The study included 52 pregnant women who applied to the emergency gynecology clinic between the 7th and 12th weeks of pregnancy and were hospitalized due to 2+ ketonuria. The control group consisted of healthy pregnant women at the same gestational age who applied to the gynecology clinic. Statistical analysis was performed with the SPSS (Statistical package for Social Sciences-SPSS Inc., version 20.0; Chicago, IL) program.

Results: There was no statistically significant difference between the groups in terms of maternal age, parity, body mass index (BMI) and elective curettage numbers ($p>0.05$). When platelet, monocyte, leukocyte and lymphocyte values were compared between the two groups, no difference was found ($p>0.05$). However, when neutrophil count, NLR and PLR results were evaluated, we observed a statistically significant difference ($p<0.05$). We also found that combined inflammatory indices, including SII and SIRI, were significantly higher in Group HEG ($p=0.000$ and $p=0.0011$, respectively).

Conclusion: The results of our study showed that neutrophil and combined systemic inflammatory indices (NLR, PLR, SII, SIRI) were associated with the presence of HEG. According to our results, NLR was determined to have the strongest diagnostic efficacy in detecting the presence of HEG.

Keywords: Combined systemic inflammatory indexes, hyperemesis gravidarum, pregnancy

Öz

Amaç: HEG tanılı hastalarda sistemik inflamatuvar belirteçlerin (NLR(nötrofil/lenfosit oranı) , PLR (platelet/lenfosit oranı), MLR (monosit/lenfosit oranı), SII(sistemik immun-inflamasyon indeksi), ve SIRI (sistemik inflamasyon cevap indeksi), normal gebelerle, ilk trimesterde karşılaştırılması amaçlandı.

Gereç ve Yöntem: Araştırmamız retrospektif tanısal değerlilik çalışmasıdır. Çalışmaya, 7-12. gebelik haftaları arasında acil kadın doğum kliniğine başvuran ve 2+ ketonüri nedeniyle hospitalize edilen 52 gebe kadın dahil edildi. Kontrol grubu ise aynı gebelik haftasında olan, kadın doğum polikliniğine başvuran sağlıklı gebelerden oluşturuldu. İstatistiksel analiz SPSS (Statistical package for Social Sciences-SPSS Inc., version 20.0;Chicago, IL) programı ile yapıldı.

Bulgular: Maternal yaş, parite, vücut kitle indeksi (BMI) ve elektif küretaj sayıları açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu ($p>0,05$). İki grup arasında trombosit, monosit, lökosit ve lenfosit değerleri karşılaştırıldığında fark bulunmadı($p>0,05$). Ancak, nötrofil sayısı, NLR ve PLR sonuçları değerlendirildiğinde istatistiksel olarak anlamlı bir fark gözlemledik ($p<0,05$). Ayrıca, SII ve SIRI'yi içeren kombine inflamatuvar indekslerin de HEG grubunda anlamlı derecede yüksek olduğunu tespit ettik (sırasıyla, $p=0,000$ ve $p=0,0011$).

Sonuç: Çalışmamızın sonuçları, nötrofil ve kombine sistemik inflamatuvar indekslerinin (NLR, PLR, SII, SIRI) HEG varlığı ile ilişkili olduğunu gösterdi. Sonuçlarımıza göre, NLR'nin HEG varlığını tespit etmede en güçlü tanısal etkinliğe sahip olduğu belirlendi.

Anahtar Kelimeler: Kombine sistemik inflamatuvar indeksler, hiperemesis gravidarum, gebelik



INTRODUCTION

Nausea and vomiting are complaints that are seen in approximately 80% of pregnant women in the first trimester of pregnancy, usually end before the 20th week of pregnancy, and can sometimes continue until birth.^[1,2] Hyperemesis Gravidarum (HEG) is a very severe form of these symptoms which can cause dehydration, ketonemia, ketonuria, electrolyte imbalance and loss of more than 5% of pre-pregnancy weight.^[3,4]

The incidence of HEG has been reported as 0.5-2% in many studies, but it has been emphasized that this rate may vary depending on ethnicity.^[5] While HEG is usually seen between the 8th and 12th weeks of pregnancy, it can last throughout pregnancy in 5% of cases.^[6] The etiology of HEG has been examined in many studies, but no clear conclusion has been reached due to the heterogeneity of the results. Hormonal changes, immunological and psychological factors, abnormal gastric motility, *Helicobacter pylori* infection, genetic predisposition and liver dysfunction, inflammation are effective in the pathophysiology of HEG.^[7-9] In the presence of chronic inflammation, relative thrombocytosis develops secondary to proliferation in megakaryocytes. As a result of increased apoptosis, lymphocyte numbers decrease. Because platelets modulate inflammatory reactions, they can also affect the monocyte/lymphocyte ratio (MLR), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR).^[10,11] It has been shown that these indicators are associated with gestational diabetes accompanied by increased inflammation, preeclampsia, preterm birth and acute appendicitis.^[12,13] Studies have reported that other inflammation indicators such as C-reactive protein (CRP), vaspin, and acute phase reactants also increase in HEG cases.^[14,15] Considering the detection of inflammation, the high cost of these tests directs the clinician to less costly and easily accessible routine hemogram tests. In addition to MLR, NLR and PLR, inflammation has been evaluated with combined inflammatory indices in recent studies. Systemic immune-inflammation index (SII) and Systemic inflammatory response index (SIRI) are newly defined combined indices that evaluate the inflammatory process and response. The negative consequences of these indices in pregnant women with coronavirus disease and their relationship with cancer patients have been evaluated.^[16-18]

However, there is not enough data regarding the relationship of these indices with the presence of HEG.

We aimed to compare systemic inflammatory markers ((NLR (neutrophil/lymphocyte ratio), PLR (platelet/lymphocyte ratio), MLR (monocyte/lymphocyte ratio), SII (systemic immune-inflammation index) and SIRI (systemic inflammation response index)) in patients diagnosed with HEG with normal pregnant women in the first trimester.

MATERIAL AND METHOD

The study was carried out with the permission of University Karamanoğlu Mehmet Bey, Faculty of Medicine Clinical Researches Ethics Committee (Date: 04.03.2024, Decision No: E-11095095-050.04-181579).

Patients who applied to Karaman Training and Research Hospital Emergency Gynecology and Obstetrics Outpatient Clinic with complaints of extreme nausea, vomiting and inability to feed, were diagnosed with HEG and were hospitalized between 01.06.2023 and 01.12.2023 were included in our study. The control group consisted of healthy pregnant women who had routine outpatient clinic follow-ups and who were not diagnosed with HEG. The inclusion criteria of our study are; singleton pregnancy, 7-12. weeks of pregnancy, presence of >+2 ketonuria in complete urine analysis, absence of chronic disease and vaginal bleeding. Multiple pregnancies, pregnant women <18 years of age, pregnant women with inflammatory diseases, or using anti-inflammatory or corticosteroid-containing drugs were not included in the study. Demographic and obstetric data of pregnant women diagnosed with HEG who applied to the emergency clinic, TIT (complete urinalysis) result taken at the time of admission, hemogram parameters (Sysmex xn-1000 device) and SII (platelet x neutrophil /lymphocyte), SIRI (neutrophil x monocyte/lymphocyte), NLR (neutrophil/total lymphocyte), MLR (monocyte/total lymphocyte), PLR (platelet/total lymphocyte) results were recorded.

Statistical Analysis

G-Power analysis was applied to determine the number of groups. According to these results, the groups were planned to include a minimum of 52 pregnant women with a power of 0.85 and a margin of error of 10%. Statistical Package for Social Sciences (SPSS Inc., version 20.0; Chicago, IL) was used in statistical analyses. All statistical data were made with SPSS 20.0 version program for Windows. The normal distribution of the data was evaluated with histogram, one of the graphical methods. Skewness-kurtosis method and Kolmogorov Smirnov test and method were used to evaluate the normal distribution of variables. Descriptive statistics were used in the demographic analysis of the patients. Numerical values are expressed as mean \pm standard deviation and minimum-maximum values. In evaluating the data, the t-test, the significance test of the difference between two means in independent groups, was applied. Statistical significance level was accepted as $p < 0.05$. Cut-off evaluation of statistically significant results was made with the ROC (Receiver-Operating Characteristics) curve.

RESULTS

Our study started with the evaluation of 60 patients, five of our patients were due to abortion; three of our patients due to loss of follow-up were not included in our sample. The average age of 52 pregnant women in each HEG and control

pregnant group were 27.2±4.6/year in the HEG group and 29.1±4.5/year in the control pregnant group and there was no statistically significant difference between HEG patients and the control group in terms of age (p>0.05).

Accordingly, when the gravida numbers of the HEG patient and control pregnant groups were compared, there was a significant difference (p<0.05), while BMI (body mass index), parity and abortion numbers did not create a significant difference between the groups (p>0.05). When the gestational weeks of the HEG patients and other groups were evaluated, the data of 10.5±2.9/week in the HEG patient group and 8.6±1.3/week in the control pregnant group were found to be statistically significant (p<0.05) (Table 1).

Table 1. Demographic data distribution of patients

Demographic features Independent variables (IVs)	Group 1 (HEG)	Group 2 (Control)	p value
Age (Mean±SD)	27.2±4.6/years	29.1±4.5/years	0.93
BMI (Mean±SD)	24.6±3.6	26.7±5.8	0.72
Gravida (Mean±SD)	1.8±0.8	2.1±1.2	0.03*
Parite (Mean±SD)	0.9±1.03	0.5±0.7	0.06
Abort (n,%)	10(19.2%)	10 (20%)	<0.81
Week of pregnancy	10.5±2.9	8.6±1.3	<0.05*

HEG:hyperemesis gravidarum, BMI: body mass index, SD: Standard Deviation Chi-square test and t-test were used in statistical analysis. *p<0.05 was considered significant

Laboratory data of hyperemesis gravidarum patients and differences between groups:

The neutrophil values of the HEG patients were found to be statistically significantly higher (p < 0.05), and the difference in WBC (white blood cell), lymphocyte, monocyte and platelet values between the 2 groups was not statistically significant (p > 0.05). While there was no significant difference between the groups when the monocyte/lymphocyte ratio was evaluated (p>0.05), a statistical difference was observed in the neutrophil/lymphocyte, platelet/lymphocyte ratios (p<0.05). However, when the SII and SIRI indices were compared, the higher results of HEG group compared to control group were statistically significant (p <0.05) (Table 2).

Table 2 Laboratory results of patients

Laboratory parameters	Group 1 (HEG) (Mean±SD)	Group 2 (Control) (Mean±SD)	P value
WBC (4.0-10.0 × 10 ⁹ /L)	9.5±2.9	8.9±1.9	0.053
Neutrophil (2.0-6.0× 10 ⁹ /L)	7.4±2.7	6.2±1.4	0.004*
Lymphocyte (1.1-3.2 ×10 ⁹ /L)	1.6±1.5	2.0±0.6	0.111
Monocyte (%)	0.46±0.15	0.64±0.9	0.190
Platelet/ml	246.9±61.5	253±56.4	0.297
SII	1721.5±753.8	753.9±252.6	0.000*
SIRI	3.4±4.3	1.9±2.8	0.011*
NLR	8±11.3	3±0.9	0.000*
MLR	0.44±0.4	0.31±0.43	0.082
PLR	231±23,5	123±35.2	0.001*

HEG:hyperemesis gravidarum, SD: Standard Deviation, WBC:white blood cell, SII: systemic immune-inflammation index, SIRI: systemic inflammation response index, NLR: Neutrophil/lymphocyte ratio, MLR: Monocyte/lymphocyte ratio, PLR: Platelet/lymphocyte ratio T-test were used in statistical analysis. *p<0.05 was considered significant.

ROC analysis evaluation of Leukocyte, Neutrophil and SII:

SII and SIRI parameters, neutrophil, NLR, PLR of HEG patients were analyzed with ROC curve and area under the curve (AUC), cut-off, sensitivity and specificity in order to guide the clinician about the patient's condition during patient follow-up. Parameters with AUC <0.6 and (P>0.05) not found to be statistically significant were excluded. For SII, AUC, cut-off, sensitivity, and specificity were 0.780, 860, 71%, and 76%, respectively. For SIRI, AUC, cut-off, sensitivity and specificity were 0.680, 1.9, 56% and 78%, respectively. AUC, cut-off, sensitivity, specificity for neutrophil were 0.645, 5.7, 78% and 62%, respectively. AUC, cut-off, sensitivity, specificity for Neutrophil/Lymphocyte ratio were 0.785, 3.17, 79% and 68%, respectively. AUC, cut-off, sensitivity, specificity for Platelet/Lymphocyte ratio were 0.776, 126.5, 77% and 62%, respectively (Figure 1).

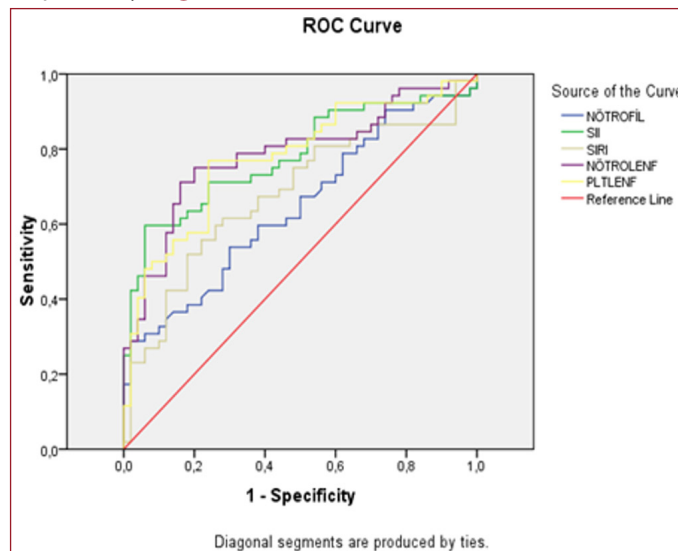


Figure 1. Receiver operating characteristic analysis of Neutrophil, SII, SIRI, Neutrophil/lymphocyte ratio, Platelet/lymphocyte ratio for the prediction of hyperemesis gravidarum

DISCUSSION

In the current study, the diagnostic value of NLR, PLR, SII, SIRI was evaluated in patients with HEG. According to the results of the current study, NLR, PLR, SII, SIRI values were increased in patients with HEG compared to those without HEG, and the sensitivity of the specified parameters was found to be low, and the selectivity was relatively high. This shows that biomarkers can be a diagnostic aid but cannot be used as an exclusion test. In our study, neutrophils, NLR, PLR, SI and SIRI stand out as clinical markers in HEG patients. HEG may progress in a severe form that may require hospitalization, and Wernicke encephalopathy may also be present.^[19] The NLR is a marker of systemic inflammation and stress.^[1-3] In HEG, studies have shown elevated NLR levels, indicating an increased neutrophil count relative to lymphocytes. This elevation suggests a heightened inflammatory response.^[20-22] Similar to NLR, the PLR is another marker of systemic inflammation. Elevated PLR levels in HEG patients reflect increased platelet counts,

which are involved in inflammatory processes and immune responses.^[23-25] The SII is a composite marker that incorporates neutrophil, platelet, and lymphocyte counts. It provides a more comprehensive assessment of the inflammatory response.^[26,27] Elevated SII levels in HEG patients suggest a robust inflammatory state involving multiple immune cell types. In the literature, there are three plausible pathogenesis explanations for the results of the study, including hormonal changes,^[28,29] immune system modulation,^[30] and possibly infections. Pregnancy induces significant hormonal changes, particularly elevated levels of human chorionic gonadotropin (hCG) and estrogen, which are believed to contribute to HEG.

Studies evaluating the relationship between inflammatory parameters and HEG were available in the literature.^[31-33] However, HEG; Although it is a clinical condition that develops during pregnancy, its cause is still not fully known. Whether hemogram parameters and their relationship with markers such as SI and SIRI are related to diagnosis and their use in treatment follow-up may reduce the duration of hospital stay. Apart from clinical conditions affecting the mother such as dehydration, tachycardia, and confusion, intrauterine growth retardation may also occur in severe HEG cases. Protection of maternal and fetal health is very decisive in the development level of countries. Clinical guidance of inflammatory processes will positively affect the length of hospital stay and hospital cost analysis. It has been discussed in the literature whether acute phase reactants can be effective along with clinical laboratory parameters that occur with pregnancy. Yoneyama et al. reported that TNF- α values were high in HEG patients.^[34] Kaplan et al. They also emphasized that TNF- α , which plays a role in immune disorders, is effective in the pathogenesis and progression of HEG.^[35] IL-6, another inflammation marker, was found to be higher in hyperemesis cases than in low-risk pregnant women.^[36] In a different study, vaspin level was evaluated and it was emphasized that this inflammation marker increased as the gestational week progressed in HEG patients.^[14] In a study involving 194 patients using routine complete blood count parameters, Çintesun et al. found the PLR and NLR results to be statistically significantly higher in HEG patients.^[37] The same results were obtained in terms of PLR, NLR and CRP values in a different series of 154 patients (38). In our study, we found PLR and NLR results, which coincide with literature data, to be significantly higher in the HEG group.

Although an increase in leukocyte, hemoglobin and hematocrit levels based on hemoconcentration is expected in the presence of HEG due to nausea, vomiting and dehydration, no significant difference was observed with the control group in the studies conducted. In our study, we only compared leukocyte values and determined that the increase in the HEG group was not significant. When the lymphocyte count was evaluated, while in some studies the lymphocyte count of HEG patients was found to be high,^[33] this difference was not observed in different studies.^[40] We observed that this parameter is also lower in HEG group than in the control group, but there is no significant difference.

Minagawa et al. In their study, they found the neutrophil level to be statistically significantly higher in HEG cases, but when they compared the lymphocyte numbers, lymphopenia did not show a significant difference.^[41] Similar to Minagawa's results, in our study, we found that the neutrophil level was significantly higher in the HEG group. In a study including 100 HEG patients, Yıldırım et al. found that the severity of HEG was associated with NLR and PLR values.^[42]

The inflammation cascade is a complex process that does not operate through a single cell or mediator, but where cells and mechanisms activate and inhibit each other. Considering that evaluating single cell activity will not be sufficient, combined indices have been defined for this purpose.^[18,42,43] In the study of Yıldırım et al., it was emphasized that SII and SIRI results were positively correlated with the presence and severity of HEG. When all parameters were evaluated in the same study, according to ROC analysis, the highest correlation was observed in SIRI and NLR indices.^[42] Our study was a study in which NLR, PLR, SII and SIRI were evaluated together. We think that we will contribute to the literature by comparing these values with ROC analysis. The predictive value of neutrophil and SIRI (AUC values 0.680, AUC: 0.645 respectively) values in HEG patients was moderate. When we evaluated the ROC analyses, we found the strongest relationship in the NLR, PLR and SII parameters.

CONCLUSION

According to the results of the current study, NLR, PLR, SII, SIRI values were increased in patients with HEG compared to those without HEG, and the sensitivity of the specified parameters was found to be low and the selectivity was relatively high. NLR was determined to have the strongest diagnostic efficacy in detecting the presence of HEG. This shows that biomarkers can be a helpful test for diagnosis, but cannot be used as an exclusion test.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Karamanoğlu Mehmet Bey, Faculty of Medicine Clinical Researches Ethics Committee (Date: 04.03.2024, Decision No: E-11095095-050.04-181579).

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

Referee Evaluation Process: Externally peer-reviewed.

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