# The Role of Systemic Immune-inflammation Index in the Severity of Hyperemesis Gravidarum

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## Abstract

# Purpose

Hyperemesis gravidarum (HEG) is one of the most common causes of hospitalization in early pregnancy. Complete blood count parameters can be used as inflammatory markers in patients with HEG. We aimed to investigate the Systemic Immune-Inflammation Index (SII) in predicting the severity of HEG.

# Methods

This cross-sectional study was performed with pregnant women who were hospitalized in the Perinatology Department, Ankara City Hospital, with the diagnosis of HEG. The study data were obtained from the electronic database of Ankara City Hospital. The study parameters were calculated from complete blood count tests and urine analysis.

# Results

A total of 469 pregnant women diagnosed with HEG were included in this study. There was a positive correlation between the increased degree of ketonuria and SII. The cut-off value of SII for predicting the severity of HEG was 1071.8, sensitivity and specificity were 59% and 59%, respectively. The cutoff value of SII to predict the length of hospitalization was 1073.6, p= 0.039; sensitivity and specificity were 56.3% and 55.5%, respectively.

# Conclusions

Considering the positive relationship between ketonuria and inflammation markers, the evaluation of SII in pregnant women with HEG may facilitate the clinical management of these patients.

## Introduction

Hyperemesis gravidarum (HEG) is a condition with severe nausea and vomiting during pregnancy. It is estimated to occur in 0.3–3.6% of all pregnancies worldwide[1]. Persistent vomiting resulting in weight loss, nutritional deficiencies, ketonuria, electrolyte imbalance, and dehydration is one of the most common reasons for hospital admission in early pregnancy[2]. Many studies have been conducted to understand the etiology and pathogenesis of HEG, but no consensus has been reached on its cause and mechanism[3]. Psychological and hormonal changes during pregnancy, thyrotoxicosis, upper gastrointestinal dysmotility, hepatic abnormalities, autonomic nerve dysfunction, nutritional deficiencies, and Helicobacter pylori infection were considered involved in the etiology[4].

In recent years, inflammation has been related to pregnancy complications, including preeclampsia, intrauterine growth restriction, and spontaneous preterm birth[5]. Many studies have reported that inflammation and oxidative stress are considered crucial in the pathophysiologic mechanism of HEG and showed that complete blood count parameters could be used as inflammatory markers in these patients[6].

A complete blood count test is a part of the routine examination and provides information about the immune system. Hematological parameters such as neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), and red blood cell distribution width (RDW) were examined to indicate inflammation in HEG patients previously[7]. These parameters were used in combination with each other and/or ketonuria, and their results were interpreted differently in studies. However, an index called the Systemic Immunity-Inflammation Index (SII) calculated based on peripheral lymphocyte, neutrophil, and platelet counts (neutrophil × platelet/lymphocyte) has not been evaluated HEG patients previously. This study aimed to investigate the relationship between the blood count parameters, SII, and the degree of ketonuria and determine the importance of these parameters in the severity of HEG.

## Material And Methods

This cross-sectional study was performed with pregnant women who were hospitalized in the Perinatology Department, Ankara City Hospital, with the diagnosis of HEG between January 2020 and November 2021. The study protocol was approved by the ethics committee of Ankara City Hospital and was conducted following the guidelines of the Helsinki Declaration(E2-21-132). The following data were obtained from the electronic database of Ankara City Hospital.

This study included 469 hospitalized pregnant women with the diagnosis of HEG. The inclusion criteria for HEG patients were as follows: persistent nausea and vomiting, loss of >5% of body weight, the presence of at least one positive ketonuria in a random urine specimen, fetal heartbeat positivity, and singleton pregnancy. Women with eating disorders, history of ovulation induction, multiple gestations, smoking, gastrointestinal disorders, thyroid disorders, urinary tract infections, and systemic diseases which may affect ketonuria like diabetes mellitus and kidney failure were not included.

The following data were recorded for each patient: age, gravidity, parity, and gestational age. The gestational age was determined using the first date of the last menstrual period and confirmed by ultrasonography through crown-rump length measurement in the sagittal plane. Venous blood samples and urine specimens were collected from the patient at the time of hospitalization as a part of routine clinical practice.

For the assessment of complete blood count (CBC), parameters including white blood cell (WBC) count, neutrophil count, lymphocyte count, hemoglobin (Hb), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT) and red cell distribution width (RDW), were all collected from patients' files. Only pretreatment laboratory results were used.

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated by obtaining the ratios of absolute neutrophil count to absolute lymphocyte count and absolute platelet count to absolute lymphocyte count, respectively. Lymphocyte-to-monocyte ratio (LMR) was calculated from the differential count by dividing the absolute lymphocyte count by the absolute monocyte count.

The SII was calculated using P x N/L, where P, N, and L were the peripheral platelet, neutrophil, and lymphocyte counts, respectively. The ketonuria was graded as 1+, 2+, 3+ and 4+. The decision to discharge patients was based on the improvement of hydration and nutritional intake.

The patients were divided into two groups based on their degree of ketonuria at the time of hospital admission as Group A and Group B. Patients with +1 and +2 degrees of ketonuria were included in Group A, those with +3 and +4 were in Group B.

Statistical analyses were performed using SPSS 17 software (SPSS, Inc., Chicago, IL, United States). Statistical methods such as descriptive frequency, percentage, mean, standard deviation, median, and interquartile range(IQR) were used to express the quantitative data. The groups with different degrees of ketonuria were compared using Mann–Whitney U test according to non-normal distribution. The Jonckheere-Terpstra test was used to determine the trend of each variable according to the degree of ketonuria. Spearman's correlation coefficient was used to estimate the relationship between the degree of ketonuria and other variables. Receiver operating characteristic (ROC) curve analysis was used to assess the optimal cut-off values of NLR, PLR, and SII for predicting the severity of HEG with sensitivity and specificity. Also, this analysis was used to identify the cut-off value of SII to predict the length of hospital stay. The P-values < 0.05 were regarded as statistically significant.

## Results

A total of 469 pregnant women with HEG were included in this study. The demographic and clinical characteristics of patients are demonstrated in Table 1. The laboratory test results, inflammation markers, and SII were analyzed and summarized in Table 2. The comparison of Group A and Group B classified according to the degree of ketonuria is shown in Table 3. The trend of each laboratory parameter according to the degree of ketonuria is shown in Table 4. RBC, PLT, PDW, NLR, PLR, and SII significantly increased with the advancing degree of ketonuria, but lymphocytes, eosinophils, and LMR decreased. Table 5 provides the correlation between ketonuria and hemogram parameters, inflammation markers, and length of hospitalization. There was a positive correlation between increased ketonuria and length of hospitalization, PCT, PDW, NLR, PLR, and SII. However, there was a negative correlation between the increase in the degree of ketonuria, the counts of lymphocytes and eosinophils, and LMR.

Table 1
Demographic and clinical characteristics of patients

| **Age** | **27.5+/-5.4** |
|---|---|
| Gravidity | 2.1+/-1.4 |
| Parity | 0.8+/-0.9 |
| Gestational age (weeks) | 9.4+/-2.6 |
| Hospitalization (days) | 2+/-1.5 |
| [a] Values are given as mean+/- standard deviation | |

Table 2
The laboratory parameters and inflammation markers of the patients

| | | |
|---|---|---|
| **WBC ($x10^9$/L)** | | **9.6 +/-2.6** |
| NEU ($x10^9$/L) | | 7.19+/-2.36 |
| LYMP ($x10^9$/L) | | 1.80+/-0.63 |
| MONO ($x10^9$/L) | | 0.44 +/-0.17 |
| HGB (g/dL) | | 12.8+/-1.4 |
| HCT (%) | | 38.3+/-3.8 |
| RDW (%) | | 14.2+/-1.5 |
| PLT ($x10^9$/L) | | 267.8+/-66.5 |
| MPV (fL) | | 8.5+/-1 |
| PCT (%) | | 0.22+/-0.05 |
| PDW (%) | | 52+/-8.9 |
| NLR | | 4.8+/-6.4 |
| PLR | | 176+/-249 |
| LMR | | 4.5+/-1.8 |
| SII ($x10^9$/L) | | 1248+/-1335 |
| KETONURIA | +1 | 133 (28.4%) |
| | +2 | 98 (20.9%) |
| | +3 | 96 (20.5%) |
| | +4 | 142 (30.3%) |

[a] Values are given as mean ± standard deviation or as number (percentage).

[b] WBC: white blood cell, NEU: neutrophil, PLT: platelet, LYMP: lymphocyte, MONO: monocyte, HGB: hemoglobin, HCT: hematocrit, RDW: red cell distribution width, PDW: platelet distribution width, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to- lymphocyte ratio, LMR: lymphocyte-to-monocyte ratio, SII: systemic immune-inflammation index

Table 3
The comparison of Group A and Group B

| | GROUP A(n=231) | GROUP B (n=238) | p value |
|---|---|---|---|
| WBC | 9.38 (8.22-11.40) | 9.23(7.82-11.35) | .312 |
| NEU | 6.67 (5.85-8.26) | 7.09 (5.44-8.70) | .893 |
| LYM | 1.88(1.56-2.26) | 1.60 (1.34-2.00) | <.001* |
| MONO | 0.44 (0.33-0.55) | 0.39 (0.32-0.52) | .137 |
| EOS | 0.07 (0.04-0.12) | 0.05(0.02-0.08) | <.001* |
| BASO | 0.02 (0.02-0.04) | 0.02 (0.01-0.03) | .396 |
| RBC | 4.54(4.26-4.79) | 4.61(4.34-4.98) | .011* |
| HGB | 12.9(11.9-13.4) | 13(11.8-13.8) | .098 |
| HCT | 38.3(35.4-40.5) | 38.6(35.4-41.6) | .298 |
| RDW | 13.7 (13.3-14.7) | 13.8 (13.2-14.9) | .838 |
| PLT | 269(221-296) | 268(219-317) | .144 |
| MPV | 8.4 (7.8-9.1) | 8.6 (7.7-9.3) | .153 |
| PCT | 0.22 (0.19-0.25) | 0.2 (0.19-0.27) | .028* |
| PDW | 51.7 (45.1-58.1) | 52.8 (46.4-59.5) | .086 |
| NLR | 3.54 (2.87-4.86) | 4.19 (3.06-5.36) | .002* |
| PLR | 130.7 (113.1-171.6) | 163.1 (132.4-225.7) | <.001* |
| LMR | 4.4(3.3-5.6) | 4.2(3.3-5.4) | .062 |
| SII | 960.9(677.7-1376.7) | 1117.2 (772.4-1708.9) | <.001* |
| Length of Hospitalization (day) | 1(1-2) | 2(1-3) | .002* |
| [a] Values are expressed as median and interquartile ranges (IQRs). | | | |
| [b] Mann–Whitney U test | | | |

Table 4
The laboratory results according to the degree of ketonuria

| | +1 (n=133) | +2 (n=98) | +3 (n=96) | +4 (n=142) | p value |
|---|---|---|---|---|---|
| WBC | 9.70 (8.36-11.70) | 9.09 (7.99-9.84) | 8.97 (7.44-10.60) | 9.62 (8.46-11.60) | .398 |
| NEU | 6.88 (5.90-8.50) | 6.53 (5.72-8.04) | 6.32 (4.96-7.72) | 7.46 (5.88-9.27) | .39 |
| LYM | 1.89 (1.68-2.36) | 1.81 (1.29-2.13) | 1.66(1.37-2.21) | 1.53(1.31-1.88) | <.001* |
| MONO | 0.41 (0.33-0.59) | 0.45 (0.32-0.49) | 0.39(0.320-0.51) | 0.38 (0.32-0.52) | .056 |
| EOS | 0.07 (0.05-0.13) | 0.06 (0.03-0.10) | 0.06 (0.35-0.95) | 0.04 (0.02-0.07) | <.001* |
| BASO | 0.03 (0.02-0.04) | 0.02 (0.01-0.03) | 0.02 (0.01-0.03) | 0.02 (0.01-0.03) | .059 |
| RBC | 4.54 (4.26-4.82) | 4.60 (4.27-4.70) | 4.57 (4.31-4.96) | 4.64 (4.36-5.02) | .006* |
| HGB | 12.9 (12.2-13.4) | 12.6 (11.7-13.5) | 12.8 (11.8-13.7) | 13.2(11.8-14.2) | .065 |
| HCT | 38.5 (36.3-39.9) | 37.5 (35.4-40.5) | 37.3 (35-40.8) | 39.6 (36-41.6) | .172 |
| RDW | 13.7 (13.2-14.5) | 13.9 (13.3-14.7) | 13.8 (13.2-14.9) | 13.7 (13.2-14.9) | .825 |
| PLT | 245 (216-294) | 273(232-292) | 281(237-311) | 275(218-321) | .049* |
| MPV | 8.4 (7.8-9.1) | 8.1 (7.8-9.2) | 8.4 (7.6-9.1) | 8.8 (7.8-9.3) | .133 |
| PCT | 0.21 (0.19-0.25) | 0.23 (0.20-0.25) | 0.22 (0.20-0.25) | 0.23 (0.19-0.27) | .006* |
| PDW | 49.7 (42.6-58.1) | 53.8 (46.7-58) | 52.3 (44.3-59.8) | 53.2 (47.3-59.3) | .010* |
| NLR | 3.37 (2.88-4.81) | 3.75 (2.87-5.40) | 3.54 (2.81-4.68) | 4.77 (3.46-5.85) | <.001* |
| PLR | 126.1 (104.5-158.2) | 154.2 (128.2-203.2) | 158.1 (121.8-202.8) | 179 (142.8-232.1) | <.001* |
| LMR | 4.6 (3.3-5.7) | 4.4 (3.6-5.5) | 4.2 (3.5-5.1) | 4.2 (3-5.6) | 0.256 |
| SII | 803.056 (66.0-1215.3) | 1105.6 (677.7-1453.2) | 953.1 (718.0-1387.9) | 1177.2 (910.2-1912.6) | <0.001* |

[a] Values are expressed as median and interquartile ranges (IQRs).

[b] Jonckheere-Terpstra Test

Table 5
The correlation between ketonuria and hemogram parameters, inflammation markers, and length of hospitalization

| | WBC | NEU | LYM | MONO | EOS | BASO | RDW | PLT | MPV | PCT | PDW | NLR | PLR | LMR | SII |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| r value | −0.039 | 0.041 | −0.282 | −0.087 | −0.310 | −0.088 | 0.010 | 0.089 | 0.071 | 0.128 | 0.119 | 0.212 | 0.332 | −0.092 | 0.233 |
| p value | 0.394 | 0.370 | <0.001* | 0.059 | <0.001* | 0.057 | 0.830 | 0.054 | 0.124 | 0.006* | 0.01* | <0.001* | <0.001* | 0.046* | <0.00 |

Spearman Correlation's Test

ROC curve analysis for assessing the cut-off value of SII to predict the severity of HEG was shown in Figure 1. The severity was defined as +4 degrees of ketonuria. The cut-off value of SII was 1071.8 x $10^9$; sensitivity and specificity were 59% and 59%, respectively (AUC: 0.637, 95% CI [ 0.582–0.693], p<.001).

The cut-off value of SII to predict the length of hospitalization was shown in Figure 2. The hospitalization over two days was defined as the top quartile for the length of hospital stay. The cut-off value of SII was 1073.6 x $10^9$ for > 2 days hospitalization ( AUC: 0.565, 95% CI: (0.501–0.628), p= 0.039); sensitivity and specificity were 56.3% and 55.5% , respectively.

## Discussion

Although the role of inflammation in the pathophysiology of HEG is not clear, subclinical inflammation associated with oxidative stress might play an important role [8, 9]. Maternal inflammation causes an increase in cytokine and chemokine levels in the fetal/placental compartments. Uncontrolled inflammation may cause ischemia and destruction in the growing fetal tissues and adverse perinatal outcomes[10]. Many studies on inflammation markers in HEG patients proposed strong associations between HEG development and inflammation. The increase in some cytokines and mediators such as TNF-alpha, IL-6, CRP, vaspin in HEG patients has indicated the inflammation in HEG[11, 12]. Also, increased Sirtuin-1 and CRP levels in the HEG patients supported this inflammatory response[13]. Therefore, it is important to assess the degree of maternal inflammation to predict perinatal outcomes.

Complete blood count parameters have been investigated in many studies to predict adverse pregnancy outcomes such as preeclampsia, preterm birth, placental invasion anomalies, and preterm premature rupture of membranes (PPROM)[14–16], but there are not enough studies in which SII is used in obstetrics. However, Tanacan et al. showed that SII and platelet counts may be useful in the prediction of adverse outcomes in pregnancies complicated by PPROM. This study emphasized that the inflammation in PPROM and thus higher value of SII could be used as an additional parameter to predict adverse outcomes in these patients [17]. In our study, we suggested that SII might be useful in demonstrating inflammation-related outcomes in HEG patients.

In recent studies, hematological parameters such as NLR, PLR, RDW, MPV, and PCT obtained from peripheral blood complete blood count have been shown to have prognostic and predictive value in various diseases such as inflammatory, autoimmune diseases, gynecological or gastrointestinal malignancies[18, 19]. In a study in which hematological parameters were evaluated as a marker of subclinical inflammation in HEG, NLR and PLR were found significantly higher in HEG patients than control groups. Also, in the same study, PDW and MPV, which are also used for platelet activation and diagnosis of many inflammatory diseases, did not differ significantly between HEG patients and the controls[20]. However, Tayfur et al. showed the PCT value to be significantly higher in HEG patients [21]. Studies on the relationship with systemic inflammatory markers obtained from complete blood count and ketonuria showed that these markers can be used in clinical practice. Our study found that NLR, PLR, PCT, and PDW increased as the degree of ketonuria increased. We also showed that SII significantly increased with the advancing degree of ketonuria, but lymphocytes, eosinophils, and LMR decreased. Increased levels of these parameters might be the consequences of an altered immune response of blood cells to physical stress in HEG.

Dehydration caused by vomiting can cause increased hemoconcentration, so hematocrit levels may raise in pregnant women with HEG. However, a previous study showed no significant changes in Hb and Hct values in patients with HEG(7). Although it was not statistically significant, our study found Hb and Hct values higher in patients with +3 and +4 ketonuria compared to those with +1 and +2 ketonuria. Hemoconcentration caused by dehydration can trigger systemic consequences such as oxidative stress and inflammation.

The relationship between the severity of disease and the degree of ketonuria is uncertain. Severe nausea and vomiting lead to ketonuria, which plays an important role in hospitalization. Some studies investigate whether HEG severity is associated with length of hospitalization, readmission, metabolic, biochemical, hematological, and clinical parameters, and inflammatory markers[22, 23]. The relationship between the degree of ketonuria and length of hospitalization was evaluated, and they found that ketonuria was not associated with the prolonged hospital stay. However, a previous study showed that women with a higher degree of ketonuria at hospital admission had a longer hospital stay[24]. In our study, we examined the relationship between ketonuria and length of stay and we found a positive correlation between increased ketonuria and length of hospitalization.

Lymphocytes, neutrophils, and platelets, which are components of the SII formula, play a role in inflammation. Neutrophils are one of the major effectors of acute inflammation. They also contribute to chronic inflammatory circumstances and adaptive immune responses. While neutrophils have a destructive effect on the immune system, lymphocyte count decreases due to increased apoptosis in chronic inflammatory processes[25]. Platelets enable to initiate and modulate immune functions by expressing several pro- and anti-inflammatory molecules[26]. Considering the role of these blood cells in inflammation separately, we thought that their inclusion as a formula might be a better indicator of inflammation, so we evaluated SII as a study parameter.

As well as the role of NLR and PLR was described in HEG patients, there is not enough data on the use of SII in obstetrics in the literature. This is the first study in which SII has been used to predict the severity of HEG to date. Considering the positive relationship between ketonuria and length of hospitalization, the evaluation of SII in pregnant women with HEG may facilitate the clinical management of these patients. So it may differentiate the patients who need longer hospitalization, especially in this pandemic period. The fact that this parameter is cost-effective, practical, and noninvasive may expand its use in obstetrics.

The strength of the study was a large number of patients and study parameters. The limitations of this study were that it did not include long-term pregnancy outcomes.

## Conclusion

HEG is one of the severe health problems in early pregnancy. SII is a cheap and easily available method, and it might be used as a parameter in patient selection for hospitalization and management. The use of SII should be supported by future studies in obstetrics.

## Declarations

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# Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

# Author Contributions

All authors contributed to the study's conception and design. Dilek Menekse Beser prepared and wrote the original draft and contributed to the data collection. Material preparation, data collection, and analysis were performed by Deniz Oluklu and Derya Uyan Hendem. Sule Goncu Ayhan performed the literature

search and the project development. Dilek Sahin was responsible for conceptualization, methodology, visualization, and reviewing and editing. All authors read and approved the final manuscript.

## Ethics approval

The study protocol was approved by the ethics committee of Ankara City Hospital and was conducted following the guidelines of the Helsinki Declaration(E2-21-132).

## Consent to participate

Informed consent was obtained from all individual participants included in the study.

## Author Contributions

DM Beser: Manuscript writing, Data collection

D Oluklu: Data collection, Data analysis

DU Hendem: Data collection, Data analysis

SG Ayhan: Literature search, Project development

D Sahin: Project development, Visualization, Reviewing, Editing

## Conflict of Interest

The authors declare that they have no conflict of interest.

### References


1. Austin K, Wilson K, Saha S. Hyperemesis Gravidarum. Nutr Clin Pract. 2019;34(2):226-41.
2. Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. N Engl J Med. 2010;363(16):1544-50.
3. Verberg MF, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. Hum Reprod Update. 2005;11(5):527-39.
4. Eliakim R, Abulafia O, Sherer DM. Hyperemesis gravidarum: a current review. American journal of perinatology. 2000;17(04):207-18.
5. Haedersdal S, Salvig JD, Aabye M, Thorball CW, Ruhwald M, Ladelund S, et al. Inflammatory markers in the second trimester before clinical onset of preeclampsia, intrauterine growth restriction, and spontaneous preterm birth. Inflammation. 2013;36(4):907-13.
6. Kan E, Emektar E, Corbacioglu K, Safak T, Sariaydin T, Cevik Y. Evaluation of relationship between inflammatory markers and hyperemesis gravidarum in patients admitted to emergency department. The American journal of emergency medicine. 2020;38(2):292-5.
7. Akar S, Gul A, Çintesun FNI, Sahin G, Ezveci H, Akyürek F, et al. Subclinical inflammation markers in hyperemesis gravidarum and ketonuria: A case–control study. Journal of laboratory physicians. 2019;11(02):149-53.
8. Kurt RK, Güler A, Silfeler DB, Ozçil MD, Karateke A, Hakverdi AU. Relation of inflammatory markers with both presence and severity of hyperemesis gravidarum. Ginekol Pol. 2014;85(8):589-93.
9. Kuscu NK, Yildirim Y, Koyuncu F, Var A, Uyanik BS. Interleukin-6 levels in hyperemesis gravidarum. Arch Gynecol Obstet. 2003;269(1):13-5.
10. Yamada N, Sato Y, Moriguchi-Goto S, Yamashita A, Kodama Y, Sameshima H, et al. Histological severity of fetal inflammation is useful in predicting neonatal outcome. Placenta. 2015;36(12):1490-3.
11. Kaplan PB, Gücer F, Sayin NC, Yüksel M, Yüce MA, Yardim T. Maternal serum cytokine levels in women with hyperemesis gravidarum in the first trimester of pregnancy. Fertil Steril. 2003;79(3):498-502.
12. Engin-Ustun Y, Tonguç E, Var T, Deveer R, Yilmaz N, Danisman N, et al. Vaspin and C-reactive protein levels in hyperemesis gravidarum. Eur Rev Med Pharmacol Sci. 2013;17(1):138-40.
13. Caglayan EK, Engin-Ustun Y, Gocmen AY, Sarı N, Seckin L, Kara M, et al. Is there any relationship between serum sirtuin-1 level and neutrophil-lymphocyte ratio in hyperemesis gravidarum? J Perinat Med. 2016;44(3):315-20.
14. Örgül G, Aydın Haklı D, Özten G, Fadiloğlu E, Tanacan A, Beksaç MS. First trimester complete blood cell indices in early and late onset preeclampsia. Turk J Obstet Gynecol. 2019;16(2):112-7.
15. Daglar HK, Kirbas A, Kaya B, Kilincoglu F. The value of complete blood count parameters in predicting preterm delivery. Eur Rev Med Pharmacol Sci. 2016;20(5):801-5.
16. Abide Yayla C, Ozkaya E, Tayyar A, Senol T, Senturk MB, Karateke A. Predictive value of complete blood count parameters for placental invasion anomalies. J Matern Fetal Neonatal Med. 2017;30(19):2324-8.

17. Tanacan A, Uyanik E, Unal C, Beksac MS. A cutoff value for systemic immune-inflammation index in the prediction of adverse neonatal outcomes in preterm premature rupture of the membranes. J Obstet Gynaecol Res. 2020;46(8):1333-41.
18. Ipek S, Cekic C, Alper E, Coban E, Eliacik E, Arabul M, et al. Can red cell distribution width be a marker of disease activity in ulcerative colitis? Int J Clin Exp Med. 2015;8(8):13848-53.
19. Zhao T, Cui L, Li A. The significance of RDW in patients with hepatocellular carcinoma after radical resection. Cancer Biomark. 2016;16(4):507-12.
20. Beyazit F, Öztürk FH, Pek E, Ünsal MA. Evaluation of the hematologic system as a marker of subclinical inflammation in hyperemesis gravidarum: a case control study. Ginekol Pol. 2017;88(6):315-9.
21. Tayfur C, Burcu DC, Gulten O, Betul D, Tugberk G, Onur O, et al. Association between platelet to lymphocyte ratio, plateletcrit and the presence and severity of hyperemesis gravidarum. J Obstet Gynaecol Res. 2017;43(3):498-504.
22. Tan PC, Jacob R, Quek KF, Omar SZ. Readmission risk and metabolic, biochemical, haematological and clinical indicators of severity in hyperemesis gravidarum. Aust N Z J Obstet Gynaecol. 2006;46(5):446-50.
23. Tan PC, Jacob R, Quek KF, Omar SZ. Indicators of prolonged hospital stay in hyperemesis gravidarum. Int J Gynaecol Obstet. 2006;93(3):246-7.
24. Koot M, Grooten I, Vd Post J, Bais J, Ris-Stalpers C, Naaktgeboren C, et al. Ketonuria is not associated with hyperemesis gravidarum disease severity. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2020;254:315-20.
25. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol. 2013;13(3):159-75.
26. Chen Y, Zhong H, Zhao Y, Luo X, Gao W. Role of platelet biomarkers in inflammatory response. Biomarker Research. 2020;8.

## Figures

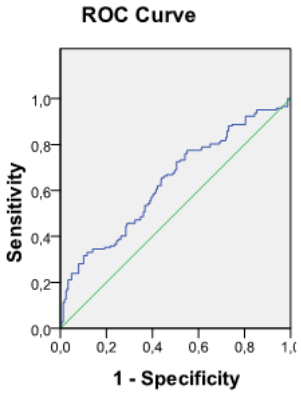


**Figure 1**

Receiver operating characteristic curves for SII for the severity of hyperemesis gravidarum

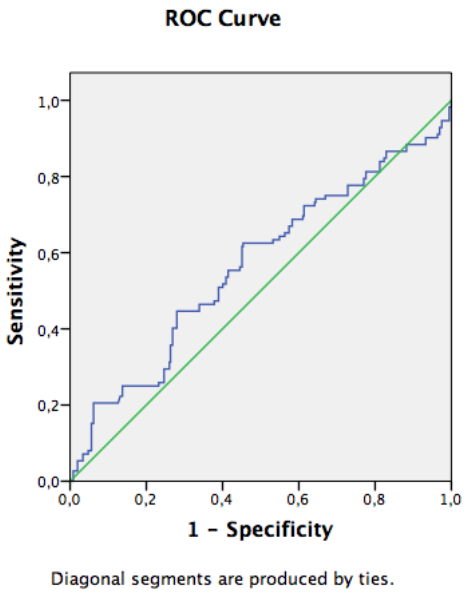


Figure 2

The cut-off value of SII to predict the length of hospitalization