European Review for Medical and Pharmacological Sciences 2023; 27: 8868-8876

Relationship between combined systemic inflammatory indices with presence and severity of hyperemesis gravidarum

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Abstract. – OBJECTIVE: Our study aims to determine the levels of systemic inflammation markers and the combined systemic inflammation indices in hyperemesis gravidarum (HG) patients and to investigate the association between the severity of the disease.

PATIENTS AND METHODS: The study population consisted of 83 pregnant women with HG and 100 healthy pregnant women matched for gestational age as a control group. We grouped the HG patients according to the Modified Pregnancy Unique Quantification of Emesis/Nausea (PUQE) scoring system as mild, moderate, and severe. We calculated the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), MPV-to-lymphocyte ratio (MPVLR), RDW-to-platelet ratio (RPR), Systemic immune-inflammation index (SII), Systemic Inflammation Response Index (SIRI), and Aggregate Systemic Inflammation Index (AISI).

RESULTS: NLR, PLR, SII, SIRI, and AISI levels were significantly higher in the HG group. These indices tended to increase as the severity of the disease increased. We found NLR, PLR, SII, SIRI, and AISI indices as the independent risk factors for the presence and severity of HG. The SIRI index, which has the highest area under the curve (AUC), sensitivity, and specificity values, was determined as the most powerful diagnostic tool in the diagnostic evaluation of the presence (AUC: 0.695; $p < 0.001$; sensitivity: 54%; specificity: 75%; cut-off: 3.14) and severity (AUC: 0.785; $p < 0.001$, sensitivity: 82%; specificity: 68%; cut-off: 2.74) of HG.

CONCLUSIONS: Our study results showed that combined systemic inflammatory indices (NLR, PLR, SII, SIRI, and AISI) are associated and correlated with the presence and severity of HG. These indices are independent risk factors for the presence and severity of HG. Combined systemic inflammatory indices are diagnostic in determining the severity of HG. The SIRI index has the best diagnostic power for both the diagnosis of HG and the determination of the severity of HG.

Key Words:
Combined systemic inflammatory indices, Hyperemesis Gravidarum, SIRI, Systemic inflammation markers.

Introduction

Nausea and vomiting is a condition that is common in the first trimester of pregnancy, affects approximately 80% of women, and usually improves before the 20th week of pregnancy but can continue until delivery[1,2]. Hyperemesis gravidarum (HG) is a pregnancy condition consisting of vomiting and severe nausea that causes weight loss, dehydration, electrolyte imbalance, and ketonuria. This disorder occurs in 0.3 - 2% of all pregnancies[3].

The pathophysiology of HG is controversial, associated with hormonal changes, psychological factors, abnormal gastric motility, *Helicobacter pylori* infection, genetic predisposition, and hepatic dysfunction[4-6]. However, the role of inflammation in the pathogenesis of HG can not be adequately illuminated with the current information. Significant associations between inflammation markers and HG have been reported[4,7]. Moreover, the major pro-inflammatory cytokines were higher in HG patients, such as tumor necrosis factor-alpha and Interleukin-6[4]. In the literature, studies[4,8-13] on novel inflammatory markers derived from routine hemogram tests are on the rise, such as platelet distribution width (PDW), red cell distribution width (RDW), mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), RDW-to-platelet ratio (RPR) and MPV-to-platelet ratio (MPVLR) could be used as inflammatory markers in numerous cases. Inflammation is a complex phenomenon that cannot be explained by evaluating one or two inflammatory cells.

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For this reason, the Systemic immune-inflammation index (SII), Systemic Inflammation Response Index (SIRI), and Aggregate Systemic Inflammation Index (AISI) are new combined inflammatory indices produced to evaluate the inflammatory process and response. SII, AISI, and SIRI indices have been previously assessed regarding their relationship with adverse outcomes in pregnant women with coronavirus disease and malignancy patients and have been found successful[14-16]. However, there is not enough data on the relationship of these indices (especially MPLR, RPR, SII, SIRI, and AISI) with the presence and severity of HG.

In this study, we aimed to investigate the relationship between the presence and severity of HG in the combined systemic inflammation indices. In addition, in our study, we aimed to determine the index with the best diagnostic power to detect HG's presence and severity.

Patients And Methods

This prospective study was conducted at the tertiary research and training hospital between January and December 2021. The population consisted of 83 pregnant women with HG (patients group) and 100 pregnant women without complaints matched for gestational age as a control group. Patients with multiple gestations, BMI > 35 kg/m², gastrointestinal and thyroid diseases, urinary tract infections, physiological disorders, diabetes mellitus, vitamin B12 deficiency, iron deficiency anemia, immunological diseases, and malignancies were excluded. Our research, which was conducted by the principles of the Declaration of Helsinki, was approved by our İnstitutional Ethics Committee with protocol number 2020-44. Written informed consent was taken from all participants.

The criteria for HG were:

- Severe vomiting (more than two times per day).
- Weight loss of more than 5% of body weight.
- The presence of at least one positive ketonuria.

The Modified Pregnancy Unique Quantification of Emesis/Nausea (PUQE) scoring system was used to determine the severity of HG. All the patients filled out the 3-question, quantifying nausea, vomiting, and retching for the first trimester[17]. The PUQE score was calculated between 4-15 points for HG patients. The HG patients were grouped as mild (≤ 6 points), moderate (7-12 points), and severe (≥ 13 points). Patients were divided into three groups: mild (n = 16), moderate (n = 34), and severe (n = 33), according to HG severity.

Age, gestational age, parity, and body mass index (BMI) were recorded at patient interviews. All gestational ages were determined by the first day of the last menstrual period and confirmed with an ultrasound. We calculated the body mass index (BMI) as body weight (kg) divided by the square of height (m²). Urine analysis for ketone was done for the detection of starvation of ketosis. Blood samples were taken antecubital vein with a 20 gauge needle in the morning between 08:00 and 09:00 after overnight fasting. Complete blood count (CBC) parameters were measured using the Mindray BC 5800 Auto Hematology Analyzer (Mindray, China), an automated blood counter. We recorded the following parameters from CBC records: platelet count, 150 to 450 10^3/μL; lymphocyte count, 0.9 to 2.9 10^3/μL; and neutrophil count, 1.7 to 7 10^3/μL; red blood cell distribution width (RDW); platelet distribution width (PDW) and mean platelet volume (MPV). The neutrophil count divided by total lymphocyte count (NLR), platelet count divided by total lymphocyte count (PLR), and MPV divided by total lymphocyte count (MPVLR) were calculated by dividing neutrophil, platelet counts, and MPV by total lymphocyte count, respectively. Also calculated RPR, RDW to platelet count ratio. Systemic immune-inflammation index (SII) was calculated using the formula: platelet count × neutrophil count/lymphocyte count (10^3/μL). Systemic Inflammation Response Index (SIRI) was calculated using the formula: neutrophil count × monocyte count/lymphocyte count (10^3/μL). Aggregate Systemic Inflammation Index (AISI) was calculated using the formula: neutrophil count × platelet count x monocyte count/lymphocyte count (10^3/μL). We compared the Systemic inflammatory score and indices between HG and control groups and between mild, moderate, and severe HG groups.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA), and *p*-values < 0.05 were considered statistically significant. Kolmogorov-Smirnov test was used to assess whether the variables followed a normal distribution. Continuous variables were presented as mean ± standard deviation (SD) if normally distributed and median (minimum-maximum value) if non-normally distributed. Numerical variables with normal distribution were compared using student's *t*-test for the paired groups and one-way ANOVA (analysis of variance) for triplet groups.

Numerical variables with abnormal distribution were compared using Mann-Whitney U for the paired groups and the Kruskal-Wallis test for triplet groups. The relationship of the variables with the presence and severity of HG was evaluated with Pearson correlation analysis. Modeling was performed with variables with a *p*-value < 0.1 in the Univariate regression analysis. With the modeling obtained, the risk factors for the presence and severity of HG were determined by multivariate regression analysis. The diagnostic efficacy of the identified risk factors in detecting the presence and severity of HG was investigated by receiver operator curve (ROC) analysis. The area under the curve (AUC) value, sensitivity, and specificity were calculated.

Results

The baseline clinical and laboratory characteristics of patients are displayed in Table I. There were no significant differences between the HG and control groups according to age, BMI, parity, gravida, and gestational age. Except for the neutrophil count, the groups' hematological laboratory findings were similar. The neutrophil counts were higher in the HG group (6.71 ± 2.20 *vs.* 6.07 ± 1.70; *p*: 0.029). NLR (4.02 ± 1.75 *vs.* 3.31 ± 1.01; *p*: 0.001), PLR (144.60 ± 44.76 *vs.* 130.33 ± 25.42; *p*: 0.007) scores, and SII (985.64 ± 138.21 *vs.* 821.05 ± 118.08; *p*: 0.005), SIRI (3.62 ± 0.71 *vs.* 2.77 ± 0.64; $p < 0.001$) and AISI (887.07 ± 114.82 *vs.* 736.44 ± 99.62; *p*: 0.004) indices were significantly higher in the HG group.

The HG severity subgroup (Mild-Moderate-Severe) analysis is shown in Table II. The demographic data (age, BMI, parity, gravida, and gestational age) did not significantly differ between the groups. Neutrophil (*p*: 0005) and platelet (*p*: 0.003) counts were significantly higher in the "Moderate and Severe" groups compared to the "Mild" group. Other hematological measurements were similar between groups. NLR (*p*: 0.001) and PLR ($p < 0.001$) ratios and SII ($p < 0.001$), SIRI (*p*: 0.001), and AISI ($p < 0.001$) indices were significantly higher in the "Moderate and Severe" groups compared to the "Mild" group. On the other hand, while MPVLR did not make a significant difference between the groups, RPR (*p*: 0.007) was significantly lower in the "Severe" group.

Risk factors for the presence of HG are presented in Table III. The relationship of demographic and laboratory data with the presence of HG was evaluated by correlation and regression analyses, as shown in Table III. Gestational age (r: -0.231;

Table I. Baseline clinical and laboratory characteristics of patient and control groups.

	Hyperemesis gravidarum group (n: 83)	Control group (n: 100)	*p*-value
Age (years)	29.11 ± 5.04	29.41 ± 5.65	0.706
BMI (kg/m^2)	25.19 ± 5.14	24.24 ± 3.96	0.159
Parity	1 (0 - 3)	1 (0 - 3)	0.120
Gravida	2 (1 - 5)	2 (1 - 4)	0.115
Gestational Age (weeks)	8.88 ± 1.63	8.23 ± 1.10	0.102
Hemoglobin (g/dl)	12.80 ± 1.19	12.77 ± 1.01	0.861
RDW (%)	13.65 ± 1.51	14.18 ± 2.45	0.088
Neutrophil count (10^3/µl)	6.71 ± 2.20	6.07 ± 1.70	0.029
Lymphocyte count (10^3/µl)	1.79 ± 0.51	1.90 ± 0.47	0.119
Monocyte count (10^3/µl)	0.79 (0.25 - 1.14)	0.80 (0.23 - 1.27)	0.247
Platelet count (10^3/µl)	243.06 ± 54.29	256.36 ± 52.77	0.096
MPV (fl)	9.40 ± 1.01	9.33 ± 1.13	0.684
PDW (%)	16.41 ± 0.70	16.61 ± 1.55	0.258
NLR	4.02 ± 1.75	3.31 ± 1.01	0.001
PLR	144.60 ± 44.76	130.33 ± 25.42	0.007
RPR	0.059 ± 0.016	0.058 ± 0.021	0.816
MPVLR	5.69 ± 1.80	5.22 ± 1.54	0.058
SII index	985.64 ± 138.21	821.05 ± 118.08	0.005
SIRI	3.62 ± 0.71	2.77 ± 0.64	< 0.001
AISI	887.07 ± 114.82	736.44 ± 99.62	0.004

Data were presented by mean ± Standard Deviation (SD) or median (minimum-maximum) as appropriate. BMI: Body Mass Index, RDW: Red cell Distribution Width, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, NLR: Neutrophil -to- Lymphocyte Ratio, PLR: Platelet -to- Lymphocyte Ratio, RPR: RDW to Platelet count Ratio, MPVLR: MPV -to- Lymphocyte ratio, SII: systemic Immune-Inflammation, SIRI: Systemic Inflammation Response Index, AISI: Aggregate Systemic Inflammation Index.

Table II. Clinic and laboratory findings according to the patient subgroups.

	Mild (n:16)	Moderate (n:34)	Severe (33)	*p*-value
Age (years)	31.19 ± 5.74	28.79 ± 4.98	28.42 ± 4.61	0.178
Body Mass Index (kg/m^2)	25.21 ± 4.89	2.42 ± 4.80	24.94 ± 5.71	0.931
Parity	1 (0 - 3)	1 (0 - 3)	1 (0 - 3)	0.269
Gravida	2 (1 - 5)	2 (1 - 4)	2 (1 - 5)	0.302
Gestational Age (weeks)	9.19 ± 1.47	8.41 ± 1.63	9.21 ± 1.63	0.093
Hemoglobin (g/dl)	12.26 ± 1.50	13.03 ± 1.21	12.82 ± 0.93	0.101
RDW (%)	13.76 ± 1.25	13.76 ± 1.51	13.48 ± 1.64	0.720
Neutrophil count (10^3/µl)	5.22 ± 1.33[a,b]	6.78 ± 2.32	7.35 ± 2.12	0.005
Lymphocyte count (10^3/µl)	1.88 ± 0.40	1.89 ± 0.59	1.64 ± 0.46	0.105
Monocyte count (10^3/µl)	0.80 (0.24 - 1.15)	0.79 (0.23 - 1.26)	0.81 (0.23 - 1.23)	0.119
Platelet count (10^3/µl)	205.13 ± 45.11[a,b]	243.56 ± 51.02	260.94 ± 53.52	0.003
Mean Platelet Volume (fl)	9.53 ± 1.09	9.36 ± 1.09	9.38 ± 0.91	0.856
PDW (%)	16.53 ± 0.76	16.25 ± 0.74	16.50 ± 0.60	0.237
NLR	2.84 ± 0.75[a,b]	3.90 ± 1.79[c]	4.71 ± 1.77	0.001
PLR	111.10 ± 23.62[a,b]	138.60 ± 44.39[c]	167.02 ± 41.57	< 0.001
RPR	0.069 ± 0.014	0.059 ± 0.019	0.053 ± 0.012[b]	0.007
MPVLR	5.23 ± 1.08	5.43 ± 1.90	6.18 ± 1.90	0.123
SII index	574.98 ± 95.83[a,b]	952.65 ± 152.71[c]	1218.73 ± 174.1	< 0.001
SIRI	2.56 ± 0.45[a,b]	3.51 ± 0.57[c]	4.24 ± 0.69	0.001
AISI	517.48 ± 85.23[a,b]	857.38 ± 140.76[c]	1,096.86 ± 152.6	< 0.001

Data were presented by mean ± Standard Deviation (SD) or median (minimum-maximum) as appropriate. The *p*-values in the far-right column belong to the ANOVA analysis, the *p*-values in the "a,b,c" explanations are from the post-hoc Tukey test. [a]Statistical difference between "Mild" and "Moderate" groups ($p<0.05$). [b]Statistical difference between "Mild" and "Severe" groups ($p<0.05$). [c]Statistical difference between "Moderate" and "Severe" groups ($p<0.05$). RDW: Red cell Distribution Width, PDW: Platelet Distribution Width, NLR: Neutrophil -to- Lymphocyte Ratio, PLR: Platelet -to- Lymphocyte Ratio, RPR: RDW to Platelet count Ratio, MPVLR: MPV -to- Lymphocyte ratio, SII: Systemic Immune-Inflammation, SIRI: Systemic Inflammation Response Index, AISI: Aggregate Systemic Inflammation Index.

Table III. Risk factors for presence of Hyperemesis gravidarum.

	Correlation		Univariate Regression		Multivariate Regression	
	r	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Gravida	0.151	0.041	1.283 (1.008 - 1.633)	0.043	1.223 (0.947 - 1.578)	0.123
Gestational Age	-0.231	0.002	0.710 (0.569 - 0.885)	0.002	1.369 (1.082 - 1.733)	0.009
RDW	0.127	0.088	1.139 (0.978 - 1.327)	0.094	1.147 (0.973 - 1.351)	0.102
Neu	0.161	0.029	1.182 (1.014 - 1.377)	0.032	1.269 (1.067 - 1.508)	0.007
Lym	0.116	0.119	1.616 (0.882 - 2.960)	0.120	1.920 (0.963 - 3.827)	0.064
Plt	0.124	0.096	1.005 (0.999 - 1.010)	0.097	1.006 (0.999 - 1.012)	0.095
NLR	0.247	0.001	1.466 (1.156 - 1.862)	0.002	1.519 (1.186 - 1.949)	0.001
PLR	0.197	0.007	1.011 (1.003 - 1.020)	0.009	1.013 (1.004 - 1.022)	0.005
MPVLR	-0.140	0.058	0.842 (0.704 - 1.009)	0.062	0.781 (0.636 - 1.004)	0.078
SII index	0.205	0.005	1.006 (1.002 - 1.018)	0.008	1.008 (1.003 - 1.017)	0.005
SIRI	0.340	< 0.001	2.074 (1.461 - 2.941)	< 0.001	2.061 (1.449 - 2.932)	< 0.001
AISI	0.210	0.004	1.082 (1.004 - 1.187)	0.007	1.012 (1.004 - 1.043)	0.004

OR: Odds Ratio, CI: Confidence Interval, r: Correlation coefficient, RDW: Red cell Distribution Width, Neu: Neutrophil count, Lym: Lymphocyte count, Plt: Platelet count, NLR: Neutrophil - to - Lymphocyte Ratio, PLR: Platelet - to - Lymphocyte Ratio, MPVLR: MPV-to- Lymphocyte ratio, SII: Systemic Immune - Inflammation, SIRI: Systemic Inflammation Response Index, AISI: Aggregate Systemic Inflammation Index.

p: 0.002), NLR (r: 0.247; *p*: 0.001), PLR (r: 0.197; *p*: 0.007), SII (r: 0.205; *p*: 0.005), SIRI (r: 0.340; $p < 0.001$) and AISI (r: 0.210; *p*: 0.004) indices were significantly correlated with the presence of HG. Gestational age (OR: 1.369; *p*: 0.009), neutrophil count (OR: 1.269; *p*: 0.007), NLR (OR: 1.519; *p*: 0.001), PLR (OR: 1.013; *p*: 0.005), SII (OR: 1.008; *p*: 0.005), SIRI (OR: 2.061; $p < 0.001$) and AISI (OR: 1.012; *p*: 0.004) indices were determined as risk factors for the presence of HG.

Risk factors for the severity of HG are presented in Table IV. The relationship of demographic and laboratory data with the severity of HG is also shown in Table IV. Neutrophil count (r: 0.334; *p*: 0.002), platelet count (r: 0.361; *p*: 0.001), NLR (r: 0.388; $p < 0.001$), PLR (r: 0.417; $p < 0.001$), SII (r: 0.463; *p*: 0.002), SIRI (r: 0.468; $p < 0.001$) and AISI (r: 0.463; $p < 0.001$) indices were found to be significantly correlated with HG severity. Gestational age (OR: 1.532; *p*: 0.023), lymphocyte count (OR: 1.204; *p*: 0.002), platelet count (OR: 1.018; *p*: 0.005), NLR (OR: 1.632; *p*: 0.003), PLR (OR: 1.025; $p < 0.001$), SII (OR: 1.005; *p*: 0.001), SIRI (OR: 1.923; *p*: 0.003) and AISI (OR: 1.009; *p*: 0.001) indices were defined as risk factors for HG severity. The SIRI index was the most potent risk factor for the presence and severity of HG.

The diagnostic power of predictors for the presence and severity of HG is presented in Table V. NLR [AUC (95% CI): 0.618 (0.528 - 0.692), *p*: 0.010] and SIRI indices [AUC (95% CI): 0.695 (0.585 - 0.746), $p < 0.001$] were found to have significant diagnostic power for the presence of HG. Variables with significant diagnostic power for HG severity were found to be neutrophil count, platelet count, NLR [AUC (95% CI): 0.756 (0.654-0.859), $p < 0.001$], PLR [AUC (95% CI): 0.737 (0.632-0.843), $p < 0.001$], SII [AUC (95%

Table IV. Risk factors for severity of Hyperemesis gravidarum.

	Correlation		Univariate Regression		Multivariate Regression	
	r	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Gravida	-0.010	0.928	0.805 (0.512 - 1.267)	0.349	0.784 (0.453 - 1.355)	0.383
Gestational Age	0.061	0.586	1.236 (0.937 - 1.631)	0.134	1.532 (1.059 - 2.216)	0.023
RDW	-0.079	0.476	0.875 (0.635 - 1.207)	0.417	0.873 (0.617 - 1.237)	0.446
Neu	0.334	0.002	1.254 (1.015 - 1.549)	0.036	1.298 (0.992 - 1.700)	0.058
Lym	-0.201	0.069	0.351 (0.130 - 0.945)	0.038	1.204 (1.052 - 1.648)	0.002
Plt	0.361	0.001	1.011 (1.002 - 1.020)	0.018	1.018 (1.005 - 1.030)	0.005
NLR	0.388	< 0.001	1.504 (1.119 - 2.022)	0.007	1.632 (1.187 - 2.244)	0.003
PLR	0.417	< 0.001	1.021 (1.009 - 1.033)	< 0.001	1.025 (1.012 - 1.038)	< 0.001
MPVLR	0.213	0.053	1.297 (1.000 - 1.681)	0.050	1.313 (1.003 - 1.720)	0.048
SII index	0.463	< 0.001	1.012 (1.002 - 1.134)	0.002	1.005 (1.002 - 1.021)	0.001
SIRI	0.468	< 0.001	1.574 (1.133 - 2.187)	0.007	1.923 (1.209 - 2.454)	0.003
AISI	0.463	< 0.001	1.021 (1.001 - 1.206)	0.002	1.009 (1.003 - 1.029)	0.001

OR: Odds Ratio, CI: Confidence Interval, r: Correlation coefficient, RDW: Red cell Distribution Width, Neu: Neutrophil count, Lym: Lymphocyte count, Plt: Platelet count, NLR: Neutrophil -to- Lymphocyte Ratio, PLR: Platelet -to- Lymphocyte Ratio, MPVLR: MPV –to- Lymphocyte ratio, SII: Systemic Immune-Inflammation, SIRI: Systemic Inflammation Response Index, AISI: Aggregate Systemic Inflammation Index.

Table V. Diagnostic power of predictors for presence and severity of Hyperemesis gravidarum.

	Hyperemesis gravidarum presence ROC Analysis		Hyperemesis gravidarum severity ROC Analysis	
	AUC (95% CI)	*p*-value	AUC (95% CI)	*p*-value
Gestational Age	0.508 (0.435 - 0.701)	0.036	0.591 (0.467 - 0.714)	0.164
Neutrophil count	0.583 (0.499 - 0.666)	0.055	0.664 (0.546 - 0.783)	0.012
Lymphocyte count	0.425 (0.341 - 0.509)	0.082	0.374 (0.250 - 0.498)	0.052
Platelet count	0.414 (0.330 - 0.498)	0.045	0.633 (0.512 - 0.754)	0.041
NLR	0.618 (0.528 - 0.692)	0.010	0.756 (0.654 - 0.859)	< 0.001
PLR	0.568 (0.479 - 0.656)	0.115	0.737 (0.632 - 0.843)	< 0.001
MPVLR	0.575 (0.491 - 0.658)	0.082	0.615 (0.488 - 0.743)	0.077
SII index	0.580 (0.493 - 0.668)	0.061	0.756 (0.654 - 0.859)	< 0.001
SIRI	0.695 (0.585 - 0.746)	< 0.001	0.785 (0.676 - 0.874)	< 0.001
AISI	0.579 (0.491 - 0.666)	0.067	0.756 (0.654 - 0.847)	< 0.001

AUC: Area Under the Curve, CI: Confidence Interval, NLR: Neutrophil -to- Lymphocyte Ratio, PLR: Platelet -to- Lymphocyte Ratio, MPVLR: MPV -to- Lymphocyte ratio, SII: systemic Immune-Inflammation, SIRI: Systemic Inflammation Response Index, AISI: Aggregate Systemic Inflammation Index.

CI): 0.756 (0.654-0.859), $p < 0.001$], SIRI [AUC (95% CI): 0.785 (0.676-0.874), $p < 0.001$] and AISI [AUC (95% CI): 0.756 (0.654-0.847), $p < 0.001$] indices. The SIRI index, which has the highest AUC, sensitivity, and specificity values, was determined as the most powerful diagnostic tool in the diagnostic evaluation of the presence (sensitivity: 54%; specificity: 75%; cut-off: 3.14) and severity (sensitivity: 82%; specificity: 68%; cut-off: 2.74) of HG (Figure 1).

Discussion

The most important results from our study are: (i) NLR, PLR, and combined systemic inflammatory indices (SII, SIRI, and AISI) were higher in the HG group compared to the control group; (ii) In HG severity subgroup analysis, we found that NLR, PLR, SII, SIRI and AISI levels increased significantly as HG severity increased (from mild to moderate and severe); (iii) NLR, PLR, SII, SIRI, and AISI indices were found to be positively correlated with the presence and severity of HG. The index with the highest correlation coefficient was SIRI; (iv) NLR, PLR, SII, SIRI, and AISI indices were found to be risk factors for the presence and severity of HG. The index with the highest odds ratio was SIRI; (v) We also found the SIRI index has the highest sensitivity and specificity rates in diagnosing the presence and severity of HG.

The primary purpose of our study was to determine the inflammatory index with the best diagnostic power in determining the presence and severity of HG. The efficacy of NLR and PLR in this patient group has been previously demonstrated in studies with different designs. In addition, we used MPVLR and RPR indices that were not tested before in the HG patient group in our study. However, our primary focus has been on the combined inflammatory indices SII, SIRI, and AISI indices.

Hyperemesis gravidarum is a condition that progresses with severe nausea and vomiting, disrupts acid-base balance, and causes fluid electrolyte disorder and ketonuria[4]. It is usually seen in the first trimester and may require hospitalization if severe and may even progress fatally, causing central pontine myelinolysis and Wernicke's encephalopathy[4,17,18]. Since the cause of HG is unknown, the current treatment is empirical and suboptimal. Several mechanisms are proposed in its etiopathogenesis, but since none can explain the etiology alone, it appears to be multifactoria[17,19]. Therefore, early diagnosis of HG is crucial to prevent maternal and fetal mortality and morbidity.

Although the relationship between the development of HG and inflammation is not fully known, studies with inflammation markers in HG patients suggest a strong relationship between them. Studies[20] show that HG is related to various factors, including inflammatory cell activation and immunological responses involving neutrophils,

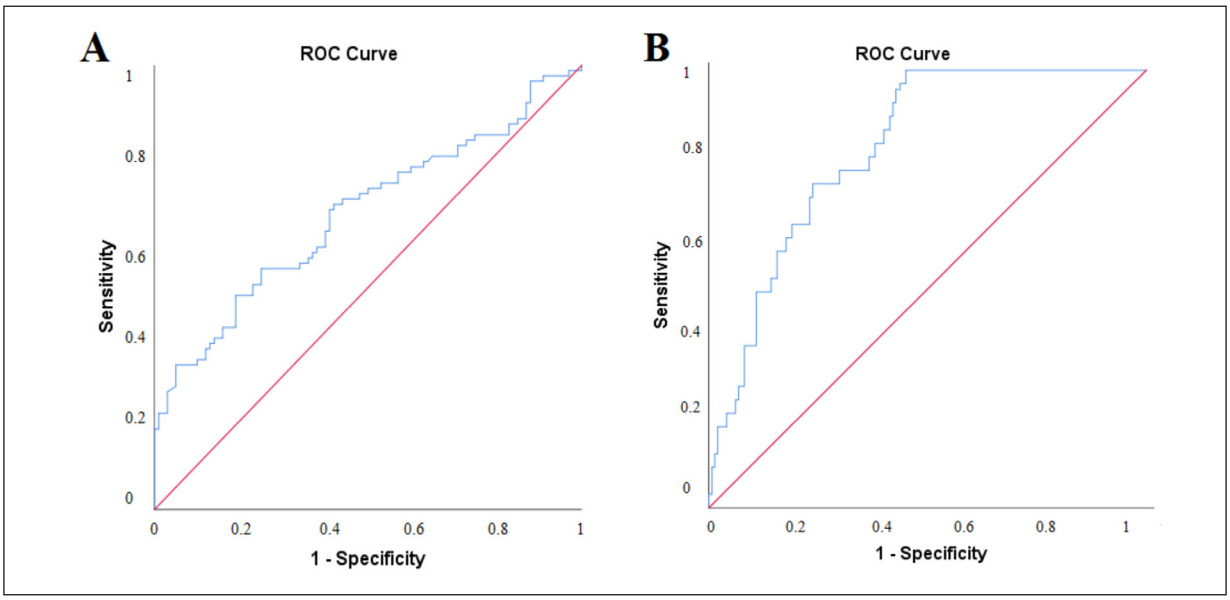

Figure 1. ROC curves for the diagnostic value of SIRI index in determining the presence and severity of Hyperemesis Gravidarum (HG). **A**, ROC Curve for the presence of HG [AUC (95% CI) = 0.695 (0.585-0.746), ($p < 0.001$)]. **B**, ROC curve for the severity of HG [AUC (95% CI) = 0.785 (0.676-0.874), ($p < 0.001$)].

lymphocytes, and platelets. In recent studies[8,9,21], it has been shown that systemic inflammatory markers such as MPV, RDW, NLR, and PLR obtained from whole blood count have predictive and prognostic values in inflammatory, autoimmune tissues, gynecological or gastrointestinal malignancies, including preeclampsia and visual artery. NLR and PLR were found to be significantly higher in HG patients[4,16,22]. Investigators have explained elevated levels of NLR and PLR due to increased neutrophil counts and decreased lymphocyte counts as a physiological immune response in stress-related conditions[22,23]. In addition, high PLR can be explained by the increase in platelet levels due to changes in intravascular fluid during the oxidative stress process[23,24]. In our study, NLR and PLR were significantly higher in HG patients. NLR and PLR were associated with HG severity. NLR and PLR levels are related and correlated with the presence and severity of HG. In addition, NLR and PLR are independent risk factors for the presence and severity of HG. PLR has no diagnostic power in the presence of HG but is diagnostic in determining the severity of HG. On the other hand, NLR is diagnostic in determining the presence and severity of HG.

Although lymphocyte counts tend to be higher in women with HG[7], there is inconsistency in the literature on this issue. Some studies[17,25] did not show a change in lymphocyte count; in others[4], lymphocyte count was lower in the HG group. There was no difference between the groups in our study regarding lymphocyte count. PDW and MPV are platelet activation markers, reflecting the platelet volume change. These parameters can be measured simply with a complete blood count device[4]. These markers showing platelet activation have been used to diagnose many inflammatory diseases[26]. Beyazit et al[22] and Çintesun et al[4] found no significant difference between HG patients and control groups in MPV and PDW. In our study, MPV and PDW values were similar in both groups. It has been reported that increased levels of MPVLR, predicting unstable platelets prone to mediator release in inflammatory processes and possible lymphopenia, may be associated with poor outcomes in patients with acute coronary syndrome[12]. MPVLR was included in the analysis with the thought that similar mechanisms may also be effective in HG patients. However, MPVLR did not make a difference in terms of the presence and severity of HG.

High values of RDW, indicating the heterogeneity of the size of circulating red blood cells, can be attributed to various underlying metabolic abnormalities such as inflammation, oxidative stress, shortening of telomeres, dyslipidemia, malnutrition, type 2 diabetes mellitus, hypertension, erythrocyte lysis and changes in erythropoietin function[13]. As in the studies of Çintesun et al[4] and Beyazıt et al[22], we obtained similar RDW values between HG and control groups. RPR, one of the newest markers of inflammatory reaction, was used to predict hepatic fibrosis in hepatitis[13]. The pathophysiological background of RPR as a marker of inflammation is unclear. The increased RDW (indicating the heterogeneity of the size of circulating red blood cells) and decreased platelet count can be explained by the elevation in its level. RPR did not make a significant difference between the groups regarding the presence and severity of HG.

Inflammation is a complex process that does not proceed through a single cell or mediator. The process proceeds through a series of cellular relationships that activate or inhibit each other. Evaluating a single cellular activity cannot be sufficient to understand the prognostic effect of inflammation. For this purpose, the combined systemic inflammatory indices SII, SIRI, and AISI were defined[16,27,28]. These indices represent the balance between inflammatory activators and inflammatory regulators. Compared to a single inflammatory indicator, these composite indicators are more stable and less sensitive to other factors.

In our study, SII, SIRI, and AISI indices were associated with HG's presence and severity. These combined systemic inflammatory indices were also found to be independent risk factors for the presence and severity of HG. The SIRI index was diagnostic for the presence of HG. Although SIRI was more robust for HG severity, all three indices were diagnostic.

HG can be defined as an oxidative state with increased reactive oxygen species (ROS) activity, decreased antioxidant activity, and reduced plasma glutathione level[29,30]. Mehmet Güney et al[29] emphasized that the oxidative state they detected in pregnant women with HG was independent of *Helicobacter pylori* infection and contributed to the pathophysiological basis of our hypothesis. In addition, while the total oxidative status (TOS) was higher in pregnant women with nausea and vomiting (NVP), the total antioxidant status (TAS) was found to be lower. It was reported that TOS increased and TAS decreased more in groups with increased NVP severity[31]. The relationship of oxidative stress with NVP severity and its relationship with HG supports our results.

It indirectly contributes to the oxidative stress-based infrastructure of our inflammatory indices. Oxidative stress may be the etiological basis of the higher detection of the inflammatory indices we tested in the HG group.

Limitations

Our study includes some limitations. The first is due to the relatively small number of participants. Another limitation is that the analysis did not include all inflammatory indexes and laboratory tests used in clinical practice. The heterogeneity among subgroups is one of the limitations as well.

Conclusions

Combined systemic inflammatory indices (NLR, PLR, SII, SIRI, and AISI) are associated and correlated with the presence and severity of HG. These indices are independent risk factors for the presence and severity of HG. Combined systemic inflammatory indices are diagnostic in determining the severity of HG. The SIRI index has the best diagnostic power for both the diagnosis of HG and the determination of the severity of HG.

Ethics Approval

Our study was approved by the Health Sciences University Kanuni Training and Research Hospital Clinical Research Ethics Committee, with protocol number 2020-44.

Informed Consent

All participants signed the informed consent form.

Conflict of Interest

The Authors declare that they have no conflict of interest.

Data Availability

Data are available upon request from the corresponding author.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' Contributions

Concept – SB, NBA, YBT; Design – SB, KİAY; Supervision – SB, KİAY; Materials – SB, NBA, YBT; Data collection and/or processing – SB, NBA, YBT; Analysis and/or interpretation – SB, KİAY; Literature search – KİAY, NBA, YBT; Writing – SB, KİAY; Critical review – NBA, YBT.

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References

1) Bulanık M, Sağsöz N, Sayan CD, Yeral Mİ, Kısa Ü. Comparison of Serum Ykl-40 and Ischemia Modified Albulmin Levels Between Pregnant Women with Hyperemesis Gravidarum and Normal Pregnant Women. Med Arch 2019; 73: 97-100.
2) Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: A prospective study of its frequency, intensity, and patterns of change. Am J Obstet Gynecol 2000; 182: 931-937.
3) Nijsten K, Jansen LAW, Limpens J, Finken MJJ, Koot MH, Grooten IJ, Roseboom TJ, Painter RC. Long-term health outcomes of children born to mothers with hyperemesis gravidarum: a systematic review and meta-analysis. Am J Obstet Gynecol 2022; 227: 414-429.e17.
4) Çintesun E, Akar S, Gul A, Çintesun FNI, Sahin G, Ezveci H, Akyürek F, Çelik Ç. Subclinical inflammation markers in hyperemesis gravidarum and ketonuria: A case-control study. J Lab Physicians 2019; 11: 149-153.
5) Buckwalter JG, Simpson SW. Psychological factors in the etiology and treatment of severe nausea and vomiting in pregnancy. Am J Obstet Gynecol 2002; 186: S210-S214.
6) Brzana RJ, Koch KL. Gastroesophageal reflux disease presenting with intractable nausea. Ann Intern Med 1997; 126: 704-707.
7) Niemeijer MN, Grooten IJ, Vos N, Bais JM, van der Post JA, Mol BW, Roseboom TJ, Leeflang MM, Painter RC. Diagnostic markers for hyperemesis gravidarum: a systematic review and metaanalysis. Am J Obstet Gynecol 2014; 211: 150.e1-150.e1515.
8) Yildirim M, Turkyilmaz E, Avsar AF. Preoperative Neutrophil-to-Lymphocyte Ratio Has a Better Predictive Capacity in Diagnosing Tubo-Ovarian Abscess. Gynecol Obstet Invest 2015; 80: 234-239.
9) Torun S, Tunc BD, Suvak B, Yildiz H, Tas A, Sayilir A, Ozderin YO, Beyazit Y, Kayacetin E. Assessment of neutrophil-lymphocyte ratio in ulcerative colitis: a promising marker in predicting disease severity. Clin Res Hepatol Gastroenterol 2012; 36: 491-497.
10) Aktar F, Tekin R, Bektaş MS, Güneş A, Köşker M, Ertuğrul S, Yılmaz K, Karaman K, Balık H, Yolbaş İ. Diagnostic role of inflammatory markers in pediatric Brucella arthritis. Ital J Pediatr 2016; 42: 3.
11) Yılmaz E, Çamcı S. The relationship between platelet indices and residual SYNTAX score in patients with ST-segment elevation myocardial infarction. Eur Res J 2022; 8: 659-669.

12) Yilmaz E, Aydin E. Prognostic value of the combination of TIMI risk score and mean platelet volume to lymphocyte count ratio in patients with acute coronary syndrome. Cor Vasa 2021; 63: 652-660.
13) Wang H, Wang J, Xia J, Yan X, Feng Y, Li L, Chen J, Liu D, Ding W, Yang Y, Huang R, Wu C. Red cell distribution width to platelet ratio predicts liver fibrosis in patients with autoimmune hepatitis. Medicine (Baltimore) 2020; 99: e21408.
14) Tanacan A, Oluklu D, Laleli Koc B, Sinaci S, Menekse Beser D, Uyan Hendem D, Yildirim M, Sakcak B, Besimoglu B, Tugrul Ersak D, Akgun Aktas B, Gulen Yildiz E, Unlu S, Kara O, Alyamac Dizdar E, Canpolat FE, Ates İ, Moraloglu Tekin O, Sahin D. The utility of systemic immune-inflammation index and systemic immune-response index in the prediction of adverse outcomes in pregnant women with coronavirus disease 2019: Analysis of 2649 cases. J Obstet Gynaecol Res 2023; 49: 912-919.
15) Chen L, Kong X, Wang Z, Wang X, Fang Y, Wang J. Pretreatment systemic inflammation response index in patients with breast cancer treated with neoadjuvant chemotherapy as a useful prognostic indicator. Cancer Manag Res 2020; 12: 1543-1567.
16) Li S, Lan X, Gao H, Li Z, Chen L, Wang W, Song S, Wang Y, Li C, Zhang H, Xue Y. Systemic Inflammation Response Index (SIRI), cancer stem cells and survival of localised gastric adenocarcinoma after curative resection. J Cancer Res Clin Oncol 2017; 143: 2455-2468.
17) Tayfur C, Burcu DC, Gulten O, Betul D, Tugberk G, Onur O, Engin K, Orcun O. Association between platelet to lymphocyte ratio, plateletcrit and the presence and severity of hyperemesis gravidarum. J Obstet Gynaecol Res 2017; 43: 498-504.
18) Netravathi M, Sinha S, Taly AB, Bindu PS, Bharath RD. Hyperemesis-gravidarum-induced Wernicke's encephalopathy: serial clinical, electrophysiological and MR imaging observations. J Neurol Sci 2009; 284: 214-216.
19) Caglayan EK, Engin-Ustun Y, Gocmen AY, Sarı N, Seckin L, Kara M, Polat MF. Is there any relationship between serum sirtuin-1 level and neutrophil-lymphocyte ratio in hyperemesis gravidarum? J Perinat Med 2016; 44: 315-320.
20) Kiyokawa Y, Yoneyama Y. Relationship between adenosine and T-helper 1/T-helper 2 balance in hyperemesis gravidarum. Clin Chim Acta 2006; 370: 137-142.
21) Dolan RD, Lim J, McSorley ST, Horgan PG, McMillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with operable cancer: Systematic review and meta-analysis. Sci Rep 2017; 7: 16717.
22) 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: 315-319.
23) 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. Am J Emerg Med 2020; 38: 292-295.
24) Tunc SY, Agacayak E, Budak S, Tunc N, Icen MS, Findik FM, Ekinci A, Gul T. Serum levels of neopterin, inflammatory markers and oxidative stress indicators in hyperemesis gravidarum. J Obstet Gynaecol Res 2016; 42: 618-624.
25) Sari N, Ede H, Engin-Ustun Y, Göçmen AY, Çağlayan EK. Hyperemesis gravidarum is associated with increased maternal serum ischemia-modified albumin. J Perinat Med 2017; 45: 421-425.
26) Kisacik B, Tufan A, Kalyoncu U, Karadag O, Akdogan A, Ozturk MA, Kiraz S, Ertenli I, Calguneri M. Mean platelet volume (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis. Joint Bone Spine 2008; 75: 291-294.
27) Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, Zhang X, Wang WM, Qiu SJ, Zhou J, Fan J. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014; 20: 6212-6222.
28) Paliogiannis P, Ginesu GC, Tanda C, Feo CF, Fancellu A, Fois AG, Mangoni AA, Sotgia S, Carru C, Porcu A, Zinellu A. Inflammatory cell indexes as preoperative predictors of hospital stay in open elective thoracic surgery. ANZ J Surg 2018; 88: 616-620.
29) Güney M, Oral B, Mungan T. Serum lipid peroxidation and antioxidant potential levels in hyperemesis gravidarum. Am J Perinatol 2007; 24: 283-289.
30) Fait V, Sela S, Ophir E, Khoury S, Nissimov J, Tkach M, Hirsh Y, Khotaba S, Tarasova L, Oettinger M. Hyperemesis gravidarum is associated with oxidative stress. Am J Perinatol 2002; 19: 93-98.
31) Verit FF, Erel O, Sav M, Celik N, Cadirci D. Oxidative stress is associated with clinical severity of nausea and vomiting of pregnancy. Am J Perinatol 2007; 24: 545-548.