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# Determination of the relationships between hyperemesis gravidarum and systemic inflammation markers: a case–control study

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## Abstract

**Background** We conducted our study to investigate the relationships between hyperemesis gravidarum (HEG) and inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR).

**Materials and methods** A total of 150 pregnant women diagnosed with HEG and 150 controls were included in our study. The data analysed included demographic variables, complete blood count results, and urinary ketonuria levels.

**Results** We found that the NLR, PLR and MLR were significantly greater in HEG patients than in controls ($p < 0.05$), indicating a potential role of systemic inflammation in the pathophysiology of HEG. Receiver operating characteristic (ROC) analysis revealed that these markers had moderate discriminative power, suggesting their utility as adjunctive diagnostic tools in clinical settings. However, no correlation was found between inflammatory markers and the severity of ketonuria.

**Conclusions** The NLR, PLR and MLR can be used as indicators of HEG as a result of the inflammatory process in pregnant women with HEG.

**Keywords** Hyperemesis gravidarum, NLR, PLR, MLR

## Introduction

Hyperemesis gravidarum (HEG) is a severe disease characterized by excessive nausea and vomiting during pregnancy, often leading to dehydration, weight loss, electrolyte imbalances, and even hospitalization. HEG occurs in approximately 0.3–3% of pregnancies and can significantly impact maternal health, potentially causing malnutrition and emotional distress throughout pregnancy [1]. The exact pathophysiology of HEG remains unclear; however, HEG is recognized as a multifactorial disorder involving hormonal changes, genetic predispositions, and possibly immunological responses [2, 3]. The importance of systemic inflammation in determining the aetiology of HEG has been shown in some studies [4, 5]. HEG patients have higher levels of haematologic inflammation indicators than healthy pregnant patients do. The monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) values were greater in the HEG group than in the control group [6]. The NLR and PLR values were also

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significantly greater in the HEG group [7]. In a recent study, the systemic immune inflammation (SII) index was greater in the severe HEG group than in the other groups [8].

The relationship between HEG and inflammation has been studied, and significant results have been reported in the literature. The existing information is inadequate to define the function of inflammation in the pathogenesis of HEG; however, it is likely that subclinical inflammation contributes to HEG development. HEG is considered a consequence of an overactive immune system, potentially linked to the production of pregnancy hormones [6].

Emerging research suggests that inflammatory responses may be central to the development and progression of HEG, as indicated by elevated levels of interleukin-6 (IL-6) and C-reactive protein (CRP) in affected patients [9, 10]. Additionally, systemic inflammatory markers, such as the NLR, PLR, and MLR, have been recognized as potential diagnostic and prognostic indicators for various inflammatory conditions and diseases [11, 12]. These markers, derived from haemograms, are convenient, cost-effective, and reliable measures of systemic inflammation, offering insights into a patient's inflammatory status without the need for complex assays [13].

Given the ongoing interest in identifying reliable diagnostic markers for HEG, this study aimed to investigate the associations between HEG and inflammatory markers, specifically the NLR, PLR, and MLR. We hypothesize that these markers are elevated in pregnant women with HEG and that they may be correlated with the severity of the condition. Through retrospective analysis, we sought to determine the potential of the NLR, PLR, and MLR as adjunctive diagnostic tools in the clinical evaluation of HEG, contributing to a broader understanding of the inflammatory mechanisms underlying this challenging condition.

## Materials and methods

This retrospective case–control study was performed in the obstetrics and gynaecology department of a referral hospital from July 2019 to July 2023. In our study, 150 patients diagnosed with HEG and 150 patients not diagnosed with HEG were included in the control group. Patients who met the following criteria were included in the HEG group: nausea/vomiting, >5% weight loss, positive ketonuria test results, and a singleton pregnancy at 11–13 weeks of gestation. The control group consisted of healthy women at similar gestational weeks who underwent routine outpatient clinic examinations. Patients who underwent ovulation induction, had eating problems for another reason, had multiple pregnancies, were smokers, had gastrointestinal system diseases, had thyroid diseases, had urinary tract infections or had any other infections were excluded.

Data such as the white blood cell (WBC) count, neutrophil (NEU) count, lymphocyte (LYM) count, haemoglobin (Hb) level, monocyte (MON) count, platelet (PLT) count, mean platelet volume (MPV), urine density, urine pH and ketonuria test results were obtained retrospectively from hospital records. The timing of routine blood tests was recorded as the time when the patient initially presented to the gynaecology and obstetrics outpatient clinic or emergency room with complaints of HEG during the diagnostic phase prior to receiving therapies for HEG. The NLR, PLR and MNR were obtained as the ratios of absolute NEU, PLT and MON values to absolute LYM values, respectively. In the urine analysis, the ketonuria results were classified as +1, +2, +3 and +4. Demographic data, maternal age, body mass index (BMI), gravidity, and parity were also recorded.

The study was approved by the Republic of Turkey Adana City Training and Research Hospital Scientific Research Ethics Committee Republic of Turkey (Date: 17.08.2023, Decision No: 2782).

### Statistical analysis

We used the Shapiro–Wilk test to determine whether continuous data were normally distributed. While the mean ± standard deviation was used for normally distributed continuous variables, the median [25-75%] was used for other variables. Categorical variables are presented as numbers and percentages. For the comparison of two independent groups, the Mann–Whitney U test was used if the distribution was not normal, and the independent samples t test was used if the distribution was normal. The relationships between the degree of ketonuria and the NLR, PLR and MLR were investigated with the Kruskal–Wallis test. The optimum cut-off values for the NLR, MNR and PLR to diagnose HEG with maximum sensitivity and specificity were determined by receiver operating characteristic (ROC) curve analysis. We considered $p<0.05$ to indicate statistical significance. Multivariate analysis of variance (MANOVA) was used to provide a more comprehensive understanding of the underlying relationships between variables, which could reveal multivariate effects that the original two-independent sample t test missed. Logistic regression analysis was used to investigate the associations between HEG and clinical factors. The possible risk factors for HEG identified with univariate analysis ($p<0.10$) were included in the multiple logistic regression analysis. Odds ratios (ORs) and their 95% confidence intervals were calculated.

## Results

The study included 150 patients diagnosed with HEG and 150 controls. The patients' serum inflammation markers, demographic characteristics and haematological values are shown in Table 1. In the statistical evaluation between

**Table 1** Demographic and laboratory measurements of the study participants

| Variables | HEG (*n* = 150) | Control (*n* = 150) | *P* value |
|---|---|---|---|
| Age (years) | 28 (19–41) | 28 (17–42) | 0.393 |
| Gravida | 2 (1–8) | 2 (1–9) | 0.836 |
| Parity | 1 (0–6) | 1 (0–4) | 0.681 |
| Gestational age (weeks) | 11 (6–13) | 11 (6–13) | 0.975 |
| Hb (g/dL) | 12.6 (8.6–15.6) | 12.1 (8.8–14) | < 0.001 |
| WBC count | 12.79 (6.45–24.74) | 9.2 (4.8–13) | 0.694 |
| Platelet count ($10^3$/µl) | 249 (120–486) | 251 (124–482) | 0.485 |
| Neutrophil count ($10^3$/µl) | 7.05 (2.44–10.83) | 6.47 (2.11–9.69) | 0.039 |
| Lymphocyte count ($10^3$/µl) | 1.46 (0.04–2.99) | 1.85 (0.27–3.22) | < 0.001 |
| Monocyte count ($10^3$/µl) | 0.52 ± 0.18 | 0.57 ± 0.17 | 0.071 |
| Urine density (g/ml) | 1024 (1002–1038) | 1018 (1002–1037) | < 0.001 |
| Ketonuria | 3 (1–4) | 0 (0–0) | < 0.001 |
| Urine pH | 6 (5–8.5) | 6.5 (5–9) | < 0.001 |
| NLR | 4.37 (1.25–91.75) | 3.52 (0.93–27.41) | < 0.001 |
| PLR | 177.37 (57.66–6750) | 141.69 (59.63–875.6) | < 0.001 |
| MLR | 0.34 (0.18–13.5) | 0.32 (0.13–1.92) | 0.011 |
| MPV (fL) | 8.82 ± 0.95 | 8.92 ± 0.88 | 0.319 |

Abbreviations: fL: femtolitre; g/dL: grams per decilitre; g/ml: grams per millilitre; Hb: haemoglobin; MLR: monocyte-to-lymphocyte ratio; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; WBC: white blood cell

Notes

Continuous data are summarized with the mean ± standard deviation and median (25–75%)

Independent samples T test was used to compare continuous variables with normal distribution

Mann–Whitney U test was used for nonnormal variables

*P* < 0.05 was consider to indicate statistical significance

**Table 2** Comparison of ketonuria and blood inflammation indicators

| Variables | Ketonuria + 1 (*n* = 28) | Ketonuria + 2 (*n* = 45) | Ketonuria + 3 (*n* = 64) | Ketonuria + 4 (*n* = 17) | *P* value |
|---|---|---|---|---|---|
| NLR | 5.01 (1.81–91.75) | 4.30 (2.07–35.72) | 4.51 (1.31–82.81) | 3.50 (0.92–27.41) | 0.462 |
| PLR | 184.43 (85.74–6750) | 177.38 (57.65–1057.14) | 176.25 (66.52–2913.22) | 169.11 (91.59–421.87 | 0.574 |
| MLR | 0.33 (0.17–13.50) | 0.36 (0.18–2.96) | 0.33 (0.13–6.63) | 0.39 (0.22–1.38) | 0.631 |

Abbreviations: MLR: monocyte-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio

Notes

Continuous data are summarized with the median (25–75%)

Kruskal–Wallis test was used

*P* < 0.05 was considered to indicate statistical significance

**Table 3** Analysis of cut-off points of the NLR, PLR and MLR values to diagnose HEG

| Variables | Cut off points | AUC | *P* value | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|
| NLR | 5.3179 | 0.648 | 0.001 | 43.3 | 80 |
| PLR | 137.4957 | 0.645 | 0.001 | 74.7 | 49.3 |
| MLR | 0.4136 | 0.585 | 0.0093 | 40 | 74.7 |

Abbreviations: AUC: area under the curve; MLR: monocyte-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio

Notes

The maximum sensitivity and specificity of HEG were established using receiver operating characteristic (ROC) curve analysis

the groups, no significant differences were detected in the WBC count, PLT count, NEU count, MON count or MPV. The median LYM counts of the HEG and control groups were 1.46 [0.04–2.99] and 1.85 [0.27–3.22], respectively. A statistically significant difference was found between the groups with respect to LYM counts. A significant difference was not detected between the groups with respect to demographic characteristics such as age, gravidity, parity and gestational week.

The median NLR of the HEG group was 4.37 [1.25–91.75], the median PLR was 177.37 [57.66–6750], and the median MLR was 0.34 [0.18–13.5]; for the control group, the values were 3.52 [0.93–27.41], 141.69 [59.63–875.6] and 0.32 [0.13–1.92], respectively. We found that the NLR, PLR and MLR values were significantly greater in the HEG group ($p < 0.05$).

When the relationships among the NLR, PLR and MLR values and the degree of ketonuria were compared, the p values were 0.462, 0.574 and 0.631, respectively, and no statistically significant results were found (Table 2).

ROC analysis was performed using the NLR, PLR and MLR to separate the HEG and control groups. The discriminatory power of the NLR, PLR and MLR between the HEG and control groups was intermediate and statistically significant. The AUC values for the NLR, PLR and MLR were 0.648, 0.645 and 0.585, respectively ($p < 0.001$, $p < 0.001$ and $p < 0.0093$, respectively). The NLR, PLR and MLR cut-off values were as follows: 5.3179, with 43.3% sensitivity and 80% specificity; 137.4957, with 74.7% sensitivity and 49.3% specificity; and 0.4136, with 40% sensitivity and 74.7% specificity, respectively (Table 3) (Fig. 1).

MANOVA was used to determine how the HEG and control groups differed in terms of the NLR, MLR and PLR. The NLR, MLR and PLR were used as the three dependent variables, and the group was used as the independent variable. Since the homogeneity of variance–covariance matrices, which is among the assumptions required to conduct this test, was not provided, Pillai's trace test was used. As a result of the analysis, it was determined that the groups had significant differences in the combined dependent variables (F = 4.938, $p = 0.002$, Pillai's trace = 0.048). When the dependent variables were

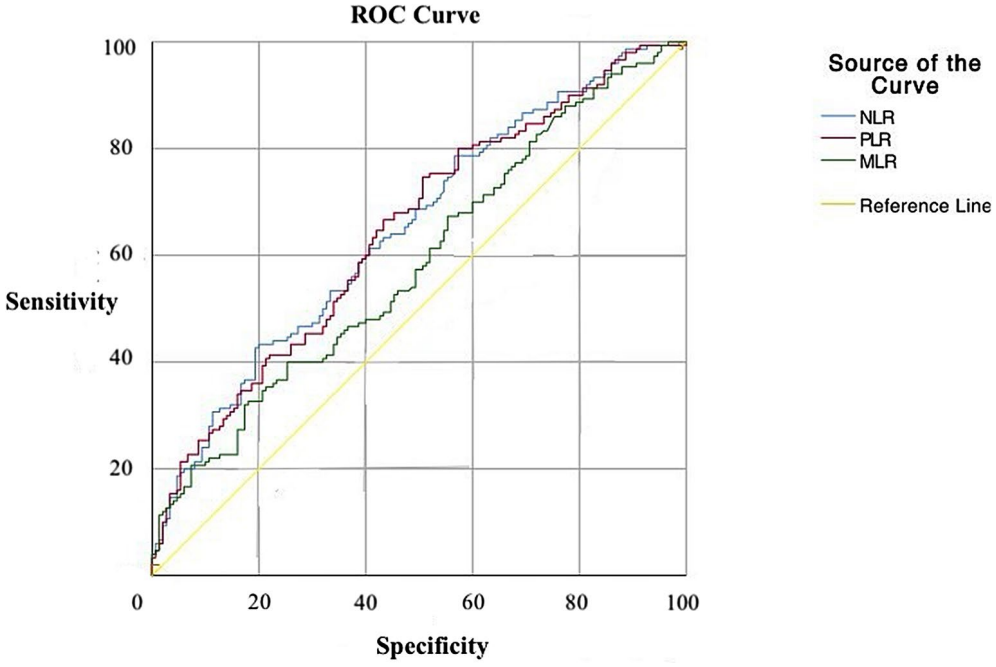


**Fig. 1** ROC curves for the NLR, PLR and MLR

**Table 4** Multiple logistic regression analysis of factors related to HEG

| Variable | OR (95% CI) | *P* value |
|---|---|---|
| NLR | 1.144 (1.072–1.221) | < 0.001 |
| Hb (g/dL) | 1.478 (1.200–1.821) | < 0.001 |
| Urine pH | 0.540 (0.363–0.802) | 0.002 |
| Urine density (g/ml) | 1.064 (1.025–1.104) | 0.001 |

Abbreviations: OR: Odds ratio

Note

[a]Variable(s) entered in step 1: NLR, PLR, MLR, Hb, Urine pH, Urine density. (These factors had a p value lower than 0.10 in the comparison of the HEG and control groups in Table 1 and the variables used for the calculation of the NLR, MLR and PLR omitted due to multicollinearity)

[b]We excluded the ketonuria variable although had a p value lower than 0.10 because all the values of the control group were 0. This affected the results and confidence intervals

[c]We used the backwards LR method for the selection of significant factors and the selection of variables was completed in Step 3: Hb, urine pH, urine density

[d]The goodness of the fit of model was good according to the Hosmer–Lemeshow Test ($p = 0.367$)

examined separately, statistically significant results were found for all the dependent variables depending on the group variable ($p < 0.001$ for the NLR, $p = 0.016$ for the MLR and $p = 0.007$ for the PLR).

In this analysis, logistic regression revealed significantly greater NLRs (OR 1.144, 95% CI: 1.072–1.221; $p < 0.001$), Hb levels (OR 1.478, 95% CI: 1.200–1.821; $p < 0.001$), urine pH levels (OR 0.540, 95% CI: 0.363–0.802; $p = 0.002$) and urine density levels (OR 1.064, 95% CI: 1.025–1.104; $p = 0.001$) in the HEG patients than in healthy controls (Table 4).

## Discussion

HEG is characterized by a complex pathophysiological mechanism in which inflammation is thought to be an important contributor [6]. Although many factors have been found to be involved in the aetiology of HEG, the effect of inflammation on the development of HEG has only begun to be accepted in recent years. Interest in the use of inflammatory indicators as diagnostic tools is increasing, although it remains limited. This study contributes to the literature by exploring the connection between HEG and inflammatory markers, with the hypothesis that patients with HEG present elevated values of these markers. The findings revealed that pregnant individuals with HEG presented elevated NLRs, PLRs, and MLRs compared with those with low-risk pregnancies. These results suggest that inflammation is part of the pathogenesis of HEG and that these indicators may be valuable in determining the severity of disease.

While HEG is diagnosed in patients with severe nausea and vomiting during pregnancy, it may lead to malnutrition and electrolyte imbalances and may be an indication for hospitalization [14]. Although the exact aetiology of HEG is not clearly known, it is suggested that HEG may occur due to various factors. These include psychological factors, hormonal changes, and abnormal gastrointestinal motility [15]. However, the overall influence of these factors has yet to be clearly defined. Furthermore, inflammation-related markers such as CRP and IL-6 levels are elevated in HEG patients, indicating that inflammation may be a part of the pathogenesis of the disease [16, 17].

Recent research has shown that systemic inflammatory markers such as the MPV, NLR, and PLR determined from complete blood counts have significant predictive and prognostic value in various conditions, including inflammatory and autoimmune disorders; gynaecological and gastrointestinal cancers; and preeclampsia and visual problems [11, 12, 18]. One study reported that both the NLR and the PLR were significantly greater in patients with HEG [7, 19, 20]. We found that the NLR, PLR and MLR values were significantly greater in the HEG group and were related to the severity of HEG. Our ROC curve revealed that the NLR, PLR, and MLR have moderate discriminative power in differentiating HEG patients from healthy pregnant women. While the sensitivity and specificity values for these markers are not high enough to serve as definitive diagnostic tools, they provide valuable insights into the inflammatory status of patients and may serve as adjunctive markers in the clinical evaluation of HEG.

Although patients with HEG should have haemoconcentration due to vomiting and dehydration, studies have shown that the Hb levels and WBC counts in HEG patients are not significantly different from those in control individuals [21, 22]. In our study, no significant difference was found in the WBC count and PLT levels between the HEG and control groups; however, a significant difference was detected in terms of the Hb level. Although LYM counts are typically thought to be greater in women with HEG [23], the literature presents conflicting findings. Some studies have shown that there is no change in LYM counts [21, 24], whereas others have shown lower counts in the HEG group [7]. In our study, we did not observe any significant difference in LYM counts between the HEG group and the control group. The MPV is an indicator of PLT activation and indicates changes in PLT size. This parameter can be easily assessed using a complete blood count device. Markers indicating PLT activation have been utilized in the diagnosis of various inflammatory diseases [25]. However, no statistically significant difference was reported in the literature when the MPV was investigated in patients diagnosed with HEG [7, 20], whereas a significant difference was found in one study [26].

Ketonuria is commonly used in the diagnosis of HEG [27]. Ketonuria serves as a parameter to assess the metabolic consequences and clinical outlook of patients with HEG; however, its relationship with the severity of HEG remains unclear. Various studies have explored this connection. One study reported that ketone levels in HEG patients were associated with longer hospital stays [28]. In contrast, some studies have shown that ketone levels have no direct relationship with the clinical severity of HEG [29, 30]. One study reported a positive correlation between the level of ketones in urine and the NLR and PLR [31]. We evaluated the same relationship in HEG patients. However, we did not find any significant relationships between ketonuria and inflammatory markers such as the NLR, PLR and MLR.

Our study has several limitations. First, our study had a retrospective design. Dehydration and malnutrition may increase the systemic inflammatory response. This point should be considered. Owing to the retrospective nature of the study, this question could not be answered according to the study results. Second, we did not use a scoring system that would allow more specific assessment of HEG. Third, we could not include the CRP level, sedimentation rate, or IL-6 level in our study because these parameters were not measured via routine screening in all patients.

In conclusion, our study demonstrated that the NLR, PLR, and MLR are elevated in pregnant women with HEG, supporting the hypothesis that inflammation is a part of the pathophysiology of this condition. However, the lack of correlation between these markers and the severity of ketonuria suggests that the relationship between inflammation and HEG is complex and multifaceted. New studies should be conducted to elucidate the mechanisms of HEG development and to investigate the advantages of the use of these markers in its management.

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#### Author contributions
All authors listed have made a substantial, direct, and intellectual contribution to the work as follow: Conceptualization, C.A. and G.U.; methodology, A.Z.N., S.A., and G.U.; software, F.I.A.; formal analysis, F.I.A. and S.K.; investigation, S.K. and C.A.; resources, G.U.; responsible for data collection, S.A.; data curation, S.A.; writing-original draft preparation, S.K., F.I.A.; writing-review and editing, A.Z.N., F.I.A.; visualization, A.Z.N.; supervision, C.A.; All authors have read and agreed to the published version of the manuscript.

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#### Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

#### Ethics approval and consent to participate
The study was conducted in accordance with the guidelines of the Helsinki Declaration. Written informed consent was obtained from all participants. The study was approved by the ethics committee of the University of Health Science Adana City Training and Research Hospital (Date: 17.08.2023, Decision No: 2782).

#### Consent for publication
Not applicable.

#### Competing interests
The authors declare no competing interests.

**Consort statement**
Our study adheres to the Consort guidelines.

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