Evaluation of the Relationship Between Hyperemesis Gravidarum With Hemoglobin to Red Cell Distribution Width Ratio and Eosinophil to Lymphocyte Ratio

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Abstract

**Introduction:** This study, it was aimed to investigate the relationship between the severity of hyperemesis gravidarum (HEG) disease and subclinical inflammatory factors such as Hemoglobin to red cell distribution width ratio (HRR), platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), monocytes to lymphocyte ratio (MLR), eosinophil to lymphocyte ratio (ELR), which are known to be closely associated with inflammation in patients with hyperemesis gravidarum.

**Material method:** This retrospective case control study was conducted between December 2020 and December 2021. A total of 215 pregnant women, 121 with hyperemesis gravidarum and 94 healthy pregnant women, were included in the study. HEG patients were divided into three groups according to the modified PUQE classification as mild (n=38), moderate (n=41), and severe (n=42).

**Results:** HRR, PLR, NLR, and MLR values were found to be statistically significantly higher in the HEG group compared to the control group, and ELR values were lower (p<0.05). MON, NEU, PCT, PLR, NLR, MLR values increase from mild to severe in HEG patients. EO, LYM, and ELR values decreased (p<0.05). There was a positive correlation between HEG and PCT (rho=0.45, p< 0.001), PLR (rho=0.76, p< 0.001), NLR (rho=0.79, p< 0.001), MLR (rho=0.81, p< 0.001) values. There was a significant negative correlation between ELR (rho= 0.72, p< 0.001) and HEG.

**Conclusion:** NLR, PLR, and PCT are inflammatory markers that increase in patients with HEG and have predictive value for HEG development. In our study, we suggested the use of two new prognostic markers for patients with HEG. We think that our study will be a source for further studies on the subject.

Introduction

Nausea and vomiting are common during pregnancy. It is an uncomfortable condition that most pregnant women experience with varying severity. It is among the most common causes of hospitalization in the first trimester of pregnancy [1]. Hyperemesis gravidarum (HEG), a severe form of nausea and vomiting in pregnancy, can cause a loss of more than 5% of body weight, electrolyte, fluid, and acid base imbalances, and the nutritional deficiency [2]. Although the prevalence of HEG varies between societies, it affects approximately 0.5%-2% of all pregnancies. In addition, it is known that the risk of recurrence increases in pregnant women with a previous HEG history [3].

There are several possible mechanisms suggested being involved in the pathogenesis of HEG. Many different pathological conditions such as hormonal changes, immunological mechanisms, Helicobacter pylori infection, abnormal gastric motility, genetic predisposition, liver dysfunction have been counted [4]. The role of inflammation in the pathogenesis of HEG is not clear enough. In some studies, it is stated that there are important links between indicators of inflammation and HEG [5-6].

As a result of chronic inflammation, thrombocytosis and proliferation occur in the blood precursor series. In addition to its role in coagulation and hemostasis, platelets also have a role in regulating inflammatory
Although complete blood count (CBC) is a simple and inexpensive method, it contains important parameters for the diagnosis of many diseases. While there are more expensive methods to evaluate the inflammatory process, white blood cell (WBC), platelet distribution width (PDW), mean platelet volume (MPV), red cell distribution width (RDW), neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and platelet crit (PCT) have been shown to reflect disease activity [8-9].

Neutrophils are a type of white blood cell that plays an important role in the body’s protection and defense. Lymphocytes are another type of white blood cell that is very important in the formation of the body’s immune response. Red cell distribution width (RDW) is a blood parameter that is measured depending on the distribution of erythrocytes over diameter or volume and has a close relationship with inflammatory factors [10]. Hemoglobin (Hb) and RDW are markers derived from red blood cells. It has been reported that these two markers reflect inflammation and correlate with cancer prognosis [11-12]. In some cancers, Hb and RDW have each been shown to be prognostic on their own. There are limited studies on the HB/RDW (HRR) ratio, which is used as a very new marker. Studies on the HRR value were specially conducted on cancer patients [13].

The aim of this study is to investigate whether HRR and ELR, which are very new parameters that have never been studied in this disease until now, as well as PLR, NLR, and MLR, will be predictive parameters for the severity of Hyperemesis Gravidarum disease

**Methods**

This retrospective case control study was conducted in the Gynecology and Obstetrics Unit of Van Training and Research Hospital. Data were obtained by examining the records of pregnant women hospitalized with the diagnosis of HEG between December 2020 and 2021. This study was conducted in line with the principles of the Declaration of Helsinki. Ethics committee approval was obtained for the study from the Van Ministry of Health University Training and Research Hospital Clinical Research and Ethics Committee with the decision number 2022/02-01 dated 18.01.2022. Verbal informed consent was obtained from all participants included in the study. A total of 215 pregnant women, including 121 pregnant women with hyperemesis gravidarum and 94 healthy pregnant women between 5-16 weeks of age, were included in the study.

The following criteria were used for the diagnosis of HEG:

1. Weight loss of 5% or more since the beginning of pregnancy
2. Vomiting at least three times a day
3. A ketonuria value of +1 or higher on a urinalysis test;

The Pregnancy Unique Quantification of Emesis/Stomach (PUQE) scoring system was used to determine severity. The PUQE score was calculated by adding the scores of the answers to the three questions. In
the original PUQE index, these questions ask how many times the patient has felt nauseous or nauseous, vomited, and retching or dry blistering in the past 12 hours. In a modified PUQE index, these symptoms were questioned for the past 24 hours. Scores from 1 to 5 were added for each question to determine the PUQE score. A patient's PUQE score can range from 4 to 15. A PUQE score of \( \leq 6 \) is classified as a mild case of HEG, between 7 and 12 as moderate and \( \geq 13 \) as severe HEG [14-15]. The same scoring system was applied for the modified PUQE used in our study. Body mass index (BMI) (kg/m2) was obtained by dividing body weight (kg) by height (m2) squared. Gestational age was determined using the first day of the last month and confirmed by sonographic examination.

Exclusion criteria: Smoking, urinary tract infections, previously diagnosed psychological disorders, gastrointestinal disorders, multiple pregnancies, eating disorders, and thyroid disorders.

From the medical records of the patients, HRR, ELR, NLR, PLR, PDW, MPV, PCT, Monocyte count (MON), White blood cell (WBC) count, Neutrophil count (NEU), Hemoglobin (Hb), Lymphocyte count (LYM), Platelet count number (PLT) and ketonuria results were pooled.

**Statistical Analysis**

Statistical analysis was performed using SPSS version 22.0. Shapiro–Wilk test was used to assess whether the variables followed normal distribution or not. Variables were reported as mean (minimum: maximum) values. A Mann–Whitney U test was used to compare patients in the Hyperemesis gravidarum (HEG) and control groups. In order to estimate the sensitivity and specificity of the NLR, PLR, MLR, ELR, HRR, and PCT values for predicting a diagnosis of HEG, receiver operatör curve (ROC) analysis was performed. A Kruskal–Wallis test was performed to compare patients with mild, moderate, and severe HEG. Moreover, a Mann–Whitney U test was used for pair wise comparison. A Spearman's correlation test was performed to determine whether there was a correlation between PCT, HRR, PLR, NLR, MLR, ELR, and HEG groups. The level of significance was set at \( \alpha = 0.05 \).

**Results**

Demographic characteristics and laboratory findings of the patients are shown in Table 1. There was no significant difference between HEG and control groups in terms of age, gestational age, and parity. BMI was found to be significantly lower in the HEG group (p<0.001). WBC, HB, PLT, MON, NEU, PCT, MPV, HRR, PLR, NLR, and MLR values were higher in the HEG group. MCV, EO, LYM, RDW, ELR values were found to be higher in the control group. There was no significant difference between the groups according to the PLT value (p>0.05).
|                                | Control group (n=113) | HEG group (n=102) | p  |
|--------------------------------|-----------------------|-------------------|----|
| **Age**                        | 29.3894 (18.00-42.00) | 29.7745 (19.00-43) | 0.63<sup>a</sup> |
| **Gravida**                    | 1 (1-4)               | 1 (1-4)           | 0.67<sup>a</sup> |
| **Gestational age (week)**     | 10.53 (7-12)          | 10.34 (7.00-12)   | 0.43<sup>a</sup> |
| **Parity (number)**            | 1 (0:5)               | 1 (0:5)           | 0.30<sup>a</sup> |
| **Body mass index (kg/m2)**    | 26.70 (22.10-30.10)   | 26.30 (22.10-30.20) | 0.001<sup>a</sup> |
| **WBC**                        | 6.5513 (5.30-8.20)    | 9.7940 (4.73-15.80) | 0.001<sup>a</sup> |
| **HB(g/dl)**                   | 12.9239 ±1.06         | 13.4814 ±1.19     | 0.001<sup>b</sup> |
| **MCV**                        | 92.2124 (90.50-96.00) | 86.2706 (73.10-99.70) | 0.001<sup>a</sup> |
| **PLT(10<sup>3</sup>/µl)**     | 265.4867 (195000-355000) | 271.9412 (166000-409000) | 0.48<sup>a</sup> |
| **MON(10<sup>3</sup>/µl)**     | 0.3762 (0.21-0.55)    | 0.5152 (0.23-0.94) | 0.01<sup>a</sup> |
| **EO(10<sup>3</sup>/µl)**      | 0.0920 (0.01-0.66)    | 0.0377 (0.01-0.09) | 0.001<sup>a</sup> |
| **NEU (10<sup>3</sup>/µl)**    | 3.4599 (2.21-10.33)   | 11.4087 (3.83-19.95) | 0.001<sup>a</sup> |
| **LYM (10<sup>3</sup>/µl)**    | 2.1245 (0.61-5.31)    | 1.4318 (0.70-1.98) | 0.001<sup>a</sup> |
| **PCT(%)**                     | 0.1978 (0.16-0.23)    | 0.2789 (0.17-0.56) | 0.001<sup>a</sup> |
| **RDW(%)**                     | 16.4965 (16.10-16.50) | 16.0735 (15.30-16.70) | 0.001<sup>a</sup> |
| **MPV(fl)**                    | 8.62 ±0.42            | 10.1765 ±0.95     | 0.001<sup>b</sup> |
| **HRR(%)**                     | 0.9802 (0.79-1.17)    | 1.0063 (0.66-1.27) | 0.04<sup>a</sup> |
| **PLR(%)**                     | 142.6973 (62.10-581.97) | 205.8392 (84.34-422.50) | 0.001<sup>a</sup> |
| **NLR(%)**                     | 1.8496 (0.42-8.07)    | 9.4553 (2.03-27.30) | 0.001<sup>a</sup> |
| **MLR(%)**                     | 0.1989 (0.06-0.56)    | 0.4041 (0.14-1.34) | 0.001<sup>a</sup> |
| **ELR(%)**                     | 0.0515 (0.001-0.32)   | 0.0245 (0.01-0.05) | 0.001<sup>a</sup> |
The levels of categories are presented as the mean standard deviation for parametric variables and median (min-max) for nonparametric variables. Values in bold represent statistically significant outcomes. Abbreviations: WBC; White Blood Cell, Hb; hemoglobin, PLT; platelet count, MON; monocyte count, EO; eosinophil count, NEU; neutrophil count, LYM; lymphocyte count, PCT; platelet crit, RDW; red cell distribution width, MPV; mean platelet volume; HRR; Hemoglobin to red cell distribution width ratio, PLR; platelet to lymphocyte ratio, NLR; neutrophil to lymphocyte ratio, MLR: monocytes to lymphocyte ratio, ELR: eosinophil to lymphocyte ratio. a Mann–Whitney U test, and b independent sample t test.

Comparison of HEG subgroups according to laboratory values is summarized in Table 2. MON, NEU, PCT, PLR, NLR, MLR values increase from mild group to severe group. On the other hand, EO, LYM, and ELR values are decreasing. A significant difference was found between the mild to the moderate group and the moderate to severe group according to MPV value (p<0.05). There was no significant difference between RDW and HRR values and HEG groups (p>0.05).
Table 2
Comparison of the Laboratory parameters of mild, moderate, and severe HEG groups.

|                  | Mild (n=38) | Moderate (n=32) | Severe (n=32) | p     |
|------------------|-------------|-----------------|---------------|-------|
| MON\(10^3/\mu l\) | 0.43 (0.39-0.47) | 0.52 (0.43-0.57) | 0.60 (0.48-0.78) | 0.001 |
| EO\(10^3/\mu l\)  | 0.05 (0.05-0.06)  | 0.04 (0.03-0.05)  | 0.01 (0.01-0.01)  | 0.001 |
| NEU \(10^3/\mu l\) | 7.10 (4.90-8.77)  | 11.14 (10.23-12.27) | 16.77 (15.92-16.37) | 0.001 |
| LYM \(10^3/\mu l\) | 1.81 (1.84-1.88)  | 1.42 (1.41-1.43)  | 0.99 (0.80-1.12)  | 0.001 |
| PCT(%)           | 0.24 (0.22-0.28)  | 0.27 (0.24-0.32)  | 0.32 (0.27-0.36)  | 0.001 |
| RDW(%)           | 16.06 (15.90-16.20) | 16.00 (15.80-16.20) | 16.15 (15.92-15.37) | 0.14  |
| MPV(\text{fl})   | 10.29 (9.50-11.10) | 9.78 (9.10-10.40)  | 10.43 (9.80-11.17) | 0.016 |
| HRR(%)           | 1.00 (0.96-1.08)  | 0.97 (0.91-1.07)  | 1.03 (0.95-1.15)  | 0.143 |
| PLR(%)           | 148.68 (123.04-171.50) | 189.12 (168.82-211.23) | 290.42 (231.41-345.60) | 0.001 |
| NLR(%)           | 3.94 (3.07-4.72)  | 7.84 (7.26-8.62)  | 17.60 (14.34-22.12) | 0.001 |
| MLR(%)           | 0.23 (0.21-0.26)  | 0.36 (0.30-0.40)  | 0.63 (0.46-0.78)  | 0.001 |
| ELR(%)           | 0.03 (0.02-0.03)  | 0.02 (0.02-0.03)  | 0.01 (0.00-0.14)  | 0.001 |

Values are expressed as mean and inter quartile ratios (IQR) 25–75%. MON; monocytes, EO; eosinophil, NEU: neutrophil, LYM: lymphocyte, PCT; platelet crit, RDW; red cell distribution width, MPV; mean platelet volume; HRR; Hemoglobin to red cell distribution width ratio, PLR: platelet to lymphocyte ratio, NLR: neutrophil to-lymphocyte ratio, MLR: monocytes to lymphocyte ratio, ELR: eosinophil to lymphocyte ratio. Bold p values indicate statistically significant.

The correlation between HEG and PCT, HRR, PLR, MLR, ELR values is shown in Table 3. A significant positive correlation was found between HEG and PCT, PLR, NLR, MLR values \((p<0.05)\). There was a significant negative correlation between ELR value and HEG \((p<0.05)\). There was no significant relationship between HRR and HEG \((p>0.05)\).
Table 3

Correlation between Hyperemesis gravidarum and PCT, HRR, PLR, NLR, MLR, ELR.

|     | R    | P    |
|-----|------|------|
| PCT | 0.458 | 0.001 |
| HRR | 0.075 | 0.452 |
| PLR | 0.760 | 0.001 |
| NLR | 0.930 | 0.001 |
| MLR | 0.815 | 0.001 |
| ELR | -0.728 | 0.001 |

Abbreviations: HRR; Hemoglobin to red cell distribution width ratio, PLR: platelet to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, MLR: monocytes to lymphocyte ratio, ELR: eosinophil to lymphocyte ratio. Bold p values indicate statistically significant.

The effect of HRR, PLR, NLR, MLR, ELR, and PCT on the diagnosis of HEG was determined by the ROC curve (Figure 1). Areas under the curve for HRR, PLR, NLR, MLR, and PCT were 0.58, 0.76, 0.96, 0.87, and 0.91, respectively (p<0.05). NLR > 3.06, PLR > 155.46, PCT > 0.22, MLR > 0.22, and HRR > 0.97 were significantly associated with increased risk of HEG. The values of ELR for the area under the curve were not statistically significant.

**Discussion**

HEG has a pathophysiological mechanism that depends on many causes. Inflammation has a critical role in HEG [16]. HEG may be severe enough to require hospitalization. It may even progress to central pontine myelinolysis and Wernicke's encephalopathy. Therefore, early diagnosis and treatment of HEG are very important for maternal and child health [17].

Although the link between HEG and inflammation is not fully understood, studies on inflammation markers in HEG patients suggest that there is a strong relationship between them [6,18]. The role of inflammatory processes in the development of HEG has been studied from various aspects. WBC, neutrophil, monocytes, lymphocyte, basophil, and eosinophil counts, which are among the hematological parameters, are important determinants of the inflammatory process. While neutrophils are common in active inflammation, lymphocyte counts reflect the regulatory pathway of the same process [19].

Caglayan et al.’s studies, no significant difference was found between the HEG and control groups in terms of lymphocyte and neutrophil counts [6]. Differently, in another study, neutrophil and monocyte counts were higher in the HEG group, while lymphocyte counts were higher in the control group [20]. In another clinical study, neutrophil levels were found to be higher in the HEG group, while the lymphocyte count was found to be lower [21]. In our study, monocyte and neutrophil counts were found to be
significantly higher in the HEG group compared to the control group. Eosinophil and lymphocyte levels were found to be lower. In addition, when the HEG subgroups are compared, monocyte and neutrophil counts increase, and eosinophils and lymphocyte counts decrease from mild to severe groups.

Mean platelet volume (MPV) is a machine calculated measurement of the average size of platelets present in the blood and is typically included in blood tests as part of the CBC. MPV is an indicator of inflammation due to increased destruction of platelets [22]. There are studies showing that there is no difference between the HEG group and control groups in terms of MPV values [23-24]. Differently, MPV values were found to be higher in the HEG group in our study. In addition, a significant difference was found between the mild to moderate group and the moderate to severe group according to MPV value (p<0.05).

Recently, it has been stated that inflammatory markers such as PCT, RDW, and MPV obtained from complete blood count have prognostic and predictive properties in various diseases such as gynecological and gastrointestinal malignancies, autoimmune diseases, and coronary artery diseases [25-26]. There are not many studies on the relationship between PCT and HEG. Tayfur et al.’s PCT values were found to be higher in women with HEG in their study. In the same study, mild, moderate, and severe HEG cases were compared and it was stated that PCT values were higher in severe HEG cases [21]. In our study, PCT values were found to be significantly higher in the HEG group than in the control group. In addition, mild, moderate, and severe HEG cases were compared, and PCT values increase as one goes from the mild group to the severe group. A positive and significant relationship was found between PCT values and HEG.

RDW, another parameter in the complete blood count, shows the distribution of red blood cell sizes. RDW tends to increase hemolysis and red blood cell production disorders. RDW is mainly used for diagnosing anemia. It has been shown that RDW is increased in acute and chronic conditions such as pulmonary embolism, acute renal failure, and skin disease [27].

It is reported that HRR alone is a stronger prognostic indicator than Hb or RDW. As the reason for this, it is thought that combining the prognostic information from Hemoglobin and RDW by HRR will provide more information than a single variable [13]. HRR is a recently used inflammatory marker derived from Hb and RDW, which are complete blood count parameters used in routine practice. In addition, it has been shown to be a bad prognostic factor alone in many cancers such as stomach cancer and lung cancer [28-29]. Cintesun et al.’s found no significant difference in RDW between the HEG and control groups in their study. In the same study, only a relationship was found between RDW and ketonuria among the available parameters. Contrary to this study, RDW was found to be higher in the control group compared to the HEG group in our study. However, no significant difference was observed between mild, moderate, and severe groups [30].

HEG patients are expected to develop hemoconcentration due to vomiting and dehydration. Bulanik et al.’s Hemoglobin and white blood count (WBC) values were not different from the control group in their
study [31]. Unlike this study, in our study, WBC values were found to be higher in the HEG group than in
the control group.

PLR and NLR are used as important markers in many diseases such as Diabetes Mellitus, kidney failure,
heart diseases, inflammatory diseases, autoimmune diseases, and hypertensive disorders [32]. It is stated
that these two special indicators increase gastrointestinal diseases, gynecological diseases,
malignancies, cardiac diseases, and inflammation [33-34]. Looking at the literature, there are a few
studies on the severity of MLR, PLR, NLR, and HEG. Soysal et al.’s In the study conducted by MLR, PLR,
and NLR levels were reported to be higher in the patient group. In the same study, a significant correlation
was found between increasing ketonuria levels and MLR, PLR, and NLR [20]. In another study, PLR and
NLR levels were found to be high in HEG patients. However, no correlation was found between PLR and
NLR values and the degree of ketonuria [30]. Kan et al.’s In their study, PLR, and NLR levels were found to
be higher in the HEG group. However, no correlation was found between the severity of the disease and
PLR and NLR values [35]. In another similar study, a significant relationship was found between NLR
levels and HEG groups [5]. In our study, PLR, NLR, and MLR values were found to be higher in the HEG
group. PLR, NLR, MLR values increase as one goes from the mild group to the severe group. A significant
positive correlation was found between HEG group and PLR, NLR, and MLR values (p<0.05). NLR> 3.06,
PLR> 155.4, and MLR> 0.22 rates were determined statistically and these parameters were significantly
associated with increased risk of HEG disease.

There is no study in the literature regarding HRR in patients with hyperemesis gravidarum. We believe that
the data we obtained in this study will lay the groundwork for future studies. In our study, HRR levels were
found to be significantly higher in the HEG group than in the control group. When the HEG subgroups
were examined, no significant difference was observed between mild, moderate and severe groups. There
was no significant correlation between HRR and HEG (p>0.05). However, in our ROC analysis, the rate of
HRR>0.97 was detected and it was found to be significantly associated with increased risk of HEG.

Eosinophil lymphocyte ratio (ELR) is a new marker evaluated in inflammation and malignancies. In one
study, high ELR levels were associated with smoking. It has been said that it may be a useful indicator of
systemic disease [36]. It has been reported that ELR helps in distinguishing those with and without
hypersensitivity to non steroidal anti inflammatory drugs in patients with bronchial asthma [37]. In
addition, it has been reported that increased ELR level worsens the survival of endometrial cancer and is
associated with the high risk group [38]. There are not many studies on ELR in the obstetric field in the
literature. It is seen that some studies have been done in other medical fields. Our study is the first in the
literature investigating the relationship between ELR and HEG patients. In our study, ELR levels were
found to be significantly higher in the healthy control group. However, in HEG subgroups, the level of ELR
decreases from mild to severe. In addition, a negative correlation was found between ELR value and HEG
in the correlation study. However, according to the data we obtained, ELR levels were not associated with
an increased risk of HEG disease.
Limitations of this study: First, the patient data was single center, the number of patients was not very large, and it was a retrospective study. Second, only HRR, PLR, NLR, ELR, MLR, and other hematological parameters are used as inflammatory markers. The strength of our study is that it is the first study that will lead to the demonstration of the relationship of MLR, PLR, and NLR as well as the new parameters ELR and HRR with HEG.

Conclusion

NLR, PLR, and PCT are inflammatory markers that increase in patients with HEG and have predictive value for HEG development. In our study, we suggested the use of two new prognostic markers for patients with HEG. These are the Hb/RDW ratio and the eosinophil to lymphocyte ratio (ELR), which are viably operated at no additional cost. Since the relationship of HRR, ELR markers with HEG has not been definitively investigated, we cannot make a definitive statement about their clinical use yet. ELR and HRR may prove to be markers of HEG as more data are collected on HRR and ELR levels to demonstrate the relationship between HEG and inflammation. We think that our study will be a source for further studies on the subject.

Declarations

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The author disclosed that they did not receive any grant during conduction or writing of this study.

Author Contribution

KN: Project development, Data collection and management, Data analysis, Manuscript writing and editing. YB: Project development, Data collection and management, Data analysis, Manuscript writing and editing. İN: Project development, Data collection and management, Data analysis, Manuscript writing and editing.

Ethics approval

This study was conducted in line with the principles of the Declaration of Helsinki. Ethics committee approval was obtained for the study from the Van Ministry of Health University Training and Research Hospital Clinical Research and Ethics Committee with the decision number 2022/02-01 dated 18.01.2022.

Informed consent
Informed consents were obtained from the study participants.

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**Figures**
Figure 1

Receiver operating characteristic curves hemoglobin to red cell distribution width ratio (HRR), platelet lymphocyte ratio (PLR), neutrophil lymphocyte ratio (NLR), monocytes to-lymphocyte ratio (MLR), eosinophil to lymphocyte ratio (ELR), and platelet crit (PCT) for the diagnosis of hyperemesis gravidarum.