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Evaluation of the Relationship between Inflammatory Markers and Patients with Hyperemesis Gravidarum

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Abstract: Background: Hyperemesis gravidarum (HG): is a more severe type of nausea and vomiting in pregnancy which is different to NVP and can cause dehydration, weight loss and electrolyte imbalance. The disease mechanism is unknown, but there is some evidence of a systemic inflammatory process. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and C reactive protein (CRP) have been suggested as possible diagnostic and prognostic markers.

Method: A case–control study was carried out at the Maternity and Pediatrics Teaching Hospital in Al Diwaniyah from February to December 2024. Twenty pregnant women with HG and 20 healthy women were enrolled; all pregnant women were <16 weeks' gestation. Demographic, PUQE, and laboratory investigations, such as CBC, coagulation profile, urinalysis, liver and renal function, thyroid function, and inflammatory markers (NLR, PLR, CRP) were gathered. Data were analyzed statistically using SPSS with p value of ≤ 0.05.

Results: There were no significant differences in baseline characteristics between groups (age, BMI, gestational age, gravidity). HG patients showed significantly higher neutrophil and platelet counts, elevated NLR (4.21 vs. 2.89, p = 0.002), PLR (133.45 vs. 115.58, p = 0.008), and CRP (1.04 vs. 0.34 mg/dL, p < 0.001). Severity analysis showed that corresponding to the severity of the disease, there is a correlation between the CRP count and the severity of the disease (p = 0.010) and the platelet count (p = 0.043). ROC analysis revealed that CRP was able to show its diagnostic usefulness with an AUC value of 0.798, specificity of 100%, and an accuracy of 79.8% at a cut-off point of >0.61 mg/dL.

Conclusions HG is accompanied by a strong systemic inflammatory response. Increased CRP and platelets are associated with severity and could be used as low cost and easily available markers for diagnosis and clinical management. To confirm these findings and investigate specific anti inflammatory treatments, larger and multi center studies are recommended.

Key words: Hyperemesis gravidarum, Inflammatory markers, C reactive protein (CRP), Neutrophil to lymphocyte ratio (NLR)

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1. Introduction

The most severe form of nausea and vomiting during pregnancy is hyperemesis gravidarum (HG), occurring in around 0.3–2% of pregnancies, and being the main cause of first trimester (1stT) hospitalisation (1,2). HG is distinguished from the typical vomiting that occurs during pregnancy by the fact that it involves vomiting that is so frequent, severe, and persistent as to cause dehydration, weight loss of more than 5% of pre-pregnancy body weight, ketonuria, electrolyte imbalance, and malnutrition (2). Symptoms typically start between the 4th and 9th week of gestation, intensify in the 12th to 15th week of gestation, and can last until the end of the 20th week of gestation (3). The severity of HG can be determined with the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score (5,6).

The causes of HG are still unknown and seem to be complex. Previous history of HG, multiple pregnancy, primigravida, fetal sex (female), psychiatric disorder, abnormal pre-pregnancy BMI, young maternal age, diabetes mellitus, molar pregnancy, and ART (assisted reproductive technology) are the known risk factors (7). Other polymorphisms in the GDF15 and IGFBP7 genes (5,8) may also play a role in disease development.

The serious complications that can occur to the mother as a result of HG include dehydration, electrolyte imbalance, vitamin deficiencies, Wernicke's encephalopathy, liver dysfunction, and psychological problems such as anxiety and depression (12). While the exact pathophysiological mechanisms are not well understood, the evidence is growing that inflammation is a large part of the reason for the development of HG (14,15). There are several inflammatory markers that have been studied in relation to HG severity: the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), platelet distribution width (PDW), and C-reactive protein (CRP) (16-18). Further, increased levels of pro-inflammatory cytokines like tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) have been noted in HG patients, suggesting that HG could be an inflammatory disorder (17,19).

Of these markers, NLR and PLR have been reported as easy to obtain, inexpensive, and readily available markers of systemic inflammation, and several studies have reported significantly elevated levels in HG women compared to healthy pregnant women (15,20,21). In addition, novel composite inflammatory markers like the Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and Aggregate Systemic Inflammation Index (AISI) have recently been described as possibly more reliable markers of inflammatory status in HG (25,26). However, the current results are inconclusive and additional research is needed to understand the link between inflammatory markers and severity of HG.

This study aimed to evaluate the relationship between the severity of hyperemesis gravidarum and inflammatory markers: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and C-reactive protein (CRP) in patients with hyperemesis gravidarum.

2. Patients and Methods:

2.1 Study design and sample size:

The current case–control study was carried out in the Maternity and Pediatrics Teaching Hospital in Al-Diwaniyah from February to December 2024. 40 pregnant women with singleton pregnancies and gestational age < 16 weeks were enrolled. The patients were randomly divided into 2 groups including 20 patients with hyperemesis gravidarum (HG) and 20 healthy pregnant women as controls. The major aim was to assess the diagnostic and predictive significance of inflammatory markers namely, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and level of C-reactive protein (CRP) with respect to the severity of HG.

Inclusion Criteria include Pregnant women diagnosed with hyperemesis gravidarum (HG) based on the Pregnancy-Unique Quantification of Emesis (PUQE) score were included in the study. Participants eligible for the study were those with a gestation age of 6 to 16 weeks, as determined by accurate last

menstrual period (LMP) and ultrasound examination. There was an exclusion criterion of pregnancy women with a history of systemic or chronic diseases, such as gastrointestinal or endocrinologic (diabetes or thyrotoxicosis), infectious, psychological and inflammatory diseases. Women who smoked or took drugs that have a known nausea and vomiting effect were also excluded. Other exclusion criteria were: urinary tract infection (UTI), documented eating disorders, body mass index (BMI) outside the normal range (18.5 to 24.9 kg/m²) and non-singleton pregnancies.

2.2 Data collection

A. History Taking

All participants underwent a comprehensive history assessment, including Personal history (age, prior diagnoses of diabetes mellitus, hypertension, or other systemic diseases), Present history (analysis of current complaints and symptom progression) and Drug history.

B. Physical Examination

A general examination was performed to assess hydration status and exclude systemic disease. Clinical signs of dehydration included thirst, concentrated urine, reduced urinary frequency, dizziness, fatigue, dry mucous membranes, and sunken eyes. Vital signs (blood pressure, temperature, heart rate, respiratory rate) were recorded, along with inspection for pallor, cyanosis, jaundice, and lymphadenopathy. Anthropometric measurements (weight and height) were obtained to calculate body mass index (BMI).

C. PUQE Scoring

The Pregnancy-Unique Quantification of Emesis (PUQE) score was administered to all participants to evaluate the severity of nausea and vomiting. The questionnaire consists of 3 parts and assessed duration of nausea, frequency of vomiting, and retching episodes over the last 24 hours (Table1). Scores ranging from 3–15. Scores of 3–6 indicated mild symptoms, 7–12 moderate, and 13–15 severe hyperemesis gravidarum.

Table 1. Pregnancy-Unique Quantification of Emesis (PUQE)

Item	Response Options	Score
1. Duration of nausea	> 6 hours	5
	4–6 hours	4
	2–3 hours	3
	≤ 1 hour	2
	Not at all	1
2. Number of vomiting episodes	≥ 7 times	5
	5–6 times	4
	3–4 times	3
	1–2 times	2
	Not at all	1
3. Number of retching episodes	≥ 7 times	5
	5–6 times	4
	3–4 times	3
	1–2 times	2
	Not at all	1

D. Laboratory Investigations

Routine laboratory tests included: Complete blood count (CBC), Coagulation profile (PT, PTT, INR), Urinalysis and ketonuria, Urea and electrolytes, Liver function tests (ALT, AST) and renal function (creatinine) ,Random blood sugar (RBS) and Thyroid function (TSH, Free T3, Free T4) In addition, inflammatory markers—neutrophil-to-lymphocyte ratio (NLR), platelet-to lymphocyte ratio (PLR), and

C-reactive protein (CRP)—were measured for all participants.

2.3 Statistical analysis

Data entry and analysis were performed using IBM SPSS Statistics (Chicago, USA). Results were expressed as counts, percentages, means, standard deviations (SD), minimum (Min), and maximum (Max), and presented in tables, charts, or graphs. Categorical variables were analyzed using Chi-square or Fisher's exact test, and continuous variables using Student's t-test or Mann–Whitney U test, as appropriate. A p value ≤ 0.05 was considered statistically significant.

2.4 Ethical considerations and official approvals

Written informed consent was obtained from all participants prior to data collection with maintaining strict confidentiality throughout the study. The study protocol was reviewed and approved by the Ethics Committee of the Iraqi Board of Medical Specialization and the Department of Obstetrics and Gynecology at Maternity and Pediatrics Teaching Hospital in Al-Diwaniyah. Approval was granted under reference number 102, dated 23/1/2024.

3. RESULTS

Demographic Characteristics

A total of 40 pregnant women were included in the study, comprising 20 patients with Hyperemesis Gravidarum (HG group) and 20 healthy pregnant women (control group). Analysis of demographic characteristics revealed no significant differences between the two groups for mean age (25.80 ±2.97 years for HG vs. 25.95 ±3.50 years for control, p = 0.395), mean Body Mass Index (BMI) (23.55 ±2.71 kg/m² for HG vs. 23.12 ±2.31 kg/m² for control, p = 0.274), mean gestational age (11.55 ±2.52 weeks for HG vs. 11.85 ±1.76 weeks for control, p = 0.518), or gravidity distribution (p = 0.749). These findings indicate that the study and control groups were well-matched for these baseline characteristics (Table 3.1).

Table 3.1: Demographic characteristics of participating pregnant women compared between study and control groups

Characteristic	HG group (n = 20) Mean ±SD	Control group (n = 20) Mean ±SD	*P*-value
Age (years)	25.80 ±2.97	25.95 ±3.50	0.395
BMI (kg/m²)	23.55 ±2.71	23.12 ±2.31	0.274
Gestational age (weeks)	11.55 ±2.52	11.85 ±1.76	0.518
	N(%)	N(%)	
Gravidity (Primigravida)	11 (55.0 %)	12 (60.0 %)	0.749
Gravidity (Multigravida)	9 (45.0 %)	8 (40.0 %)	

Comparison of inflammatory markers between the HG and control groups revealed several significant differences (Table 3.2). The mean neutrophil count was significantly higher in the HG group (6.14 ±2.02 X 10^3/ml) compared to the control group (5.32 ±1.96 X 10^3/ml; $p = 0.043$). Conversely, the mean lymphocyte count was significantly lower in the HG group (1.72 ±0.32 X 10^3/CC) compared to the control group (1.84 ±0.56 X 10^3/CC; $p = 0.039$). The mean platelet count was also significantly higher in the HG group (291.79 ±93.99 X 10^3/CC) compared to the control group (238.65 ±39.42 X 10^3/CC; $p = 0.024$).

Both platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) were significantly elevated in the HG group. Mean PLR was 133.45 ±59.07 in the HG group versus 115.58 ±32.86 in the

control group (p = 0.008), and mean NLR was 4.21 ±1.68 in the HG group versus 2.89 ±0.66 in the control group (p = 0.002). Furthermore, C-reactive protein (CRP) levels were significantly higher in the HG group (1.04 ±0.76 mg/dL) compared to the control group (0.34 ±0.16 mg/dL; $p < 0.001$).

Table 3.2 Markers of inflammatory response compared between study and control groups

Characteristic	HG group (n = 20) Mean ±SD	Control group (n = 20) Mean ±SD	*P*-value
Neutrophils (X 10^3/ml)	6.14 ±2.02	5.32 ±1.96	0.043
Lymphocytes (X 10^3/CC)	1.72 ±0.32	1.84 ±0.56	0.039
Platelets (X 10^3/CC)	291.79 ±93.99	238.65 ±39.42	0.024
PLR	133.45 ±59.07	115.58 ±32.86	0.008
NLR	4.21 ±1.68	2.89 ±0.66	0.002
CRP (mg/dL)	1.04 ±0.76	0.34 ±0.16	<0.001

Demographic characteristics were also compared across different severity levels of HG (severe, moderate, mild), showing no significant variations in age, BMI, gestational age, or gravidity across these subgroups ($p > 0.05$).

When inflammatory markers were analyzed according to HG severity (Table 3.4), no significant differences were observed for mean neutrophil count, mean lymphocyte count, mean PLR, and mean NLR ($p > 0.05$). However, mean platelet count showed a significant variation with disease severity (p = 0.043), with higher counts in severe cases (269.64 ±118.42 X 10^3/CC), followed by moderate (250.40 ±77.81 X 10^3/CC) and mild cases (234.90 ±101.99 X 10^3/CC). A highly significant difference was also found in mean CRP levels across severity groups (p = 0.010), with the highest levels in women with severe HG (2.01 ±0.35 mg/dL). While severe cases had significantly higher CRP, the difference between moderate (0.65 ±0.44 mg/dL) and mild (0.79 ±0.69 mg/dL) presentations was not significant.

Table 3.4 Markers of inflammatory response compared based on severity of hyperemesis gravidarum

Characteristic	**Severe (n = 5) Mean ±SD**	**Moderate (n = 8) Mean ±SD**	**Mild (n = 7) Mean ±SD**	**P-value**
Neutrophils	6.16 ±2.60	5.78 ±1.98	6.53 ±1.86	0.695
Lymphocytes	1.81 ±0.32	1.71 ±0.38	1.67 ±0.28	0.844
Platelet count	269.64 ±118.42	250.40 ±77.81	234.90 ±101.99	0.043
PLR	106.62 ±73.11	115.35 ±66.26	116.15 ±48.09	0.925
NLR	4.21 ±1.61	4.63 ±1.79	3.74 ±1.73	0.635
CRP	2.01 ±0.35	0.65 ±0.44	0.79 ±0.69	0.010

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic value of CRP for HG. The analysis indicated a valid diagnostic potential with an Area Under the Curve (AUC) of 0.798 (95% CI: 0.641 to 0.908, $p < 0.001$). A cutoff value of >0.61 mg/dL for CRP yielded a sensitivity of 60.0%, a specificity of 100.0%, and an overall accuracy of 79.8% for diagnosing HG (Figure3.1).

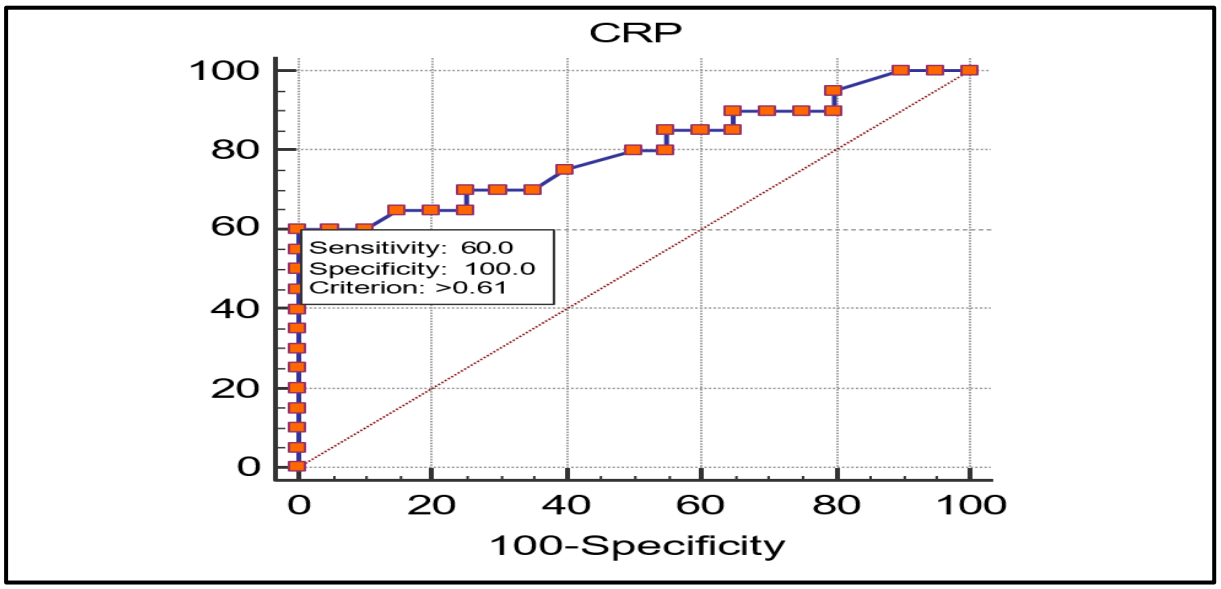


Figure 3.1 ROC curve of C-reactive protein (CRP) for cutoff determination in diagnosing hyperemesis gravidarum

4. DISCUSSION

The most severe type of nausea and vomiting in pregnancy is Hyperemesis Gravidarum (HG) defined by persistent vomiting and eventual weight loss, dehydration and ketonuria (27). The prevalence of all pregnancies is large and HG is challenging to manage because of its complicated and poorly defined pathophysiology (28, 29). The aim of the present study was to examine the relationship between inflammatory markers and HG patients. The study was particularly aimed to assess the Neutrophil-to-lymphocyte ratio (NLR), Platelet-to-lymphocyte ratio (PLR) and C-reactive protein (CRP) in patients with HG.

Our study found no statistically significant differences between the HG and control groups regarding mean age (25.80 ± 2.97 years vs. 25.95 ± 3.50 years, p = 0.395), Body Mass Index (BMI) (23.55 ± 2.71 kg/m² vs. 23.12 ± 2.31 kg/m², p = 0.274), mean gestational age (11.55 ± 2.52 weeks vs. 11.85 ± 1.76 weeks, p = 0.518), or gravidity (p = 0.749). These results indicate similarity between the groups at the baseline measurement, which reduces the risk of confounding due to these factors in the analysis of inflammatory markers. Our findings are in line with several previous studies that also did not find any significant demographic differences between HG patients and controls (30-32). In the current study, we found no correlation between pre-pregnancy BMI with HG (33), whereas a systematic review and meta-analysis performed by Ioannidou et al. (2019) suggested that this may be correlated with HG. This uniformity of demographic parameters within each HG severity group also suggests that other factors than these baseline patient parameters are likely responsible for the clinical manifestations of HG severity.

Our study showed a statistically significant difference between HG vs control for inflammatory biomarkers supporting the hypothesis that systemic inflammation plays a role in the etiology of HG. The HD compared to control group presented a significant differentiation of many inflammatory markers; examples of significant differences include mean neutrophils level (HG - 2,060, p-value =0.043), mean lymphocytes levels (HG - 10,210, p value = 0.039), and mean platelets levels of (HG- 375,000, p value = 0.024). Thus the PLR (p value =0.008) and NLR (p value =0.002) are high in the HG group. However, the HG group had a very significantly higher CRP level, too ($p < 0.001$).

The elevated neutrophil levels in HG patients is consistent with previous reports by Kan et al. (2020), Yildirim et al. (2023), Aslan et al. (2022) and Özay et al. (2021), which all indicated increased levels of innate immunity activation in HG (30, 32, 34, 35). Aslan et al., 2022 (32) noted a decrease in

lymphocytes in our HG group, whereas other researchers did not (Kan et al., 2020; Özay et al., 2021; Yildirim et al., 2023), which may be due to differences in study samples, sample sizes and methods. However, platelet count was found significantly higher in HG patients which coincides with the results of Kan et al. (2020) and Aslan et al. (2022) (30,32), but differs from the results of Özay et al. (2021), Uçkan et al. (2023) and Yildirim et al. (2023) (34,36). These differences highlight the importance of a uniform methodology and increased cohort size.

Also, among our HG participants, higher PLR and NLR are favorable for pro-inflammatory processes, since a high overall platelet and neutrophil activity and low overall lymphocyte activity leads to a high inflammatory response. These findings corroborate the results of Kan et al., 2020; Aslan et al., 2022; and Yildirim et al. (2023) (30,32,34). On the other hand, Özay et al. and Uçkan et al. (2021 & 2023) did not find any significant difference in PLR and NLR between groups, which may be attributed to methodological differences or the differences in the sample size (35, 36).

Our HG group had significantly elevated CRP levels, which is a good indicator of acute systemic inflammation as was found by Kan et al. (2020) and Özay et al. (2021) (30, 35). Oğlak et al. (2020) however, did not determine any significant differences in CRP levels, which could be due to the difference in study design or CRP threshold values (31). In summary, the findings from our study and a large amount of literature suggest an inflammatory status in HG.

On investigating the inflammatory markers in relation to the degree of severity of HG, no statically significant difference was elucidated for inflammatory indicators such as neutrophil count, lymphocyte count, platelet–lymphocyte ratio (PLR) and neutrophil–lymphocyte ratio (NLR) across the varying levels of disease severity. A significant difference in mean platelet count ($p = 0.043$) and mean CRP ($p = 0.010$) was seen in relation to the severity of the disease, however. The mean platelet count was highest among severely affected women and moderate and mild decreased in number, indicating a possible activation of platelets in the severity of HG. The difference between mean CRP levels of women with moderately and mildly affected HG was not statistically significant, although the mean CRP levels were the highest among women with severe HG.

In this study, we found that the severity of HG is directly related to platelet count, which agrees with Tayfur et al. (2017) (37). However, the results of the significant increase in the mean of CRP among women with severe HG was similar to the results obtained by Kan et al. (2020) who found that CRP was significantly correlated with HG severity and that it was highest in women who were severely affected by HG (30). Furthermore, Rosiyana et al., (2022) confirmed these results, in that they reported that the CRP value was found to be significantly higher from mild to severe HG severity (38). The observations of elevated platelet counts and CRP levels across women with severe HG support their use as clinical markers for more severe HG, and serve to further confirm the inflammatory mechanisms of severe HG.

In addition, our research also failed to identify any significant differences in neutrophils or lymphocytes among all the severity ranges of HG. These results corroborate those from Kan et al. (2020) and Tayfur et al. (2017) (30,37). Other studies, however, have reported data that do not coincide with the results found by us: Uçkan et al. (2023) reported no statistically significant difference between the groups of patients regarding the values of CRP and platelet count, but they did report statistically significant difference in PLR and NLR (36). Similarly, Yildirim et al. (2023) found that several inflammatory markers (neutrophil count, platelet count, NLR, PLR and global inflammatory index) showed statistically significant correlation with the severity of the HG groups (34). Such differences reflect the diversity of HG, and emphasize the importance of further studies to understand the interactions between inflammatory markers and their respective roles in relation to HG severity. Potential sources of variation in results between patients include differences in sample size, sample type, and measurement of inflammatory markers used.

The ROC curve revealed that the threshold value of CRP ≥ 0.61 mg/dL had a sensitivity of 60, specificity of 100, accuracy of 79.8, and an AUC of 0.798 ($p<0.001$), indicating a high degree of diagnostic validity for the diagnosis of HG. The specificity of the test suggests that CRP may be a very useful tool for the

diagnosis of HG, especially as it is easily available and inexpensive in a clinical context.

5. Limitations

This study was limited by the small number of patients and single center study design, which may limit generalizability. The inconsistent results on inflammatory markers in HG may be due to variations in previous studies. Furthermore, the capacity to discriminate the severity of HG was poor for some markers and newer inflammatory markers were not well studied.

6. Conclusion

The authors conclude that Hyperemesis Gravidarum (HG) is associated with a significant systemic inflammatory response. Neutrophils, platelets, NLR, PLR and CRP were also elevated in the HG group compared to the HC group; but lymphocytes were decreased. Disease severity was significantly related to CRP and platelet count which could be helpful as a clinical marker. Contrary to this, only none of these factors, such as age, BMI, gestational age, and gravidity, were found to have significant effects on HG severity. These results indicate that inflammatory processes are likely to be important in the pathophysiology and severity of HG.

Authors declaration

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