Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1534004

J Med Palliat Care. 2024;5(5):238-246

Indicators of prolonged hospital stay and rehospitalizations in hyperemesis gravidarum

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Cite this article as: Demir Çendek B, Şeyhanlı Z, Akay A, et al. Indicators of prolonged hospital stay and rehospitalizations in hyperemesis gravidarum. *J Med Palliat Care*. 2024;5(5):238-246.

Received: 15.08.2024 ◆ **Accepted**: 20.09.2024 ◆ **Published**: 26.10.2024

ABSTRACT

Aims: Hyperemesis gravidarum (HG) can significantly impact the quality of life of pregnant women and is the primary factor leading to hospitalization during the first half of the pregnancy. The aim of this study is to determine the ability of basic laboratory indicators that determine the severity of HG and the indices that can be calculated from them to predict the total length of hospital stay and the number of recurrent hospitalizations.

Methods: A retrospective analysis was conducted on women diagnosed with HG at a tertiary hospital from 2018 to 2021. Following the application of the inclusion criteria, we included a total of 100 eligible patients with HG (study group) and 130 healthy pregnant women (control group). Subsequently, the groups were subjected to a comparative analysis.

Results: The study group had higher levels of hemoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), red blood cell (RBC), white blood cells (WBC), neutrophil, mean platelet volüme (MPV), ketonuria, and lower levels of thyroid-stimulating hormone (TSH), eosinophil ($p<0.005$, for all). Additionally, neutrophil-to-lymphocyte ratio (NLR), systemic immune inflammation index (SII), systemic inflammatory response index (SIRI), and AST to platelet ratio index (APRI) ($p<0.05$, for all) were significantly higher in the study group than in the control group, but serum delta neutrophil index (DNI), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR) and pan-immune inflammation value (PIV) were statistically similar in both groups.

Conclusion: To the best of our knowledge, this is the first study to investigate the prediction of total hospital stay along with the number of recurrent hospitalizations with laboratory parameters in HG patients. The NLR, SII, SIRI, APRI, WBC, AST, neutrophil, and ketonuria have the potential to serve as valuable, economically viable, and readily available objective indicators for the diagnosis of HG and the prediction of recurrent hospitalization and duration of hospitalization.

Keywords: Hyperemesis gravidarum, complete blood count, ketonuria, hospitalization, predicting rehospitalization

INTRODUCTION

Nausea and vomiting in pregnancy (NVP) is a common and often recurring symptom that occurs frequently during pregnancy. The prevalence of NVP among pregnant women during the initial trimester ranges from approximately 50% to 80%.[1] Hyperemesis gravidarum (HG) is a term used in medicine used to describe severe nausea and vomiting that occurs during pregnancy. Most NVP cases resolve spontaneously during pregnancy. A small percentage develop HG, causing dehydration and ketonuria. These complications require hospitalization due to persistent symptoms, nutritional deficiencies, and electrolyte imbalance.[2]

Multiple potential mechanisms have been proposed to be implicated in the pathogenesis of HG. Numerous pathological conditions, including hormonal fluctuations, immunological mechanisms, *Helicobacter pylori* infection, aberrant gastric motility, genetic predisposition, and liver dysfunction, have been documented.[3] The precise cause of HG remains uncertain.[4] Multiple risk factors have been documented in relation to HG, encompassing nulliparity, low maternal age, multiple gestation, fetal anomalies, a prior pregnancy complicated by HG, female gender, psychiatric disorders, and both elevated and diminished maternal prepregnancy weight.[5–7]

NVP is the prevailing indication for hospital admission during the early stages of pregnancy. Indeed, it ranks as the second most prevalent reason for hospitalization during pregnancy,

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following only premature birth.[8,9] HG frequently results in hospitalization during the early stages of pregnancy, thereby causing adverse outcomes such as unemployment, reduced social engagement, and diminished overall well-being. Clinical diagnosis is still the main method, so any indicator of disease severity may be useful. The relationship between hematological parameters and the presence and severity of HG is still not well understood. Few studies have examined HG women's re-hospitalization risk factors. In the present study, we aimed to investigate to what extent do laboratory indicators such as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), serum delta neutrophil index (DNI), systemic immune inflammation index (SII), systemic inflammatory response index (SIRI), pan-immune inflammation value (PIV), the aspartate aminotransferase (AST) to platelet ratio index (APRI) from first trimester complete blood count (CBC) and ketonuria contribute to the prognostication of hospitalization in individuals diagnosed with HG.

METHODS

A retrospective analysis was conducted on clinical data from patients who were admitted to the hospital's early pregnancy department with a diagnosis of HG between 2018 and 2021. The control group comprised pregnant women who were in good health and fell within the same gestational age as the study group. These women consistently attended our prenatal clinic. This study received local ethics committee approval (Date: 28.02.2024, Decision No: 02/13) and was conducted in accordance with the guidelines specified in the Declaration of Helsinki.

The study included a cohort of 230 pregnant women, with 100 pregnant women diagnosed with HG during the gestational period of 6-14 weeks (study group), and 130 pregnant women serving as healthy controls during the same gestational period (control group). The determination of gestational age was achieved by utilizing the first day of the most recent menstrual period and subsequently confirming it through sonography. The hospital's electronic medical system was used to collect all patient demographic and clinical data. The age, gestational age, gravidity, and parity of each patient were recorded. The diagnostic criteria for HG included the following: a minimum of three instances of intense vomiting per day, a weight loss exceeding 5% before pregnancy, and the presence of at least one positive result for ketonuria in the dipstick urine test.

This study excluded first-trimester CBC data and women with missing data. In addition, the study excluded patients with gastrointestinal disorders, diseases that induce nausea and vomiting like diabetic ketoacidosis, thyroid disorders, neurological conditions that elevate intracranial pressure and lead to vomiting, and inflammatory diseases.

The randomization process for the control group consisted of selecting healthy pregnant women with gestational ages that matched those of the participants admitted to the outpatient clinic. The process was carried out in a sequential manner, directly after the admission of each woman who joined the HG group, following the application of the exclusion criteria.

During the hospitalization of all patients, blood and urine samples are routinely collected as a standard procedure. After being collected, all samples were tested on a daily basis using the same automated analyzer in the laboratory of the hospital. The CBC parameters, such as neutrophil count (NC), lymphocyte count (LC), white blood cells (WBC), monocyte count (MC), eosinophil count (EC), hemoglobin level, hematocrit (HCT), platelet count (PC), platelocrit (PCT), mean platelet volume (MPV), red blood cell (RBC), red cell distribution (RDW), DNI and biochemical parameters, such as alanine aminotransferase (ALT), AST, thyroid-stimulating hormone (TSH) values were documented. Ketonuria was classified into four grades: 1+, 2+, 3+, and 4+. Subsequently, the blood parameters and ratios of systemic inflammation, such as NLR, PLR, MLR, SII, SIRI, PIV, and APRI, were computed for each participant in the study. The calculations were based on the parameters obtained from the CBC using the specified formulas: "NL=NC/LC; PLR=PC/LC; MLR=MC/LC; SII=PCxNC/LC; SIRI=MCxNC/LC; PIV=PCxMC/LC; APRI=(AST/normal upper limit of AST/patient's PCx100".

The individual was granted release from the hospital subsequent to a notable enhancement in their oral food consumption capacity.

Statistical Analysis

The statistical analysis was conducted using the IBM® SPSS® Statistics v29.0 software, also known as the Statistical Package for the Social Sciences (SPSS), developed by IBM in Armonk, New York, USA. The suitability of numerical data for normal distribution was analyzed according to the Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical data were given as median (interquartile range (IQR) or min-max) or mean±SD. Categorical variables were presented as numbers (percentage) and the chi-square test was used. In this study consisting of two independent groups, Mann Whitney U test was used for non-parametric numerical variables and independent sample t test was used for parametric variables. In addition, by receiver operating characteristic (ROC) curve analysis, the cut-off values of immune markers with an area under the curve (AUC) greater than 0.5, along with their 95% confidence interval (CI) values, sensitivity and specificity values were reached. Correlation tests were used to evaluate the relationship between independent variables. Significant results were considered when $p<0.05$.

RESULTS

Among the 230 individuals included in the sample, it was noted that 100 participants (43.5%) were allocated to the HG group, also known as the study group, whereas 130 participants (56.5%) were assigned to the control group. Demographic, clinical, and laboratory characteristics and outcomes between the groups are shown in Table 1. Age, gravida, parity, and gestational age did not differ between study and control groups ($p>0.05$). According to Table 1, the study group had higher rates of hospitalization days, recurrent hospitalizations, extended hospital stays, and previous HG history ($p<0.001$, for all). The study group had higher levels of ALT (13.3 U/L vs. 12 U/L, $p=0.029$), AST (17 U/L vs. 16 U/L,

Table 1. Demographic, clinical, and laboratory characteristics and outcomes between study and control groups

Variable	Study group	Control group	p-value
Participant (n,%)	100 (43.5)	130 (56.5)	
Age (years, median, IQR)	27 (8)	27 (9)	0.177[a]
Gravida (n, median, IQR)	2 (2)	2 (1)	0.813[a]
Parity (n, median, IQR)	2 (1)	1 (2)	0.469[a]
Gestational age (day, Mean±SD)	69.95±16.77	73.10±29.06	0.304[b]
First hospitalization (n, %)			<0.001[c]
No	0 (0)	130 (100)	
1 day	39 (39)	0 (0)	
2 days	36 (36)	0 (0)	
≥3 days	25 (25)	0 (0)	
Re-Hospitalization (n,%)			<0.001[c]
No	0 (0)	130 (100)	
1	68 (68)	0 (0)	
2	22 (22)	0 (0)	
≥3	10 (10)	0 (0)	
Total length of hospital stay			<0.001[c]
No	0 (0)	130 (100)	
1 day	34 (34)	0 (0)	
2 days	26 (26)	0 (0)	
≥3 days	40 (40)	0 (0)	
Previous HG			<0.001[c]
No	51 (51)	128 (98.5)	
Yes	49 (49)	2 (1.5)	
RBC (10^6/µL, mean±SD)	4.508±0.361	4.327±0.802	**0.024**[b]
Hemoglobin (g/dl, mean±SD)	12.94±0.97	12.62±1.14	**0.023**[b]
HCT (%, mean±SD)	38.32±2.79	38.04±3.99	0.540[b]
Platelets (10^3/mm^3, mean±SD)	263.820±70.06	263.592±57.95	0.970[b]
PCT (µg/L, mean±SD)	0.209±0.048	0.205±0.043	0.540[b]
WBC (10^3/mm^3, mean±SD)	8.620 (2.840)	7.870 (2.380)	0.001[a]
Neutrophil (10^3/mm^3, mean±SD)	6.610 (2.335)	5.580 (2.497)	<0.001[a]
Lymphocyte (10^3/mm^3, median, IQR)	1.590 (0.685)	1.610 (0.573)	0.077[a]
Monocyte (10^3/mm^3, median, IQR)	0.360 (0.170)	0.380 (0.157)	0.281[a]
Eosinophil (10^3/µL, median, IQR)	0.050 (0.050)	0.700 (1.025)	<0.001[a]
RDW (%, median, IQR)	13.8 (1.0)	13.9 (1.4)	0.213[a]
DNI (median, IQR)	-3.0 (3.85)	-3.5 (4.13)	0.676[a]
MPV (fl, Median, IQR)	8 (1.1)	7.8 (0.8)	0.020[a]
TSH (mU/L, median, IQR)	0.72 (1.25)	1.15 (1.21)	<0.001[a]
Ketonuria (median, IQR)	4 (0)	0 (0)	<0.001[a]
AST (IU/L, median, IQR)	17 (6)	16 (5)	<0.001[a]
ALT (IU/L, median, IQR)	13.3 (9)	12 (6)	0.029[a]
NLR (median, IQR)	3.83 (2.66)	3.27 (1.32)	<0.001[a]
PLR (median, IQR)	169.23 (85.66)	159.07 (53.85)	0.117[a]
MLR (median, IQR)	0.24 (0.13)	0.24 (0.10)	0.248[a]
SII (median, IQR)	1094.42 (794.11)	899.72 (413.46)	<0.001[a]
SIRI (median, IQR)	1.76 (1.20)	1.31 (0.91)	0.002[a]
PIV (median, IQR)	64.40 (43.94)	60.10 (34.23)	0.39[a]
APRI (median, IQR)	0.20 (0.09)	0.17 (0.7)	<0.001[a]

[a]= Mann Whitney U Test, [b]= Indepented t test, [c]=Chi Square test, Bold p values are statistically significant (p<0.05)

Abbreviations: HG; Hyperemesis gravidarum, RBC; Red blood cell, HCT; Hematocrit, PCT; Plateletcrit, WBC; White blood cell, RDW; Red cell distribution width, MPV; Mean platelet volüme, ALT; Alanine aminotransferase, AST;Aspartate aminotransferase, TSH; Thyroid stimulating hormone, DNI; Delta neutrophil index, PLR; Platelet to lymphocyte ratio, NLR; Neutrophil to lymphocyte ratio, MLR; Monocytes to lymphocyte ratio, SII; Systemic immune-inflammatory index, SIRI; Systemic inflammatory response index, PIV; Pan-immune inflammation value, APRI; Aspartate aminotransferase to platelet ratio index.

Table 2. Evaluation of laboratory results that are statistically significant between the groups with receiver operating characteristic (ROC) curves analyses

Test result variables	Area under curve	Std. error	Asymptotic sig.	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Ketonuria	0.942	0.022	<0.001	0.899	0.984
NLR	0.683	0.041	<0.001	0.603	0.763
SII	0.679	0.042	<0.001	0.596	0.762
Neutrophil (10^3/mm^3)	0.666	0.041	<0.001	0.586	0.746
AST (IU/L)	0.660	0.041	<0.001	0.581	0.740
WBC (10^3/mm^3)	0.630	0.042	0.003	0.546	0.713
SIRI	0.629	0.043	0.003	0.544	0.713
APRI	0.604	0.043	0.017	0.520	0.689
ALT (IU/L)	0.586	0.043	0.051	0.501	0.670
Hemoglobin (g/dl)	0.576	0.043	0.080	0.493	0.660
RBC (10^6/µL)	0.560	0.043	0.171	0.476	0.644
MPV (fl)	0.559	0.045	0.176	0.472	0.647
TSH (mU/L)	0.353	0.039	<0.001	0.276	0.429
Eosinophil (10^3/µL)	0.088	0.021	<0.001	0.047	0.130

Bold p values are statistically significant (p<0.05)
Abbreviations: RBC; Red blood cell, WBC; White blood cell, ALT; Alanine aminotransferase, AST; Aspartate aminotransferase, TSH; Thyroid stimulating hormone, MPV; Mean platelet volüme, NLR; Neutrophil to lymphocyte ratio, SII; Systemic immune-inflammatory index, SIRI; Systemic inflammatory response index, APRI; Aspartate aminotransferase to platelet ratio index

p<0.001), hemoglobin (12.94 g/dl vs. 12.62 g/dl, p=0.023), RBC (4.508 10^6/µL vs. 4.327 10^6/µL, p=0.024), WBC (8.620 10^3/mm^3 vs. 7.870 10^3/mm^3, p=0.001), NC (6.610 10^3/mm^3 vs. 5.580 10^3/mm^3, p<0.001), MPV (8 fl vs. 7.8 fl, p=0.020), ketonuria (4 vs. 0, p<0.001), and lower levels of TSH (0.72 mU/L vs. 1.15 mU/L, p<0.001), EC (0.050 10^3/µL vs. 0.700 10^3/µL, p<0.001). Additionally, NLR, SII, SIRI and APRI (p<0.05 for all) were significantly higher in the HG group than in the control group, but DNI, PLR, MLR and PIV were statistically similar in both groups.

To evaluate laboratory results that are statistically significant between the groups, ROC curves were calculated and shown in Table 2. Ketonuria showed an AUC of 0.942 (95% CI: 0.899-0.984) and the optimal cut-off value was set at +2.75, resulting in a sensitivity of 80.5% and a specificity of 100% (p<0.001) (Figure 1). Also, the AUC for NLR was 0.683 (cut-off 3.47, 95% CI: 0.603-0.763, p<0.001, sensitivity 70.7%, specificity 54%), for SII it was 0.679 (cut-off 965.75, 95% CI: 0.596-0.762, p<0.001, sensitivity 69.6%, specificity 61.3%), for SIRI it was 0.629 (cut-off 1.468, 95% CI: 0.544-0.713, p=0.003, sensitivity 62%, specificity 61.3%), for AST it was 0.660 (cut-off 15.2 IU/L, 95% CI: 0.581-0.740, p<0.001, sensitivity 75%, specificity 49.2%), for NC it was 0.666 (cut-off 5.780 x10^3/mm^3, 95% CI: 0.586-0.746, p<0.001, sensitivity 71.7%, specificity 56.6%), for WBC it was 0.630 (cut-off 7.975 x10^3/mm^3, 95% CI: 0.546-0.713, p=0.003, sensitivity 68.5%, specificity 54%), for APRI it was 0.604 (cut-off 0.184, 95% CI: 0.520-0.689, p=0.017, sensitivity 60.9%, specificity 63.5%) (Figure 2).

In Table 3, correlation analysis was performed between the number of hospitilization days at the first hospitalization, the number of recurrent hospitalizations, the total length of hospital stay due to HG, and previous HG history and laboratory parameters in HG patients. It was revealed that there was a significant positive correlation between the

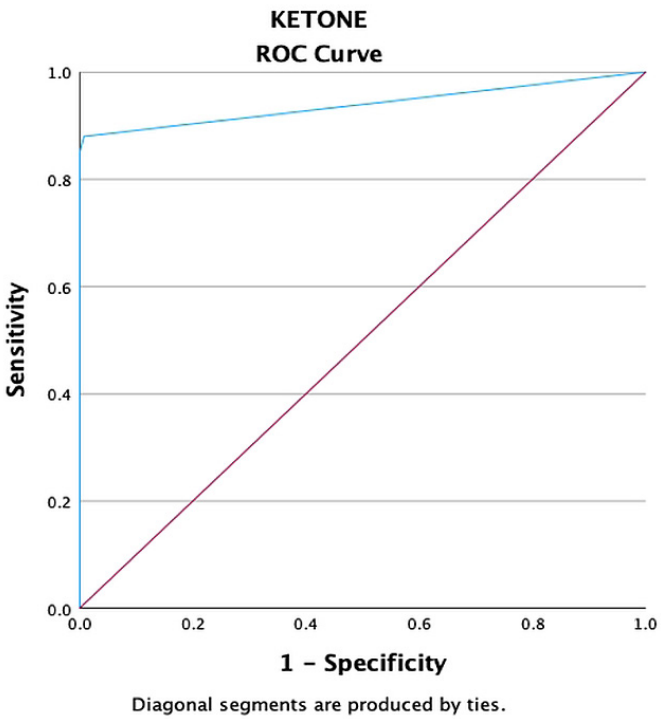

Figure 1. Receiver operating characteristic (ROC) curves of ketone

number of days of hospitalization in the first hospitalization, the number of recurrent hospitalizations, the total hospital stay due to HG, and ketonuria, NLR, SII, NC, WBC, SIRI, APRI, AST, ALT and hemoglobin (p<0.05, for all). While ketonuria, NLR, SII, NC, WBC, SIRI, AST and hemoglobin showed a significant positive correlation with previous HG history, APRI and ALT did not show a significant correlation. RBC and MPV did not show a significant correlation with the number of recurrent hospitalizations, total hospital stay due to HG, previous HG history (p>0.05, for all). While MPV

Table 3. Spearman correlation coefficients between hospitalization characteristics and previous HG with laboratory parameters in HG patients

		First hospitalization	Re-Hospitalization	Total length of hospital stay	Previous HG
Ketonuria	Correlation coefficient	.833	.844	.831	.559
	Sig.	<.001	<.001	<.001	<.001
NLR	Correlation coefficient	.272	.291	.259	.232
	Sig.	<.001	<.001	<.001	<.001
SII	Correlation coefficient	.231	.280	.248	.262
	Sig.	<.001	<.001	<.001	<.001
Neutrophil (10^3/mm^3)	Correlation coefficient	.274	.252	.223	.163
	Sig.	<.001	<.001	<.001	.013
AST (IU/L)	Correlation coefficient	.268	.274	.266	.196
	Sig.	<.001	<.001	<.001	.003
WBC (10^3/mm^3)	Correlation coefficient	.215	.180	.162	.136
	Sig.	.001	.006	.014	.040
SIRI	Correlation coefficient	.191	.189	.162	.136
	Sig.	.004	.004	.014	.040
APRI	Correlation coefficient	.217	.198	.195	.080
	Sig.	<.001	.003	.003	.232
ALT (IU/L)	Correlation coefficient	.166	.169	.174	.119
	Sig.	.013	.012	.009	.077
Hemoglobin (g/dl)	Correlation coefficient	.161	.152	.158	.164
	Sig.	.015	.022	.017	.014
RBC (10^6/µL)	Correlation coefficient	.110	.108	.105	.108
	Sig.	.096	.105	.114	.104
MPV (fl)	Correlation coefficient	.141	.124	.129	.020
	Sig.	.033	.061	.053	.767
TSH (mU/L)	Correlation coefficient	-.272	-.285	-.300	-.213
	Sig.	<.001	<.001	<.001	.002
Eosinophil (10^3/µL)	Correlation coefficient	-.685	-.697	-.687	-.477
	Sig.	<.001	<.001	<.001	<.001

Bold p values are statistically significant (p<0.05)
Abbreviations: RBC; Red blood cell, WBC; White blood cell, ALT; Alanine aminotransferase, AST; Aspartate aminotransferase, TSH; Thyroid stimulating hormone, MPV; Mean platelet volüme, NLR; Neutrophil to lymphocyte ratio, SII; Systemic immune-inflammatory index, SIRI; Systemic inflammatory response index, APRI; Aspartate aminotransferase to platelet ratio index

showed a significant positive correlation with the number of days of hospitalization at the first hospitalization, RBC did not show a significant correlation. It was revealed that there was a significant negative correlation between the number of days of hospitalization during the first hospitalization, the number of recurrent hospitalizations, the total duration of hospital stay due to HG, previous HG history, and TSH and EC (p<0.05, for all). A cut-off value of 0.075 was determined for EC, with a sensitivity of 85.6% and specificity of 69.1% (AUC: 0.932, p<0.001, 95% CI: 0.870-0.953). Similarly, a cut-off value of 0.910 was established for TSH, with a sensitivity of 67.3% and specificity of 54.7% (AUC: 0.647, p<0.001, 95% CI: 0.571-0.724). These values were found to have diagnostic value for the control group, as depicted in Figure 3.

Table 4 displays the pregnancy outcomes of patients belonging to both the study and control groups. While all patients in the control group were included, only 66 patients in the study group were able to obtain pregnancy results. When assessing the pregnancy outcomes of the HG group, it was noted that 2 (3%) patients experienced an abortion during the first trimester, 53 (80.3%) patients gave term birth, 9 (13.6%) patients gave preterm birth, and 2 (3%) patients gave postterm birth (p<0.001, for all).

DISCUSSION

The occurrence of NVP ranks as the second most prevalent diagnosis for antenatal hospitalization, accounting for 11.4% of all indications. The average duration of hospitalization for this condition is 2.7 days.[8] In the present study, it was observed that 40% of the HG group necessitated hospitalization for a cumulative duration of 3 days or longer, while 34% were hospitalized for a duration of less than 2 days. Additionally, a significant proportion of hospitalized women, ranging from 19% to 30%, experience subsequent hospitalizations within the same pregnancy.[3,10,11] A study conducted by Piwko et al.[12] examined the economic impact of NVP in the United States. The study determined that the cost of drug treatment for mild NVP (nausea and vomiting of pregnancy) was $40, while the cost for HG (hyperemesis gravidarum) was estimated

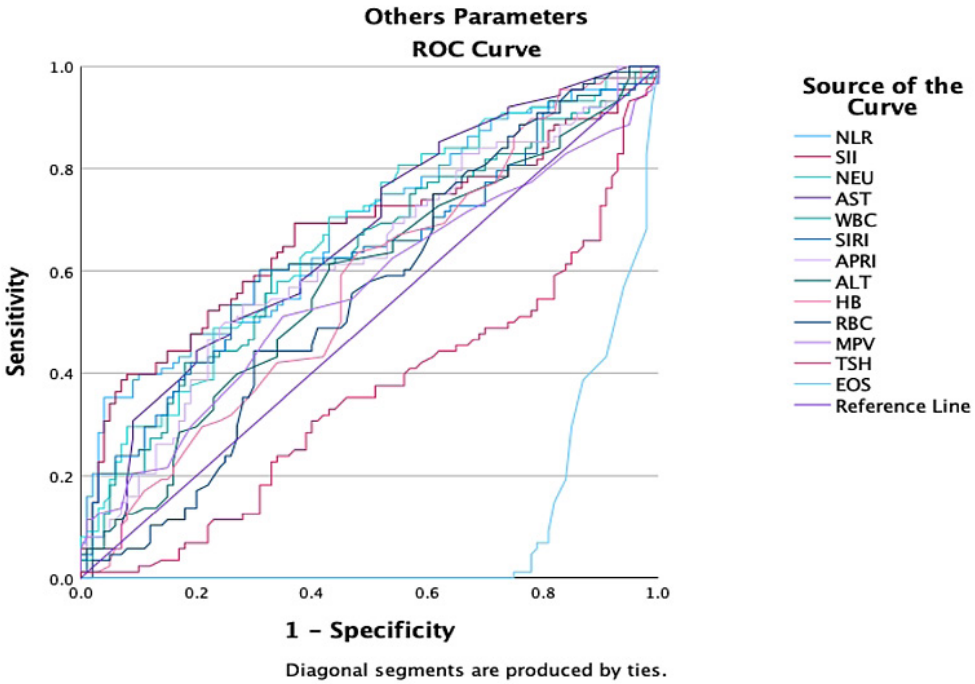

Figure 2. Receiver operating characteristic (ROC) curves of other parameters in the study group

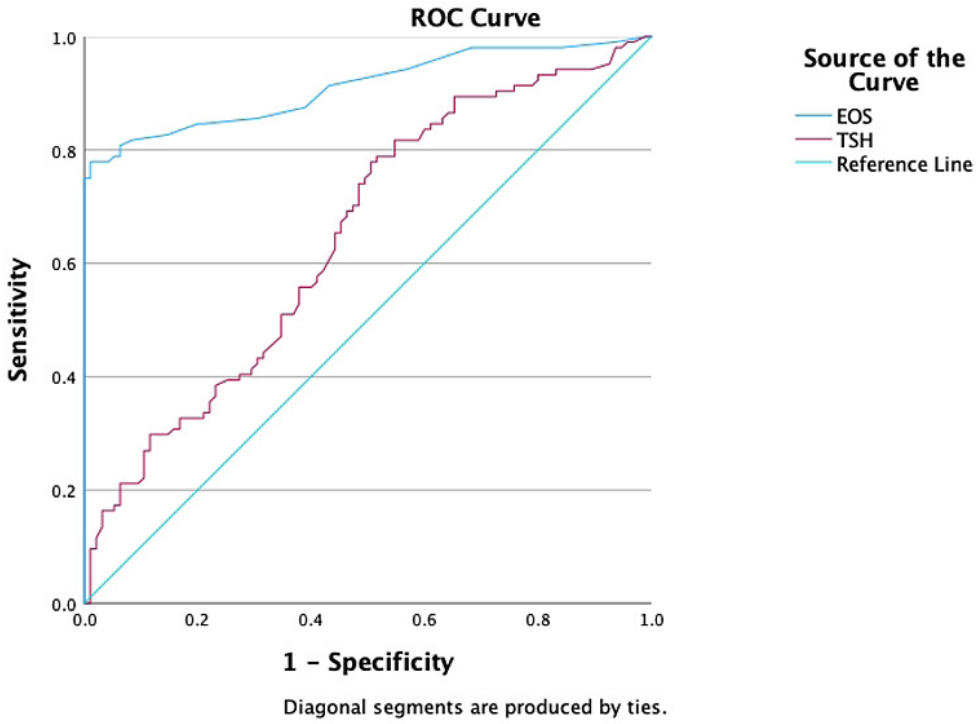

Figure 3. Receiver operating characteristic (ROC) curves of EOS and TSH in the control group

to be $267. The study documented that the mean hospital expenditure for each patient admission for HG was $12,453. The identification of patients with HG who are susceptible to an extended hospital stay offers several benefits. Firstly, it aids in the development of treatment strategies aimed at reducing the duration of hospitalization. Secondly, it aids in the identification of women who are at risk of re-hospitalization. Thirdly, it enhances the effectiveness of their treatment plan, prevents the need for additional hospital admissions, and helps alleviate the economic burden on the nation.

Prior research has primarily examined the factors that increase the risk of HG, the outcomes for both the mother and the fetus, and the factors that contribute to hospitalization. There is a scarcity of research in the literature that investigates laboratory markers for extended hospitalization caused by HG. The study conducted by Tan et al.[13] found that there was

Table 4. Outcome of pregnancy between study and control groups

Variable	Study group	Control group	p-value
Outcome of pregnancy (n)	66	130	<0.001
First trimester abortion (n,%)	2 (3)	0 (0)	
Term birth (n,%)	53 (80.3)	128 (98.5)	
Preterm birth (n, %)	9 (13.6)	2 (1.5)	
Postterm birth (n,%)	2 (3)	0 (0)	

an independent association between hematocrit values of 41% or higher and an extended duration of hospitalization.The study conducted by Topçu et al.[14] aimed to identify risk factors associated with HG and investigate their potential correlation with both the duration of hospital stay and the severity of HG. Nevertheless, it was observed that factors such as age, body mass index, gestational week, need for combined antiemetic use, CBC parameters, liver and kidney function tests did not exhibit any significant association with the duration of hospital stay. However, it was found that serum maternal TSH levels below 0.1 μIU/mL and a frequency of 5 vomitings per day were significant predictors of longer hospital stays.

Research on NVP has focused on inflammatory indices and cell lines obtained from the CBC. The study conducted by Tayfur et al.[15] revealed significant differences in NC, LC, and PC, as well as NLR, PLR, and PCT, between the HG and control groups. This article was conducted in response to the increasing interest in inflammatory markers obtained from a single CBC. Furthermore, to our knowledge, this is the first study to investigate the prediction of total hospital stay along with the number of recurrent hospitalizations with hematological parameters and ketonuria values in HG patients. Nevertheless, due to the intricate nature of altered inflammation, it would be impractical, unreproducible, and devoid of significance to base decisions solely on a solitary cell line, such as NC, LC, or PC. In the present study, we examined the NLR, PLR, MLR, SII, SIRI, APRI and PIV assays, which collectively evaluate distinct inflammatory cell lines and have been previously examined for their potential in predicting and prognosticating various diseases involving inflammation in their pathogenesis.[16–19] Our study examined the correlation between hematological parameters, and ketonuria values, and the duration of initial hospitalization, total hospital stay, and recurrent hospitalizations in patients with HG. We found that as the values of ketonuria, NLR, SII, NC, WBC, SIRI, APRI, AST, ALT, and hemoglobin increased, there was a significant increase in both the number of hospitalizations and the duration of hospitalization. In addition, on the contrary to these laboratory parameters, it was observed that the decrease in TSH and EC values significantly increased the initial hospitalization time, total hospital stay and the number of recurrent hospitalizations. Hyperthyroid disorder, a potential risk factor for severe HG and an increased likelihood of hospitalization, should be evaluated and managed in all patients.[3] Consistent with the literature, in our study, it was observed that as the TSH value decreased, re-hospitalization and total hospitalization time increased. When all the results are evaluated, patients with thyroid dysfunction should be evaluated and treated in order to reduce possible serious complications, prolonged and recurrent hospitalizations and costs in first trimester pregnancies.

Ketonuria serves as a diagnostic parameter for severe HG; however, the association between the severity of the disease and the extent of ketonuria remains uncertain. Multiple studies have investigated potential correlations between the disease severity and the extent of ketonuria.[20–22] The severity of the condition was assessed based on the readmission rate[20] and the duration of hospitalization exceeding 4 days.[21,22] There was no significant association found between ketonuria and an extended duration of hospitalization.[22] Further research has shown that there is no significant correlation between the presence of ketonuria and the severity of HG in relation to the need for admission again.[20,21] A comparative analysis between patients with and without hyperemesis gravidarum (HG) revealed that the HG group displayed elevated levels of ketonuria. Furthermore, it was discovered that a greater length of hospital stay was linked to elevated levels of ketonuria.[23] In our study, we observed that as the ketonuria value increased in the HG group, the initial hospitalization time, total hospital stay and the number of recurrent hospitalizations increased in a positive correlation (p<0.001).

A significant correlation was observed between a short gestational period during pregnancy and the likelihood of re-hospitalization.[24] Numerous studies consistently validate a heightened prevalence of HG during the initial weeks of gestation and the first trimester.[11,20,25] The participants in our study were patients in their first trimester.

Prior research on hospitalization resulting from HG indicates that women with a history of HG were more likely to be admitted to the hospital during their subsequent pregnancy.[3,10,26] The findings of our study validate these results, demonstrating a significant likelihood of HG in women who have previously been diagnosed with HG during subsequent pregnancies (p<0.001). Furthermore, our study revealed that the length of initial hospitalization in cases of HG did not have a statistically significant impact on the likelihood of re-hospitalization (p=0.276). Nevertheless, it was noted that a prior occurrence of HG resulted in a statistically significant rise in re-hospitalization. Upon dividing the HG group into subgroups based on the number of hospitalizations, it was observed that individuals with 2 or more hospitalizations had a significantly higher history of HG (96.9% vs 25%) (p<0.001). In addition, it was found that individuals with a prior history of HG had a 91.176-fold (95% CI: 11.552-719.641) increased risk of being hospitalized again due to HG in future pregnancies. The affects of HG on women's perspectives towards family planning, their desires to conceive again, and their levels of anxiety and trepidation regarding future pregnancies necessitate meticulous examination.[27] The attitudes and anxieties experienced by women who have previously experienced HG may have an impact on their likelihood of being readmitted to the hospital.

Limitations

There are certain constraints in our study. Both groups have small populations. Our retrospective study could not use validated tools like the Pregnancy-Unique Quantification of Emesis and Nausea score because the hospital's database was inaccessible. This tool and supplementary variables like weight data in a prospective study can validate the index and improve medical care for women with HG.

CONCLUSION

NVP is a prevalent condition during pregnancy and seldom advances to severe HG necessitating hospitalization. Physicians can utilize the NLR, SII, SIRI, APRI, WBC, AST, NC, and ketonuria to assess the likelihood of a prolonged hospital stay and the frequency of recurrent hospitalizations. However, additional research is required in large-scale population studies. It is crucial to identify patients who are at a high risk of developing HG in order to prevent recurrent hospitalizations, prolonged hospital stays, potential complications, and to minimize economic expenses.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committe of Etlik Zübeyde Hanım Women's Dıseases Training and Research Hospital (Date: 28.02.2024 Decision No: 02/13)

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. 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(4):931-937. doi:10.1016/s0002-9378(00)70349-8
2. Cedergren M, Brynhildsen J, Josefsson A, Sydsjö A, Sydsjö G. Hyperemesis gravidarum that requires hospitalization and the use of antiemetic drugs in relation to maternal body composition. *Am J Obstet Gynecol*. 2008;198(4):412.e1-415. doi:10.1016/j.ajog.2007.09.029
3. Fell DB, Dodds L, Joseph KS, Allen VM, Butler B. Risk factors for hyperemesis gravidarum requiring hospital admission during pregnancy. *Obstet Gynecol*. 2006;107(2 Pt 1):277-284. doi:10.1097/01.AOG.0000195059.82029.74
4. Committee on practice bulletins-obstetrics. ACOG practice bulletin no. 189: nausea and vomiting of pregnancy. *Obstet Gynecol*. 2018;131(1):e15-e30. doi:10.1097/AOG. 0000000000002456
5. Depue RH, Bernstein L, Ross RK, Judd HL, Henderson BE. Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome, and other maternal factors: a seroepidemiologic study. *Am J Obstet Gynecol*. 1987;156(5):1137-1141. doi:10.1016/0002-9378(87)90126-8
6. Eliakim R, Abulafia O, Sherer DM. Hyperemesis gravidarum: a current review. *Am J Perinatol*. 2000;17(4):207-218. doi:10.1055/s-2000-9424
7. Rochelson B, Vohra N, Darvishzadeh J, Pagano M. Low prepregnancy ideal weight:height ratio in women with hyperemesis gravidarum. *J Reprod Med*. 2003;48(6):422-424.
8. Bacak SJ, Callaghan WM, Dietz PM, Crouse C. Pregnancy-associated hospitalizations in the United States, 1999-2000. *Am J Obstet Gynecol*. 2005;192(2):592-597. doi:10.1016/j.ajog.2004.10.638
9. Gazmararian JA, Petersen R, Jamieson DJ, et al. Hospitalizations during pregnancy among managed care enrollees. *Obstet Gynecol*. 2002;100(1):94-100. doi:10.1016/s0029-7844(02)02024-0
10. Fejzo MS, Macgibbon KW, Romero R, Goodwin TM, Mullin PM. Recurrence risk of hyperemesis gravidarum. *J Midwifery Womens Health*. 2011;56(2):132-136. doi:10.1111/j.1542-2011.2010.00019.x
11. Lacasse A, Lagoutte A, Ferreira E, Bérard A. Metoclopramide and diphenhydramine in the treatment of hyperemesis gravidarum: effectiveness and predictors of rehospitalisation. *Eur J Obstet Gynecol Reprod Biol*. 2009;143(1):43-49. doi:10.1016/j.ejogrb.2008.11.007
12. Piwko C, Koren G, Babashov V, Vicente C, Einarson TR. Economic burden of nausea and vomiting of pregnancy in the USA. *J Popul Ther Clin Pharmacol*. 2013;20(2):e149-160.
13. Tan PC, Jacob R, Quek KF, Omar SZ. Readmission risk and metabolic, biochemical, haematological and clinical indicators of severity in hyperemesis gravidarum. *Aust N Z J Obstet Gynaecol*. 2006;46(5):446-450. doi:10.1111/j.1479-828X.2006.00632.x
14. Topçu H, İskender C, Oskovi A, Timur H, Dağlar K, Danışman N. Risk factors of prolonged hospitalization in patients with hyperemesis gravidarum. *Cukurova Med J*. 2015;40(1):113-118.
15. Tayfur C, Burcu DC, Gulten O, et al. Association between platelet to lymphocyte ratio, plateletcrit and the presence and severity of hyperemesis gravidarum. *J Obstet Gynaecol Res*. 2017;43(3):498-504. doi:10.1111/jog.13228
16. Tolunay HE, Kahraman NÇ, Varlı EN, et al. First-trimester aspartate aminotransferase to platelet ratio index in predicting intrahepatic cholestasis in pregnancy and its relationship with bile acids: a pilot study. *Eur J Obstet Gynecol Reprod Biol*. 2021;256:114-117.
17. Chen JH, Zhai ET, Yuan YJ, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. *World J Gastroenterol*. 2017;23(34):6261-6272. doi:10.3748/wjg.v23.i34.6261
18. Fucà G, Guarini V, Antoniotti C, et al. The pan-immune-inflammation value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the Valentino and TRIBE first-line trials. *Br J Cancer*. 2020;123(3):403-409. doi:10.1038/s41416-020-0894-7
19. Qi Q, Zhuang L, Shen Y, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. *Cancer*. 2016;122(14):2158-2167. doi:10.1002/cncr.30057
20. Tan PC, Jacob R, Quek KF, Omar SZ. Readmission risk and metabolic, biochemical, haematological and clinical indicators of severity in hyperemesis gravidarum. *Aust N Z J Obstet Gynaecol*. 2006;46(5):446-450. doi:10.1111/j.1479-828X.2006.00632.x

21. Tan PC, Tan NC, Omar SZ. Effect of high levels of human chorionic gonadotropin and estradiol on the severity of hyperemesis gravidarum. *Clin Chem Lab Med*. 2009;47(2):165-171. doi:10.1515/CCLM.2009.041

22. Tan PC, Jacob R, Quek KF, Omar SZ. Indicators of prolonged hospital stay in hyperemesis gravidarum. *Int J Gynaecol Obstet*. 2006;93(3):246-247. doi:10.1016/j.ijgo.2006.03.012

23. Derbent AU, Yanik FF, Simavli S, et al. First trimester maternal serum PAPP-A and free β-HCG levels in hyperemesis gravidarum. *Prenat Diagn*. 2011;31(5):450-453. doi:10.1002/pd.2715

24. Morris ZH, Azab AN, Harlev S, Plakht Y. Developing and validating a prognostic index predicting re-hospitalization of patients with hyperemesis gravidarum. *Eur J Obstet Gynecol Reprod Biol*. 2018;225:113-117. doi:10.1016/j.ejogrb.2018.04.028

25. Peled Y, Melamed N, Hiersch L, Pardo J, Wiznitzer A, Yogev Y. The impact of total parenteral nutrition support on pregnancy outcome in women with hyperemesis gravidarum. *J Matern Fetal Neonatal Med*. 2014;27(11):1146-1150. doi:10.3109/14767058.2013.851187

26. Atanackovic G, Wolpin J, Koren G. Determinants of the need for hospital care among women with nausea and vomiting of pregnancy. *Clin Invest Med*. 2001;24(2):90-93.

27. Poursharif B, Korst LM, Fejzo MS, MacGibbon KW, Romero R, Goodwin TM. The psychosocial burden of hyperemesis gravidarum. *J Perinatol*. 2008;28(3):176-181. doi:10.1038/sj.jp.7211906