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Original Article

The Relationship Between the HALP Score and Gastric Cancer Prognosis

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ABSTRACT

Background: Gastric adenocarcinoma is the fifth most common malignancy worldwide and the third leading cause of cancer-related deaths. As most patients are diagnosed in the advanced stage of the disease, the prognosis is dismal. Therefore, researchers have developed various scoring systems to predict prognostic factors. One of these is the HALP scale, which consists of hemoglobin, albumin, lymphocytes and platelets. This study aims to assess the utility of the HALP score as a prognostic tool in predicting the clinical outcomes of patients with gastric adenocarcinoma.

Methods: A retrospective review of patients who underwent gastrectomy for gastric cancer between 2018 and 2021 in the Department of Surgical Oncology, Gulhane Medical School Training and Research Hospital, University of Health Sciences. A total of 158 patients who underwent surgery for the diagnosis of gastric adenocarcinoma were included in the study. Hemoglobin, albumin, lymphocytes and platelet values were obtained from patient files. HALP scores were calculated and correlations with clinicopathologic factors were investigated.

Results: We found a significant negative correlation between the HALP score and T stage and N stage. Increasing the HALP score increases the likelihood of early-stage disease ($p= 0.008$ and $p= 0.001$). We found a significant negative correlation between the HALP score and the number of metastatic lymph nodes and tumor diameter ($p<0.001$ and $p<0.001$). One unit increase in HALP score leads to a 4.7 unit decrease in tumor diameter and a 14.8 unit decrease in metastatic lymph node count.

Conclusion: This study provides insights into the potential utility of the HALP score in predicting clinical outcomes for gastric cancer patients. While these findings are promising, research with large patient data is essential to validate the prognostic value of the HALP score and determine its clinical applicability. The HALP score may assist clinicians in risk stratification and therapeutic decision-making, and ultimately contributing to improved patient outcomes in the management of gastric cancer.

Keywords: Gastric cancer, HALP score, mortality, prognosis

INTRODUCTION

Gastric adenocarcinoma is the fifth most common malignancy worldwide and the third leading cause of cancer-related deaths (1). Adenocarcinomas comprise more than 95% of all gastric cancer cases histopathologically (2).

As most patients are diagnosed in the advanced stage of the disease, the prognosis is dismal (3). In the context of gastric adenocarcinoma, prognostic factors are currently limited to clinicopathological properties, such as tumor size, grade, invasion, lymph node involvement, and molecular markers like HER2 overexpression (4). Nevertheless, there may be significant differences in survival rates between patients with the same TNM stage. These variations have led scientists to search for new biomarkers to accurately predict the prognosis.

One such biomarker is the hemoglobin, albumin, lymphocyte, and platelet (HALP) score calculated using HALP scoring. A review of the literature reveals that the first article on gastric cancer and the development

of HALP as a prognostic tool was published in 2015 by Chen et al (5). The HALP score, evaluating both the immune system and nutritional condition, is valuable as a prognostic factor in many cancer types, particularly gastrointestinal malignancies (6).

The aim of this study is to assess the utility of the HALP score as a prognostic tool in predicting the clinical outcomes of patients with gastric adenocarcinoma and to identify subgroups with a significant risk of poor survival.

METHODS

Study Population

A retrospective review of patients who underwent gastrectomy for gastric cancer between 2018 and 2021 in the Department of Surgical Oncology, Gulhane Medical School Training and Research Hospital, University of Health Sciences. A total of 166 patients were identified. Five patients with pathology results showing complete response after neoadjuvant treatment and three patients with pathology diagnosis of non-adeno cancer (neuroendocrine tumor, lymphoma) were excluded from the study. A total of 158 patients who underwent surgery for the diagnosis of gastric adenocarcinoma were included in the study. There was no upper age limit in our study and all individuals over 18 years of age were included.

Establishment of HALP Score

Preoperative blood samples obtained during the preparation for anesthesia were analyzed for Hgb, albumin, lymphocytes, and platelets. The Hemogram, Albumin, Lymphocyte, and Platelet (HALP) score for each patient was retrospectively calculated using the following formula:

HALP Score = (Hemoglobin level (g/dL) × Lymphocyte count (10^3/μL)) x (Albumin level (g/dL) / Platelet count (10^3/μL))

Study Design

We retrospectively reviewed the patient files. Clinicopathologic parameters and demographic data were extracted. First, the HALP scores of the patients were calculated by the formula. The relationship between the HALP score and demographic and clinicopathologic parameters was evaluated. The possible relationship between HALP score and T stage, N stage, number of lymph node metastases, tumor size, lymphovascular invasion (LVI), and perineural invasion (PNI), which have a significant role in the prognosis of gastric cancer, was investigated. A regression analysis was performed to determine the efficacy level of these parameters that have a statistically significant relationship with the HALP score. The impact of the HALP score on early gastric cancer prognosis was investigated. Survival data of the patients were recorded.

STATISTICAL ANALYSIS

Data were analyzed by using SPSS version 22.00. For the homogeneity and normality analysis of the scaled data, Kolmogorov-Smirnov and Shapiro-Wilks tests were performed. One-Way ANOVA, Kruskal Wallis, post hoc multiple comparison (Bonferroni) tests were utilized for the analysis of multiple groups. The Mann Whitney-U test was used in the two-group scaled analysis. Univariate regression was calculated by Binary Logistic regression and Multinominal Logistic regression analysis model. The Spearman correlation test was performed for dependency analysis of the scaled data. $P<0.05$ was deemed statistically significant.

RESULTS

Patient Characteristics

The 158 patients who underwent gastrectomy for gastric adenocarcinoma were evaluated in this study. 101 of the patients were male and 57 were female. The mean age was 61.70 years (range 27-88). The tumor was localized in the small curvature in 50 patients, the antrum in 59 patients, and the proximal in 49 patients. In 52.5% of the patients, gastrectomy was performed following neoadjuvant treatment. None of our patients had peritoneal carcinomatosis or intra-abdominal ascites. 62 (39.2%) and 63 (39.9%) patients were in the T4 and T3 stages, respectively. There were 111 patients with lymph node metastasis, and the mean count of metastatic lymph nodes was 7.02. 120 patients had LVI and 105 patients had PNI. The mean value of hemoglobin (Hgb) was 11.86 g/dL (range 7.5-16.1), the mean value of albumin was 3.51 g/dL (range 2.10-4.60), the mean value of lymphocyte was 1.73 10^3 /μl (range 0.3-4) and the mean value of the platelet was 252.27 10^3 /μl (range 75-531). The median value of the HALP score was 0.32 (range 0.05-1.14). Of the patients, 87 were alive, and follow-up was ongoing. The demographic and clinicopathologic distribution of all patients is detailed in **Table 1**.

Comparison of the HALP Score with Clinicopathological factors

First, we performed normality and homogeneity tests on the HALP score. We found that they were not equally distributed in both analyses. There was no significant difference in the distribution of the median value of the HALP score by gender, showing a homogeneous distribution ($p=0.947$). There was no significant difference in the distribution of the HALP score according to tumor localization and it was the highest in patients with the antrum localization. A significant difference was found in the distribution of the HALP score by T stage ($p=0.008$). This difference is attributed to the relationship between the median HALP score of T1 and T4 patients (Post-Hoc Bonferroni test T1 between T4 HALP score $p=0.024$). Similarly, there was a significant difference in the distribution of the HALP scores of

Table 1. Demographic characteristics of patients

Age, years, mean±SD, range	**61.70±12.21 (27-88)**
Gender, n(%)	
Male	**101 (%63.9)**
Female	**57 (%36.1)**
Tumor Localization, n(%)	
Lesser curvature	**50 (%31.6)**
Distal	**59 (%37.3)**
Proximal	**49 (%31)**
Operation, n(%)	
Distal Gastrectomy	**54 (%34.2)**
Total Gastrectomy	**104 (%65.8)**
Neoadjuvant Treatment, n(%)	
No	**83 (%52.5)**
Yes	**75 (%47.5)**
Tumor size, mm, mean±SD, range	**4.99±3.15 (1-16)**
Degree of T invasion, n(%)	
T1	**21 (%13.3)**
T2	**12 (%7.6)**
T3	**63 (%39.9)**
T4	**62 (%39.2)**
Lymph Node Dissection, number, mean±SD, range	**27.70±12.42 (13-66)**
Lymph Node Metastasis, number, mean±SD, range	**7.02±9.03 (0-43)**
N stage grade, n(%)	
N0	**47 (%29.7)**
N1	**31 (%19.6)**
N2	**28 (%17.7)**
N3	**52 (%32.9)**
TNM Stage, n(%)	
Stage 1	**24 (%15.2)**
Stage 2	**32 (%20.3)**
Stage 3	**92 (%58.2)**
Stage 4	**10 (%6.3)**
LVİ, n(%)	
No	**38 (%24.1)**
Yes	**120 (%75.9)**
PNİ, n(%)	
No	**53 (%33.5)**
Yes	**105 (%66.5)**
Hgb, g/dL, mean±SD, range	**11.86±1.84 (7.50-16.10)**
Albumine, g/dL, mean±SD, range	**3.51±0.46 (2.10-4.60)**
Lymphocyte, 10^3 /µl, mean±SD, range	**1.73±0.69 (0.30-4)**
Platelet, 10^3 /µl, mean±SD, range	**252.27±85.53 (75-531)**
HALP Score, mean±SD, range	**0.32±0.19 (0.05-1.14)**
Survival, n(%)	
Li Table 1. Demographic Characteristics of Patients ve Ex	**87 (%55.1)**
	71 (%44.9)

SS; standard deviation, LVİ; lympho-vascular invasion, PNİ; peri-neural invasion, Hgb; Hemoglobin

the N stages (p=0.001). This difference is attributed to the relationship between the median HALP score of the n0 group (0.37) and the n3 group (0.21) (Post-Hoc Bonferroni test n0 between n3 HALP score p=0.001). We observed a significant distribution of LVI and PNI levels in the HALP scores (p=0.013 and p=0.009). The median HALP score was 0.36 in LVI-negative patients and 0.29 in LVI-positive patients. Similarly, the median HALP score of PNI-negative patients was 0.36 and the median HALP score of PNI-positive patients was 0.27 (Table 2).

We investigated the correlation between the HALP score and the number of metastatic lymph nodes and tumor diameter. We determined a significant negative correlation between both parameters and the HALP score (Table 3). Each one-unit increase in the HALP score leads to a 14.8240 unit decrease in the number of metastatic lymph nodes (p<0.001). Similarly, a one-unit increase in the HALP score leads to a 4.775 unit decrease in tumor diameter (p<0.001).

Univariate analysis of the HALP score for T stage, N stage, LVI status and PNI status

We performed a regression analysis to evaluate the effect of the HALP score on T stage, N stage, LVI, and PNI levels. We previously found that the HALP score was lower in T4 group patients and higher in T1 group patients. In the multinominal logistic regression, considering T4 patients as the reference category, the probability of higher HALP scores in T1 and T2 group patients was statistically significant. This probability was higher in T1 patients and was increased by 3.806 times. There was no significant relationship between T3 and T4 group patients. We accepted n3 patients as the reference category in the N stage analysis. The probability of having high HALP scores in the patients in the n0 and n2 groups was statistically significant compared to the patients in the n3 group. Binary logistic regression analysis was performed for LVI and PNI. We found a negative correlation with the HALP score in both parameters. An increase in the HALP score was associated with an increased likelihood of negative LVI and PNI (OR=0.133, 95% CI: 0.017-0.733, p=0.022 and OR=0.129, 95% CI: 0.022-0.759, p=0.024) (Table 4).

DISCUSSION

A standardized neoadjuvant/adjuvant chemotherapy and surgical treatment protocol is implemented for gastric cancer with well-defined guidelines. The effectiveness of this treatment is evaluated by analyzing the results of surgical treatment and survival analysis based on clinical and pathological stage. However, the standardized treatment approaches for tumor size, lymph status, metastasis status and disease survival analyses have shortcomings such as the inability to evaluate individual patient factors. The HALP score, calculated using hemoglobin, albumin, lymphocyte and platelet parameters, is used as an indicator of both the immunological and nutritional status of patients. In the last several years, HALP score has emerged in the literature as a new prognostic biomarker that has been used to predict a number of clinical outcomes in the context of various neoplasms. XU et al published a negative correlation between HALP score and prognosis

Table 2. Distribution of Clinico-pathologic factors according to HALP scoring system

Clinico-pathological Factors	HALP Score, median, range	P değeri
Gender, n(%)		
Male	0.30 (0.052-0.898)	p=0.947[U]
Female	0.29 (0.057-1.143)	
Tumor Localization, n(%)		
Lesser Curvature	0.28 (0.063-0.985)	
Antrum	0.34 (0.057-0.898)	p=0.160[H]
Kardia	0.29 (0.052-1.143)	
Degree of T invasion, n(%)		
T1	0.41 (0.11-0.898)	
T2	0.36 (0.057-0.702)	p=0.008[H]
T3	0.33 (0.052-0.985)	
T4	0.24 (0.057-1.143)	
Degree of N invasion, n(%)		
N0	0.37 (0.086-0.898)	
N1	0.34 (0.052-0.985)	p=0.001[H]
N2	0.32 (0.083-1.143)	
N3	0.21 (0.057-0.707)	
TNM Stage, n(%)		
Stage 1	0.42 (0.110-0.898)	
Stage 2	0.29 (0.057-0.766)	p<0.001[H]
Stage 3	0.29 (0.052-1.143)	
Stage 4	0,13 (0,068-0,411)	
LVİ, n(%)		
No	0.36 (0.069-0.766)	p=0.013[U]
Yes	0.29 (0.052-1.143)	

in rectal cancer patients. Sun e al, showed that low HALP was associated with worse overall survival, outperforming other hematological markers in biliary tract adenocancer patients (7,8).

In this study, we evaluated the effectiveness of the HALP score in a large series of gastric adenocarcinoma patients. As remarkable results of our study, the number of metastatic lymph nodes and tumor diameter determined a significant negative correlation with the HALP score (p<0.001). An increase in the HALP score was associated with an increased likelihood of negative lymphovascular invasion and perineural invasion (OR=0.133, 95% CI: 0.017-0.733, p=0.022 and OR=0.129, 95% CI: 0.022-0.759, p=0.024).

The HALP score, calculated using hemoglobin, albumin, lymphocyte and platelet parameters, is used as an indicator of both the immunological and nutritional status of patients. Anemia is a common paraneoplastic syndrome in patients with malignancies, especially in esophageal and gastric cancers located in the upper digestive tract, due to both oral intake disorders and chronic bleeding from the tumor (9). What is the role of these HALP score components in cancer pathogenesis and the mechanisms that are hypothesized to underlie them?

Platelets are known to secrete vascular endothelial growth factor (VEGF) and aggravate tumor angiogenesis. For this reason, they are thought to play a key role in the metastasis of tumor cells (10,11). Chronic low hemoglobin is a well-documented, cheap and easily accessible parameter that occurs in cancer patients by various mechanisms. One of the roles of chronic low hemoglobin in cancer patients is the secretion of

Table 3. Distribution of Clinico-pathologic factors according to HALP scoring system

Correlation of Number of lymph node dissection number					
Clinicopathological Factors		N		rho	p value
1- Age		158		-0.190	0.017
2- Tumor Diameter		158		-0.370	<0.001
3- Lymph Node Metastasis		158		-0.346	<0.001
Regression					
Dependent Variables	Independent Variable	B	95% Cl for B	t	p value
1- Age	HALP Score	-11.926	-21.877-1.975	-2.367	0.019
2- Tumor Diameter		-4.775	-7.276-2.274	-3.771	<0.001
3- Lymph Node Metastasis		-14.824	-21.935-7.714	-4.118	<0.001

Table 4. Univariate analysis of HALP score for T stage, N stage, LVİ status and PNİ status of Clinico-pathologic factors according to HALP scoring system

Variables	B	O.R	95% Cl for O.R		P value
			Lower	Upper	
T Stage					
T1	3.806	44.966	3.205	630.806	0.005
T2	3i540	34.473	1.494	795.601	0.027
T3	1.632	5.112	0.625	41.820	0.128
Reference category T4					
N Stage					
n0	4.708	110.83	8.531	1439.91	<0.001
n1	2.772	15.99	0.964	265.34	0.053
n2	3.660	38.88	2.303	656.32	0.001
Reference category n3					
LVİ	-2.184	0.113	0.017	0.733	0.022
PNİ	-2.046	0.129	0.022	0.759	0.024

proinflammatory cytokines such as interleukin-6 (IL-6) from immune cells. IL-6, together with IL- and TNF alpha, is one of the most potent proinflammatory cytokines known. IL-6 stimulates Hepcidin release from the liver and inhibits iron absorption and release by cancer cells (12-14). Another feature is that it reduces erythropoiesis (15).

Two significant parameters affecting blood albumin levels are nutritional status and metabolic status of the patient. CRP and albumin concentrations, utilized in various prognostic scoring systems, were used in many studies involving patients with malignancies and evaluating survival and treatment efficacy (16-18). In one of these studies, Liv et al. showed a decrease in mortality rates in cachectic malignancy patients whose serum albumin levels were increased. As a result of these studies, albumin has been accepted as a good marker for prognosis (19). In cancer patients, lymphocytes are thought to play an important role in the detection and elimination of tumor cells. Based on this idea, lymphopenia is thought to play an important role in prognosis (20).

In order to have an idea about the prognosis of patients with malignancies, the HALP score includes all four of these parameters. Platelets are included in the denominator of the calculation, while hemogram, albumin and lymphocytes are in the numerator. Therefore, a high HALP score is used as a positive indicator of prognosis to identify patients with low immune-nutritional function and to determine risk stratification.

The present study on gastric adenocarcinoma shows that the evaluation of HALP score as a prognostic index is useful considering the publications on other cancer types in the literature. The main discussion at this point is whether the results of the HALP score should be perceived as a prognostic index or evaluated as a precautionary measure for possible clinical outcomes (21). There are limitations regarding the practical use of this score, the timing of calculation and its contribution to treatment planning. The clinical reflection of this prognostic index will be meaningful if inferences can be derived on how to plan the treatment of patients with significant cutoff values obtained from retrospective cases. Clarification of the clinical implications at this stage, such as whether a nutritional or immunomodulatory supportive treatment is to be implemented based on the HALP score, or whether treatment should be prolonged, changed or discontinued early in the planning of possible neoadjuvant treatment, would be the potential subject of prospective randomized studies.

Among patients with resectable disease, including stage III/IV patients, nomograms based on T stage and N stage, comprehensive treatment, age at diagnosis, grade and tumor size perform well in personalized prediction of likely survival (22). The HALP score provides a chance to intervene in possible preoperative treatment or nutritional status, which may add dynamism and clinical relevance to the HALP score.

In conclusion, our study provides a framework for investigating the prognostic potential of the HALP score in gastric cancer. Real-world research efforts are required to confirm its clinical utility and to pave the way for improved patient outcomes in the management of this challenging malignancy.

DECLARATIONS

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study, and they were allowed to withdraw at any time.

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