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Could the HALP score indicate poor prognosis in colorectal cancer patients?

Ömer Çağlıyan[1], Hilmi Yazıcı[2], Ahmet Can Yaşar[3], Yaşar Çağlar Bekki[3], Sedat Tan[3], Erkan Oymacı[3], Ahmet Mücteba Öztürk[3], Mehmet Yıldırım[3]

[1]Department of Surgical Gastroenterology, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, İstanbul, Türkiye
[2]Department of General Surgery, Marmara University, Pendik Training and Research Hospital, İstanbul, Türkiye
[3]Department of General Surgery, University of Health Sciences Türkiye, İzmir City Hospital, İzmir, Türkiye

ABSTRACT

Objective: Colorectal cancer (CRC) is a major health problem worldwide. According to estimates for the year 2030, cancer will be the number one cause of death for both genders. CRC is the third most common type of cancer and the second most common cause of cancer-related deaths. Various parameters are needed to provide information about the course and prognosis of the disease.

Material and Methods: The study included 103 patients diagnosed with CRC between 2017 and 2023. The patients' HALP scores were retrospectively analyzed together with clinical data. The relationship between survival times, disease stage, and treatment response was examined.

Results: The obtained data showed that low HALP scores were associated with worse overall survival. Although the HALP score cut-off value was found to be different in various studies conducted on benign or malignant diseases, a low HALP score indicates a poor prognosis. In our study, a HALP score below 23 was found to be associated with low overall survival.

Conclusion: This study suggests that a low HALP score is associated with poor prognosis and could serve as a valuable prognostic marker in the clinical management of CRC patients. However, certain limitations must be considered. While albumin is a marker of systemic inflammation and nutritional status, its specificity is limited in acute and chronic inflammatory conditions, which may impact the prognostic value of the HALP score. Further investigation into the biological mechanisms underlying this relationship and the potential of the HALP score in predicting treatment response would enhance its clinical applicability.

Keywords: Colorectal cancer, HALP score, prognosis, survival

INTRODUCTION

Cancer is a significant health problem worldwide. Estimates for 2030 predict that cancer will be the number one cause of death for both genders (1). Colorectal cancer (CRC) is the third most common type of cancer and the second most common cause of cancer-related deaths (2). The American Cancer Society predicts that approximately 153,020 people will be newly diagnosed with CRC in 2023 (2).

The most commonly used method for staging colon CRC is tumour, node, metastasis (TNM) staging. TNM staging is a scoring system that evaluates the invasion of the tumor into the colon layers, the number of metastases to the lymph nodes of the relevant colon segment, and whether there is metastasis to distant organs (3,4). The stage of the disease is still the most important prognostic factor for CRC. Nevertheless, recent research has focused on different prognostic factors for CRC.

It is well known that systemic inflammation and nutrition play a role in the proliferation of cancer cells, local invasion, and metastasis to lymph nodes or distant organs (5). Deficiencies in immunity and nutrition have been associated with cancer cells exhibiting aggressive behavior. In previous studies, blood cells such as platelets, monocytes, neutrophils, and lymphocytes have been associated with tumor proliferation, invasion, and distant organ metastasis, and have been found to be significant (6). Attempts have been made to obtain information about the course

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Corresponding Author
Hilmi Yazıcı
E-mail: hilmiyazici@hotmail.com
ORCID ID: orcid.org/0000-0001-7470-0518

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of cancer by comparing different inflammatory markers. Several inflammatory markers, such as neutrophil to lymphocyte ratio, platelet-lymphocyte ratio and systemic inflammation response index, have been defined and used to predict prognosis in various types of cancers (6-9). The hemoglobin, albumin, lymphocyte, platelet score (HALP) index, which was first described by Chen et al. (10), includes a combination of hemoglobin, albumin, lymphocyte, and platelet values. This index indicates nutritional status and systemic inflammation, and provides information about the patient's prognosis. HALP score has been used to determine the prognosis of patients in intensive care units with various types of cancer, such as prostate, breast, and lung cancer (11-16).

In this study, we investigated whether the HALP index can be used as a prognostic marker for CRC.

MATERIAL and METHODS

A retrospective analysis was conducted on data from patients who underwent CRC surgery between 2017 and 2023 at University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital General Surgery Clinic. Patients who were admitted to our clinic, but whose HALP score could not be calculated due to lack of data and whose disease stage could not be determined, were excluded from the study. Patients' demographic data, radiological images, pathology records, operative notes, and laboratory values were recorded.

Clinical and pathological variables of all included patients were collected from electronic medical records. These included age, gender, comorbid diseases, tumor characteristics (location, degree of differentiation, presence of lymphovascular/perineural invasion, and staging features), presence of mismatch repair mutation, type of surgery performed, total number of lymph nodes removed, number of positive nodes, and information on complications. In addition, preoperative serum albumin, hemoglobin, lymphocyte, and platelet values were collected for all patients to calculate the HALP index. All patients were staged according to the 8th edition American Joint Committee on Cancer TNM staging system (17).

HALP index was calculated with the following formula: Hemoglobin level (g/L) × albumin level (g/L) × lymphocyte count (/L) / platelet count (/L) (10). To investigate the prognostic impact of the HALP score, we determined a cut-off value, calculated by the receiver operating characteristics (ROC) analysis, obtained from the study group. The HALP score cut-off value was calculated as 23. The threshold based on the Youden index (sensitivity + specificity - 1) was chosen to estimate sensitivity and specificity. The cohort of the study was analyzed in two groups according to the determined HALP cut-off.

The primary outcome of this study was to evaluate whether HALP has a prognostic value for CRC.

The secondary outcomes involved evaluating whether HALP predicts early hospital mortality in patients undergoing CRC surgery.

This study was approved by the Ethics Committee of the University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital (no: 2023-200, date: 27.11.2023), and it was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all patients.

Statistical Analysis

SPSS version 24.0 (SPSS Inc. IBM, Chicago, U.S.) was used for statistical analysis. The continuous data were presented as mean ± standard deviation, median, and interquartile range, and categorical data were presented as numbers and frequencies. The proportion or frequency was compared between the two groups using Fisher's exact test or the χ^2 test, and differences in continuous variables were evaluated using the Student's t-test and the Mann-Whitney U test for non-parametric values. Survival curves were compared using the Kaplan-Meier method and the log-rank test. Cox regression analysis was used for univariate and multivariate overall survival (OS) analysis.

RESULTS

In our center, 245 patients underwent CRC surgery between January 2017 December 2023. One hundred forty-two patients were excluded from the study because of loss of follow-up, and lack of data. A total of 103 patients were included in the study.

According to ROC analysis, the HALP score cut-off value was calculated as 23. Group 1: HALP score <23. Group 2: HALP score >23 (Figure 1).

The HALP <23 group yielded 60 patients, while the HALP >23 group included 42 patients. Patient demographics such as age, gender, and comorbid disease were similar between the groups. However, the mean hemoglobin level, the mean albumin level, the mean lymphocyte count, and the median platelet counts were significantly different in both groups, as expected (Table 1).

Postoperative outcomes are summarized in Table 2. Only one perioperative mortality case was observed in each group, and the result was not statistically significant. Tumor localization and pathological outcomes were also similar between the two groups.

Univariate and multivariate Cox regression analyses were performed to evaluate prognostic factors for CRC. In the univariate analysis, age, comorbid disease, stage M, and the HALP score were found to be significant in CRC prognosis. However, in

the multivariate analysis, only stage M and the HALP score were poor independent prognostic factors for CRC patients' prognosis (Table 3).

The five-year OS was 68.4% in the HALP <23 group, while the OS was 83.3% in the HALP >23 group. The Kaplan-Meier analysis showed that the HALP <23 group has worse survival outcomes than the HALP >23 group, with a significant result (log-rank: 0.012). Survival curves of the two groups are shown in Figure 2.

DISCUSSION

The HALP index is a criterion that can be used to determine prognosis and survival in cancer patients. It is easy, cheap to calculate. It is calculated using only four parameters, with all parameters examined for all patients preoperatively. Systemic inflammation plays a crucial role in tumorigenesis. Growing evidence indicates the critical role of lymphocytes, especially in tumor suppression. Moreover, hemoglobin, lymphocytes, and platelet values reflect the synthesis ability of the hematopoietic system. However, its reliability as a prognostic marker in CRC should be carefully interpreted, considering certain limitations. Albumin is a negative acute phase reactant. It varies in inflammatory conditions in the body and in the presence of cancer. Low albumin values are observed in long-term malnutrition. Although albumin is commonly used as a marker of nutritional status and systemic inflammation, its specificity is limited in both acute and chronic inflammatory conditions. This variability may weaken the prognostic significance of the HALP score in CRC patients, where chronic inflammation is a hallmark of disease progression (18). Therefore, the HALP score can be a guide prognosis and survival, not only in malignant but also in benign diseases. Studies on the HALP score are available not only in malignant diseases but also in benign diseases. In a study conducted by Tian et al. (19), they associated low HALP scores with acute ischemic stroke and recurrence within 90 days. In a meta-analysis published by Li et al. (20), high platelet and low lymphocyte values were associated with poor prognosis and OS in cancer patients with an impaired platelet-lymphocyte ratio. A study conducted by Gasparyan et al. (21) found that a high platelet-lymphocyte ratio and a high platelet count in patients are highly predictive of rheumatic disease.

There are limited numbers of studies that investigate the HALP score in relation to CRC prognosis. Different cut-off values for the HALP score have been found in various studies. In the study conducted by Calderillo Ruiz et al. (14) on hispanic-based colon cancer patients, the cut-off value for the HALP score was calculated as 15. Guo et al. (22) reported that HALP score is an important prognostic factor in their study on patients with metastatic prostate cancer. And in this study, the HALP

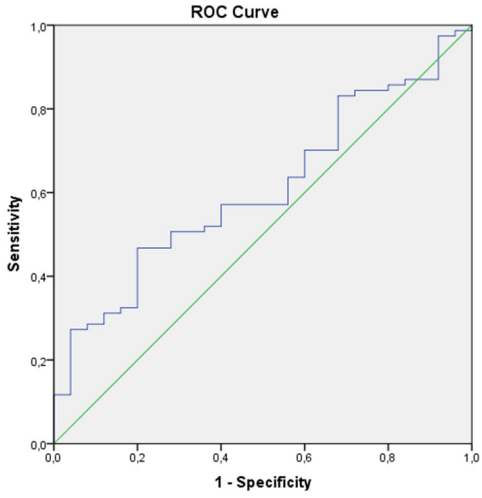

Figure 1. ROC curve analysis for the HALP score.

Area	Std. error	Asymptotic sig. Lower bound	Asymptotic 95% confidence interval	
			Upper bound	
0.607	0.060	0.108	0.490	0.725

Table 1. Basic characteristics between lower and higher HALP groups

n=103	**HALP <23 (n=60)**	**HALP >23 (n=42)**	**p**
Age (mean ± SD)	65.1 (±12.8)	63.7 (±13.3)	0.588
Gender (%) Male Female	 33 (55%) 27 (45%)	 30 (71%) 12 (29%)	0.091
Comorbid diseases Presence Absence	 42 (70%) 18 (30%)	 27 (64%) 15 (36%)	0.544
Pre-operative hemoglobin (g/dL) (mean ± SD)	10.6 (±1.9)	12.6 (±1.9)	<0.001
Pre-operative albumin (g/dL) (mean ± SD)	3.5 (±0.5)	4.1 (±0.6)	<0.001
Pre-operative lymphocyte (mL) (mean ± SD)	1.3 (±0.7)	2 (±0.7)	<0.001
Pre-operative platletel (cells*10^9L) [median (IQR)]	349 (IQR: 165)	256 (IQR: 124)	<0.001

IQR: Interquartile range, HALP: Hemoglobin, albumin, lymphocyte, platelet score, SD: Standard deviation

score cut-off value was determined as 32.4. In the study by Güç et al. (23) on patients with non-small cell lung cancer, the HALP score cut-off value was found to be 23.24. In our study, the cut-off value for the HALP score was found to be 23. In the study conducted by Ekinci et al. (12) on patients with renal cell carcinoma, the HALP score cut-off value was determined to be 27.7, and an HALP score below 27.7 was associated with poor prognosis. In a study by Zhai et al. (7), the HALP score cut-off value in patients with non-small cell lung cancer was considered 48, and a low HALP score was found to be associated with lower OS. Zhang et al. (24) examined various biomarkers and scores in patients with intrahepatic cholangiocarcinoma. In their study, the HALP score cut-off value was 43.6 and the HALP score was found to be associated with intrahepatic recurrence and lymph node metastasis (24). Farag et al. (11) reviewed studies including various types of cancer, such as gastric, gastrointestinal, lung, esophageal, pharyngeal, bladder/urothelial, prostate, and gynecological cancers, and mentioned HALP scores. In the analyses, the HALP score cut-off value was between 20-49. Duran et al. (25) in their study on breast cancer patients, reported the HALP score to be 29.01. Although the HALP score alone was not sufficient to predict axillary lymph node positivity, it was found to be associated with advanced or aggressive tumors (25).

Albumin is a negative acute phase reactant. Many different factors affect serum albumin levels, and it has been shown to lack sensitivity and specificity as an indicator of nutritional status. Specifically, acute and chronic inflammatory conditions affect serum albumin levels by altering hepatic protein metabolism and

Table 2. Pathological outcomes in both groups

n=103	HALP <23 (n=60)	HALP >23 (n=42)	p
B			
Right colon	17 (28%)	13 (31%)	
Transverse colon	6 (10%)	1 (2%)	
Left colon	9 (15%)	8 (19%)	0.616
Sigmoid colon	10 (17%)	8 (19%)	
Rectum	16 (27%)	9 (22%)	
FAP*/synchrone	2 (3%)	3 (7%)	
Operation			
Right hemicolectomy	23 (38%)	13 (31%)	
Left hemicolectomy	9 (15%)	9 (21%)	
Anterior resection	6 (10%)	5 (13%)	0.552
Low anterior resection	15 (25%)	11 (26%)	
Abdominoperineal resection	5 (9%)	1 (2%)	
Total colectomy	2 (3%)	3 (7%)	
Hospital mortality	1	1	0.797
Stage T			
T1	3 (5%)	2 (5%)	
T2	3 (5%)	4 (10%)	0.637
T3	29 (48%)	23 (55%)	
T4	25 (42%)	13 (30%)	
Stage N			
N0	31 (52%)	20 (48%)	0.670
N1	19 (32%)	12 (29%)	
N2	10 (16%)	10 (23%)	
Stage M			
M0	53 (88%)	38 (90%)	0.731
M1	7 (12%)	4 (10%)	
Pathological stage			
Stage I	5 (8%)	5 (12%)	
Stage II	23 (38%)	16 (38%)	0.933
Stage III	25 (42%)	17 (40%)	
Stage IV	7 (12%)	4 (10%)	
MSI			
High	9 (15%)	6 (14%)	0.920
Low	51 (85%)	36 (86%)	
Harvested lymph nodes [median (IQR)]	21 (20)	20 (16)	0.151
Tumor positive lympph nodes (mean ± SD)	2.3 (±4)	2.4 (±4.4)	0.904

IQR: Interquartile range, HALP: Hemoglobin, albumin, lymphocyte, platelet score, SD: Standard deviation, FAP: Familial adenomatous polyposis, MSI: Microsatellite instability

Table 3. Univariate and multivariate overall survival analysis for colorectal cancer

n=124	HR	95% CI	p	HR	95% CI	p
Gender	1.272	0.549-2.950	0.576			
Age	1.061	1.023-1.100	**0.001**	1.039	0.997-1.084	0.070
Comorbid diseases	7.771	1.827-33.054	**0.006**	2.473	0.872-7.013	0.089
Tumor localization	0.904	0.675-1.334	0.419			
Operation type	0.978	0.568-1.996	0.841			
Stage T (T1-T2 vs. T3-T4)	5.140	0.489-54.024	0.173			
Stage N (N0 vs. N+)	1.309	0.594-2.885	0.504			
Stage M	3.303	1.190-9.764	**0.022**	5.287	1.170-23.888	**0.030**
MSI	1.291	0.386-4.332	0.678			
HALP	0.327	0.130-0.821	**0.017**	0.314	0.123-0.793	**0.014**

HR: Hazard ratio, CI: Confidence interval, MSI: Microsatellite instability, HALP: Hemoglobin, albumin, lymphocyte, platelet score

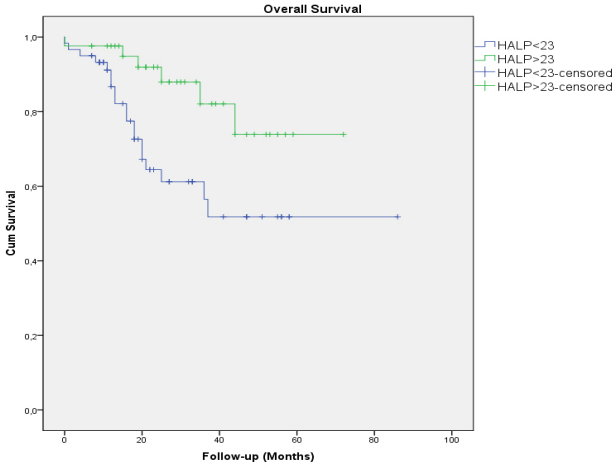

Figure 2. Overall survival in HALP <23 and HALP >23 groups. (Log-rank: 0.012).

HALP: Hemoglobin, albumin, lymphocyte, platelet score

inducing capillary leakage. This being the case, serum albumin is no longer considered a reliable nutritional marker in inflammatory states but rather a marker for disease severity (26). It is seen often in hospitalized patients and is associated with a poor clinical cours (27). There are many factors that affect serum albumin levels. Although it provides information about nutritional status, its specificity is low (28). The real reason for low serum albumin levels has been a subject of debate for a long time. It is known that malnutrition is related to hypoalbuminemia (29). Albumin levels have also been found to be low in acute and chronic inflammation. Therefore, it seems logical to include the albumin multiplier in the calculation of the HALP score because CRC patients are associated with both chronic inflammation and malnutrition.

Hemoglobin is responsible for carrying oxygen in the blood. It is found in red blood cells, and one of its building blocks is iron. In colorectal cancers, blood may be present in the stool due to spontaneous bleeding of the cancer. Low hemoglobin may be associated with colorectal cancers in older ages (30). In addition, anemia may be seen in conditions such as chronic inflammation (31). There is a hemoglobin multiplier in the HALP score calculation, so a low HALP score may be associated with a low hemoglobin value.

Study Limitations

This study has some limitations as well. First, its retrospective design might lead to some selection biases. Second, the relatively small number of patients might affect the strength of the statistical analysis. Finally, this study was conducted in a single center; hence, this may affect the generalizability of the results.

CONCLUSION

HALP score is an easy and inexpensive method to calculate. In CRC cases, poor HALP score is associated with low OS. Therefore, using the HALP score in CRC cases can provide information about OS.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital (no: 2023-200, date: 27.11.2023), and it was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all patients.

Footnotes

Author Contributions

Concept - Ö.Ç, H.Y., A.C.Y., Y.Ç.,B., S.T., E.O., A.M.Ö., M.Y.; Design - Ö.Ç, H.Y., A.C.Y., Y.Ç.,B., S.T., E.O., A.M.Ö., M.Y.; Data Collection or Processing - Ö.Ç., Y.Ç.B., A.C.Y.; Writing - H.Y., S.T., E.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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