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The ability of HALP score to distinguish between malignant and benign colorectal neoplasms and its prognostic importance in colorectal cancers

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Abstract

Systemic inflammation and nutritional status play important roles in the development and progression of various cancers, including colorectal cancer. The prognosis for malignancies can be predicted using the inflammatory marker known as HALP (calculated by hemoglobin, albumin, lymphocytes, and platelets). Furthermore, recent studies have claimed the HALP score to help distinguish between benign and malignant lesions. We aimed to research the diagnostic importance of the HALP score in the differentiation of malignant (colorectal cancer) and benign colorectal neoplasms (colorectal adenomas and hyperplastic polyps) and its prognostic significance in colorectal cancer patients. Patients diagnosed with colorectal cancer, colorectal adenoma, and hyperplastic polyps were evaluated retrospectively between January 2017 and January 2022. The median HALP score in the colorectal cancer group was significantly lower than the other groups (colorectal adenoma and hyperplastic polyps) ($p<0.001$). There was no statistical difference between the median HALP scores of the colorectal adenoma and hyperplastic groups ($p=0.525$). ROC analysis found the cut-off value of the HALP score as 41.01 to differentiate colorectal cancer from benign colorectal lesions (sensitivity= 0.73, specitivity=0.62, 95% CI=0.67-0.76, $p<0.001$). The HALP level below 28.1 was associated with worse overall survival ($p=0.046$) and was shown to be an independent prognostic factor in the colorectal cancer group. The HALP score can be used to differentiate colorectal cancer from benign colorectal neoplasms and as a prognostic factor in colorectal cancer.

Keywords: Colorectal cancer, benign colorectal neoplasms, HALP score, overall survival

Introduction

Colorectal cancer (CRC), the third most common cancer in the world, is the second most important cause of cancer-related mortality [1]. Approximately 85% of CRCs are sporadic and grow slowly with the accumulation of multiple genetic mutations in adenomatous lesions originating from the glandular epithelium of the colon [2]. Hyperplastic polyps (HPPs), juvenile polyps, hamartomas, and pseudopolyps are non-neoplastic polyps. In particular, HPPs are common and have a very low malignant potential, whereas adenomatous polyps show gradual dysplastic changes over time [3]. In the absence of particular diagnostic indicators, the pathologic diagnosis of HPP, CRA, and CRC primarily relies on histological investigation to identify epithelial morphological alterations.

Nutritional conditions and systemic inflammation are crucial for the onset and progression of many malignancies, including CRC [4,5]. Additionally, many easily accessible hematological indicators of immunological or nutritional function, including

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serum hemoglobin [6], albümin [7], lymphocyte, and platelet [8], have been widely employed in clinical practice. A novel inflammation index known as HALP, which combines hemoglobin, albumin, lymphocytes, and platelets, has been discovered in recent investigations. It may be utilized as a prognostic marker in patients with numerous malignancies, including colorectal cancer [5,9]. It was previously shown that the HALP score is a valuable marker in differentiating benign and malignant prostate masses [10]. Additionally, it has been proposed that the HALP score can differentiate between malignant and benign causes of acute mechanical bowel obstruction [11].

Therefore, in this research, our goal was to evaluate the diagnostic importance of the HALP score in the differentiation of malignant and benign colorectal neoplasms and its prognostic significance in patients diagnosed with CRC.

Materials and Methods

This study was designed as cross-sectional and retrospective. Between January 2017 and January 2022, patients older than 18 diagnosed with CRC, CRA, and HPP in the gastroenterology clinic were included in the study. Patients with hereditary polyposis syndrome, synchronous colorectal neoplasms, extracolonic malignancies, chronic liver diseases, chronic kidney failure, chronic heart failure, and hematological conditions other than iron deficiency anemia were excluded. Demographic data, tumor localization in the colon (right, left, and rectum), TNM staging, vascular invasion, perineural invasion, and tumor differentiation grade were recorded. In the CRC group, overall survival (OS) was calculated as the interval from diagnosis to exitus or the final visit. Initial laboratory parameters at diagnosis were recorded. Hemoglobin (g/L), albumin (g/L), lymphocyte (/L), and platelet (/L) counts were used to determine HALP.

IBM SPSS Statistics 22.0 was employed for analysis. The Shapiro-Wilk and Kolmogorov-Smirnov tests were applied to evaluate if the data had a normal distribution. The non-normally distributed variables were utilized in the Kruskal-Wallis and Mann-Whitney U tests. The differences for categorical variables were compared using the Chi-square test. ROC analysis was used to establish the HALP level cut-off value. Kaplan Mayer statistics were used to calculate survival times, and the Log-Rank Test was used to show the difference in survival times between groups of CRC patients. The threshold for statistical significance was a p-value of 0.05 or lower.

Zonguldak Bülent Ecevit University Faculty of Medicine Clinical Research Ethics Committee approved the study (Protocol No: 2022/04 Approval Date: 23 February 2022).

Results

Five hundred-four patients with 206 CRC, 200 CRA, and 98 HPP were included in the study. The CRC group's median age was 68 (63-73), significantly older than the other groups (p=0.003). Male gender dominance was prominent in the CRC and CRA groups (p=0.011) (Table 1).

Table 1: Demographic characteristics of the study population

		CRC	HPP	CRA
Gender, n (%)	Male	128 (62.1%)	56 (57.1%)	146 (73%)
	Female	78 (37.9%)	42 (42.9%%)	54 (27%)
Age, median (IQR)		68 (63-73)	64.5 (57-72)	64 (57-71.5)
Hemoglobine, median (IQR)		11.6 (10.3-12.8)	13 (11.6-14.6)	13.4 (11.8-14.7)
Albumin, median (IQR)		3.9 (3.5-4.2)	4.4 (4.1-4.6)	4.4 (4.1-4.6)
Lymphocyte, median (IQR)		1700 (1200-2200)	1900 (1500-2300)	1900 (1500-2500)
Platelet, median (IQR)		264 (206-323)	231.5 (193-275)	224 (179.5-284.5)
HALP level, median (IQR)		28.1 (16.32-41.12)	48.5 (31.0-62.7)	48.7 (30.2-67.5)
Alcohol, n (%)	Yes	28 (13.6%)	3 (3.6%%)	11 (5.5%)
	No	178 (86.4%)	95 (96.4%)	189 (94.5%)
Smoking, n (%)	Yes	86 (41.7%)	15 (15.7%%)	28 (14.0%)
	No	120 (58.3%)	83 (84.3%)	172 (86.0%)

CRC: colorectal cancer, HPP: hyperplastic polyp, CRA: colorectal adenoma, IQR: interquartile range

According to the TNM stage of 206 patients in the CRC group, 96 (46.6%) were stage 2, and 74 (35.9%) were stage 3. Considering the cancer localization of the CRC group, 66 (32%) were located in the right colon, 84 (40.8%) in the left colon, and 56 (27.2%) in the rectum. Besides, 123 (59.7%) had a history of vascular invasion, 131 (63.6%) had perineural invasion, and 194 (94.2%) had a history of surgery for CRC. At the last visit of the CRC group, 143 (69.4%) were alive, and the median OS was 44.5 (24-72) months (Table 2).

The median HALP score in the CRC group was 28.1 (16.3-41.1), significantly lower than the other groups (p<0.001). The median HALP score was 48.7 (30.7-67.5) in the CRA group, and the median HALP score was 48.5 (31.0-62.7) in the HPP group, and the two groups were statistically not different (p=0.525). The cut-off value of the HALP score was found to be 41.01 when ROC analysis was used to differentiate cancer from benign lesions (sensitivity=0.73, specitivity=0.62, AUC±SE=0.72±0.02, 95% CI=0.67-0.76, p<0.001) (Figure 1).

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Table 2. Clinicopathological characteristics of colorectal cancers

		n (%)
Differentiation	Undifferentiated	17 (8.3%)
	Poor	151 (73.3%)
	Well	38 (18.4%)
Localization	Right	66 (32%)
	Left	84 (40.8%)
	Rectum	56 (27.2%)
Vascular invasion	No	123 (59.7%)
	Yes	83 (40.3%)
Perineural invasion	No	131 (63.6%)
	Yes	75 (36.4%)
Operation	No	12 (5.8%)
	Yes	194 (94.2%)
TNM stage	1	12 (5.8%)
	2	96 (46.6%)
	3	74 (35.9%)
	4	24 (11.7%)
Exitus	Yes	63 (30.6%)
	No	143 (69.4%)
Median overall survival, months (IQR)	44.5 (24-72)	

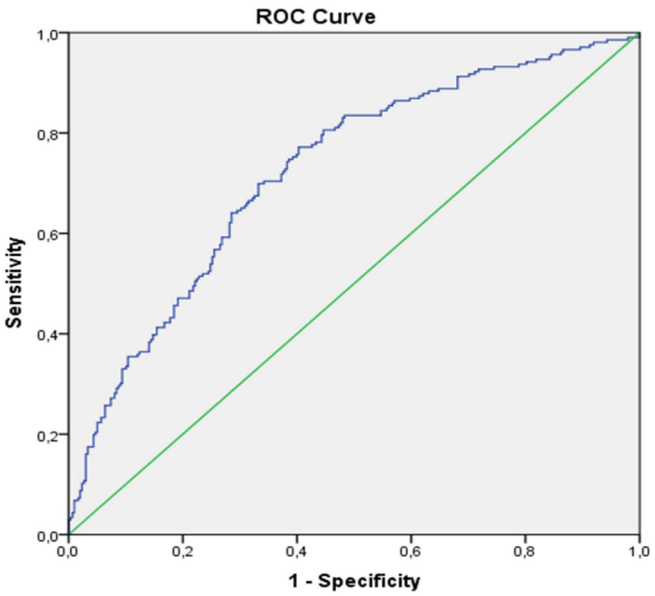

Figure 1. ROC analysis for HALP levels to differentiate between malign and benign colorectal neoplasms

There was no significant relationship between age (p=0.231), gender (p=0.644), smoking (p=0.609), alcohol habit (p=0.943), tumor localization (p=0.903), tumor differentiation grade (p=0.115), and OS. However, OS was significantly different according to vascular invasion status (p=0.010), perineural invasion status (p<0.001), and operation history (p<0.001) (Table 3).

Table 3. Univariate analysis of factors affecting overall survival in colorectal cancer

		Mean survival±SE	Lower bound	Upper bound	p-value
Gender	Male	92.4±5.2	82	102.7	0.644
	Female	107.7±7.9	92.1	123.3	
Age		112.1±7.2	98	126.3	0.231
		87.9±5.9	76.3	99.6	
Smoking	No	101.7±7.6	86.9	116.8	0.609
	Yes	90.8±6.5	77.9	103.7	
Alcohol	No	102.3±6.3	89.9	114.8	0.943
	Yes	94.7±10.5	74	115	
Differentiation	Undifferentiated	71.8±14.3	43.7	99.9	0.115
	Poor	103.2±6.7	90	116.3	
	Well	87.4±7.7	72.3	102.5	
Localization	Right	116.4±8.4	99.8	132.9	0.903
	Left	93.0±6	81.2	104.8	
	Rectum	85.7±6.9	71.9	99.4	
Vascular invasion	No	101.3±5	91.4	111.2	**0.010**
	Yes	91.3±8.2	75.2	107.4	
Perineural invasion	No	111.9±7.3	97.5	126.4	**<0.001**
	Yes	71.9±7.1	58	85.9	
Operation	No	27.4±9.7	8.3	46.4	**<0.001**
	Yes	106.3±5.9	94.7	117.9	
Stage	1-2	98.7±4.2	90.5	106.9	**<0.001**
	3	97.3±8.4	80.6	113.9	
	4	30.3±3.9	22.6	38	
HALP level	≤28.1	84.7±6.2	72.3	97	**0.046**
	>28.1	109.1±7.6	94.1	124.1	

To predict mortality, the ROC analysis found no significant cut-off value for the HALP level (AUC=0.560, p=0.167). The median HALP score for CRC patients was 28.1; this level was considered the cut-off. In Kaplan-Meier analysis, HALP levels below this value were associated with worse OS (p=0.046) (Figure 2).

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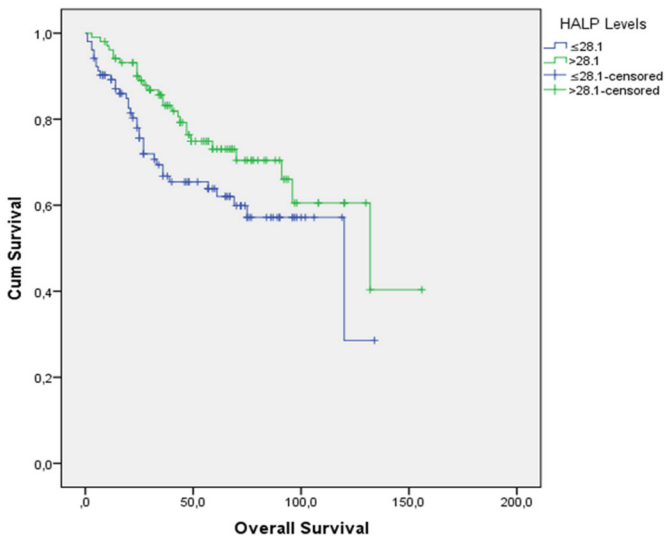

Figure 2. The effect of HALP on overall survival in colorectal cancer

In the multivariate analysis of these parameters, it has been shown that perineural invasion, no chance of operation, advanced TNM stage, and HALP score below 28.1 were independent risk factors for worse OS (Table 4).

Table 4. Multivariate analysis of factors affecting overall survival in colorectal cancer

	HR	95.0% CI		p-Value
		Lower	Upper	
Vascular invasion	1.117	0.627	2.209	0.611
Perineural invasion	2.227	1.117	4.224	**0.014**
Operation	3.064	1.355	6.929	**0.007**
Stage	1.805	1.196	2.722	**0.005**
HALP	1.692	1.02	2.809	**0.042**

HR: hazard ratio, CI: confidence interval

Discussion

The body's inflammatory response and nutritional status can be demonstrated by the HALP score, a parameter calculated from hemoglobin, albumin, lymphocyte, and platelet counts [5]. Systemic inflammatory response indicators are reliable predictors of prognosis in cancer patients [4].

In the present research, the median HALP score of patients with CRC was significantly lower than that of patients with CRA or HPP (benign colorectal neoplasms). If a cut-off value <41.01 was used for the HALP score, the sensitivity and specificity for detecting CRC were 73 percent and 62 percent, respectively. The HALP score has recently been shown to be used to differentiate mechanical bowel obstruction due to malignant causes from mechanical bowel obstruction due to benign causes [11] and to distinguish prostate cancer from benign prostatic hyperplasia [10]. Depending on lymphocytes, platelets, albumin, and hemoglobin levels, we calculated patients' HALP scores to reflect their nutritional and inflammatory state. We observed that the median HALP score of patients with CRA and HPP was not different. The similarity of nutritional and inflammatory conditions in patients with CRA and HPP can be explained by the lack of malignant differentiation in these patients. However, to our knowledge, no study was found in which the HALP score was investigated to differentiate benign and malignant colorectal neoplasms.

In the CRC group, when the median HALP score was accepted as a cut-off of 28.1, we found a difference in OS between the low and high HALP score groups. A lower HALP score was also demonstrated to be an independent prognostic factor for CRC. Similar to the cut-off value in our findings, Jiang et al. [5] showed that a cut-off value of less than 26.5 for the HALP score was an independent risk factor for OS in locally advanced CRC patients. Our CRC patient cohort included all stages of the TNM classification, but most were staged 2-3. In the study of Yalav et al. [12], a cut-off value of less than 15.73 for the HALP score in CRC patients who underwent curative surgery was shown to be an independent risk factor for OS. The lower cut-off value in the latter study might be related to the fact that the study group included only early-stage CRC patients. HALP was linked to the prognosis of patients undergoing surgery for CRC in the study by Dagmura et al. [13]. Additionally, their research revealed a good relationship between HALP and survival. Hemoglobin molecule that transports oxygen to body tissues. Anemia results in relative hypoxia in tumoral tissues [14]. Hypoxia alters gene expression, which leads to subsequent proteome changes, and may promote tumor development, invasion, and metastasis [15]. Albumin also represents the nutritional status and is found to be low, as expected in cancer patients [16]. The importance of lymphocytes for clinical and prognostic processes in CRC has been demonstrated due to the interaction between tumor-infiltrating lymphocytes, malignant cells, and immune function [17]. Platelets release pro-angiogenic substances to promote angiogenesis during tumor growth and the development of metastases [18]. As a result, the prognosis of cancer patients is positively impacted by high amounts of hemoglobin, albümin, and lymphocytes; nevertheless, high quantities of platelets should be viewed negatively. When the HALP score is calculated with the above components, it is reasonable to see that patients with CRC with a lower HALP score have a worse overall survival rate in our study.

In addition to the low HALP score, we found TNM stage, perineural invasion, and inoperability, which were proven to be prognostic factors for CRC [19-21], as independent prognostic factors. However, According to Zhang et al.'s [22] study on patients with CRC, a new prediction model including preoperative nutritional and inflammatory markers outperforms the TNM classification in terms of prognostic performance.

The primary limitations of the present study are its retrospective methodology, which was conducted in a single center. The other

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limitation of our study was the low sensitivity and specificity of HALP, an independent predictor in many cancers. Finally, the cross-sectional format of our study prevented the evaluation of the HALP score as the disease progressed.

Conclusions

In patients with colorectal neoplasms, the HALP score could be calculated simply, effectively, and repeatedly. While the median HALP score of the CRC group was lower than the CRA and HPP groups, the median HALP scores of the CRA and HPP groups were similar. The HALP score below 41.01 was used for distinguishing CRC from benign colorectal neoplasms (CRA or HPP). Furthermore, it has been demonstrated that a HALP score below 28.1 is an independent prognostic factor in CRC patients.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Zonguldak Bülent Ecevit University Faculty of Medicine Clinical Research Ethics Committee approved the study (Protocol No: 2022/04 Approval Date: 23 February 2022).

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