EJMI

DOI: 10.14744/ejmi.2024.14917
EJMI 2024;8(2):113–118

Research Article

Pretreatment HALP Score Predicts Prognosis in Patients with Esophageal Cancer Treated with Chemoradiotherapy

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Abstract

Objectives: We aimed to evaluate the relation of the pre-treatment hemoglobin-albumin-lymphocyte-platelet (HALP) score with survival and prognosis of locally advanced esophageal squamous cell carcinoma (ESCC) patients receiving chemoradiotherapy (CRT).

Methods: We retrospectively included 45 patients with esophageal squamous cell carcinoma who were treated with chemoradiotherapy. The HALP score was calculated as hemoglobin level (g/L)*albumin level (g/L)*lymphocyte count (/L)/platelet count(/L).

Results: According to the receiver operating characteristic (ROC) curve, the median of the HALP score was 42.36. According to this value, the patients were divided into two groups; Group 1 included 28 patients who had a HALP score <42.36 and Group 2 included 17 patients who had a HALP score >42.36. Median OS was 20.5 months in Group 1 and the median OS was not reached in Group 2 (p=0.033). Median PFS in all patient groups was 15.2 months. The median PFS was 12.2 months in Group 1 and 30.9 months in Group 2 (p=0.127). Univariate Cox regression analysis showed that pre-treatment low levels of HALP were associated with a short median time of OS (p=0.042).

Conclusion: Our study suggested that pretreatment low HALP score was associated with poor OS in patients with locally advanced ESCC who were treated with CRT.

Keywords: Esophageal cancer, hemoglobin-albumin-lymphocyte-platelet (HALP) score, overall survival (OS)

Cite This Article: *Sucuoğlu İşleyen Z, Beşiroğlu M, Şimşek M, Yasin Aİ, Topçu A, Akçakaya A, et al. Pretreatment HALP Score Predicts Prognosis in Patients with Esophageal Cancer Treated with Chemoradiotherapy. EJMI 2024;8(2):113–118.*

Esophageal cancer is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death. The two major histologic subtypes of esophageal cancers are squamous cell carcinoma (SCC) and adenocarcinoma (AC).[1]

In locally advanced esophageal cancer, the tumor invades surrounding tissue or lymph nodes but there is no distant metastasis. Traditionally, the mainstay treatment for esophageal cancer is surgery. However, the treatment of locally advanced esophageal cancer requires a multidisciplinary approach. It is known that the addition of radiotherapy (RT), chemotherapy (CT), or chemoradiotherapy (CRT) to surgical treatment as adjuvant or neoadjuvant purpose contributes positively to overall survival (OS).[2] The addition of surgery to treatment of patients with a complete response (CR) after CRT is still controversial. In some studies, CRT alone or surgery after CRT was compared in patients with esophageal SCC, and no difference in survival was

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Submitted Date: December 10, 2023 **Accepted Date:** July 11, 2024 **Available Online Date:** July 19, 2024

found. Despite improvements in treatment modalities, the prognosis of esophageal cancer is still poor because it is usually diagnosed at advanced stages.[3, 4]

The nutritional and inflammatory status of cancer patients is associated with prognosis. It has been reported that malnutrition is as common as 79% before initiation of treatment in patients with esophageal cancer.[5] In esophageal cancer patients, two main causes of malnutrition are dysphagia and anorexia. Inadequate nutrition can lead to deterioration in the quality of life, worsening in treatment tolerance, and treatment discontinuation in cancer patients.[6]

Albumin is one of the parameters that show nutritional status in cancer patients. Various parameters indicating inflammatory status such as platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) in cancer patients have been studied and reported to be associated with prognosis.[6, 7]

Hemoglobin, albumin, lymphocyte, and platelet (HALP) score has previously been investigated in several types of cancers such as prostate cancer, pancreatic cancer, small cell lung cancer (SCLC), and gastric cancer.[7-9] In a study conducted on esophageal squamous cell carcinoma (ESCC) patients, it was shown that the pretreatment HALP score was related to CRT response and progression-free survival (PFS).[10]

Therefore, the present study aimed to evaluate the relation of the pre-treatment HALP score with survival and prognosis of locally advanced ESCC patients receiving CRT.

Methods

Study Design and Patients

We retrospectively analyzed the data of patients with locally advanced esophageal cancer between 2014-2021 referred to department of medical oncology. The inclusion criteria were as follows: (1) pathologically confirmed; ESCC, (2) patients with locally advanced disease, (3) treated with CRT (4) patients who received carboplatin/paclitaxel or cisplatin/5-FU as concurrent CT. We excluded patients who had distant metastases or with non-SCC histology, Eastern Cooperative Oncology Group Performance Status (ECOG PS) >2, or under 18 years of age. The Clinical Research Ethics Committee of Bezmialem Vakif Universitey approved the study (2022/313).

Patient Evaluation

The clinical characteristics of patients included in the study were noted. Patients in the study started CT and RT concurrently. The response assessment of CRT was performed with standard computed tomography and/or 18 F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT). Treatment response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria. CR was defined as the absence of detectable lesions and partial response (PR) was defined as a >30% decrease in tumor size. Progressive disease (PD) was determined as the appearance of one or more new lesions and/or a >20% growth in tumor size, and stable disease (SD) was defined as neither PD nor PR. The objective response rate (ORR) was established as the sum of CR and PR. PFS was calculated as the time from the date of diagnosis until the first PD or death. OS was calculated as the time from the date of diagnosis to the date of death or last follow-up.

Laboratory results such as hemoglobin and albumin levels, and platelet and lymphocyte counts were obtained before treatment according to medical records. The HALP score was calculated as hemoglobin level (g/L)*albumin level (g/L)*lymphocyte count (/L), platelet count (/L).

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences version 20 (SPSS, v20). The characteristics of the patients were evaluated with descriptive analysis. Kolmogorov-Smirnov test was performed to evaluate whether the data were within the normal distribution range. Qualitative variables were defined by frequencies and percentages. Continuous and ordinal variables were defined by the mean and standard deviation or median and range. Pearson chi-square test was used to check qualitative variables. Survival analysis was performed using the Kaplan-Meier method and log-rank test. The determinative factors of OS and PFS were examined with Cox regression analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were applied to measure indexes that predict survival. The statistical significance level was accepted as a p value <0.05.

Results

Forty-five patients with locally advanced ESCC who received CRT were included in the study. While four of the patients received cisplatin/5-FU, forty-one patients received carboplatin/paclitaxel regimen.

The mean age of the patients was 55.8 (standard deviation: 11.6). Of the 45 patients, 26 (57,8%) were female and 19 (42,2%) were male, and the ECOG PS was 0-1. Nineteen (42%) patients were active smokers. The primary tumor was localized in the proximal esophagus in ten (22.2%), thoracic esophagus in 29 (64.4%), and distal esophagus in six (13,3%) patients. Twenty-five (55,6%) patients were clin-

ically lymph node-positive, and after completion of CRT 19 (42.2%) patients underwent esophagectomy.

According to the receiver operating characteristic (ROC) curve, the median value of the HALP score was 42.36 [AUC: 0.746 (0.603-0.889, 95%CI)). According to this value, the patients were divided into two groups; Group 1 included 28 patients who had a HALP score <42.36 and Group 2 included 17 patients who had a HALP score >42.36. The HALP score showed no differences regarding gender, age, smoking status, alcohol consumption, tumor stage, lymph node involvement, and tumor localization (Table 1).

The median follow-up time in the study was 20 months. Median OS in all patient groups was 21.5 months (range: 11.7-31.3) (95% CI). Median OS was 20.5 (range:10.6-30.3) months in Group 1 and the median OS was not reached in Group 2 (p=0.033) (Fig. 1). Median PFS in all patient groups was 15.2 months (range: 5.5-24.9) (95%CI). The median PFS was 12.2 (range: 5.7-18.6) months in Group 1 and 30.9 (range: 5.7-56.2) months in Group 2 (p=0.127) (Fig. 2).

Clinical ORR and CR were obtained in 86.8% (n=33) and 39.5% (n=15) of the patients, respectively. There was no statistically significant difference between HALP groups 1 and 2 (p=0.875, p=0.311; respectively) (Table 2). Univariate Cox regression analysis showed that pre-treatment low levels of HALP were associated with a short median time of OS [p=0.042, HR: 0.36 (0.14-0.96)] (Table 3).

Discussion

With the developments in the oncology field, the 5-year survival rate of esophageal cancer has increased. This improvement in survival rate is associated with the common use of neoadjuvant CRT in locally advanced esophageal cancer. In a phase III randomized clinical trial, improved survival was reported with neoadjuvant CRT followed by surgery compared to surgery alone.[11] Despite recent developments, the survey of esophageal cancer is still poor.

It is well known that inflammation and the nutritional status of patients with cancer are strongly associated with tumor

Table 1. Clinicopathological features of patients with locally advanced ESCC[1], and their relationship with hemoglobin, albumin, lymphocyte, and platelet (HALP)

		HALP[2] Score		
Characteristic	**All, n (%)**	**Low, n=28 (62.2%)**	**High, n=17 (37.8%)**	**p**
Age,y				0.967
<60	24 (53)	15 (62.5)	9 (37.5)	
>60	21 (%46)	13 (61.9)	8 (38.1)	
Gender				0.175
Female	26 (57)	14 (53.8)	12 (46.2)	
Male	19 (42)	12 (46.2)	5 (26.3)	
Smoking				0.912
Yes	19 (42)	12 (63.2)	7 (36.8)	
No	26 (57)	16 (61.5)	10 (38.5)	
Alcohol				0.163
Yes	7 (15.6)	6 (85.7)	1 (14.3)	
No	38 (84.4)	22 (57.9)	16 (42.1)	
Localization				0.118
Cervical	10 (22.2)	9 (90)	1 (10)	
Thoracic	29 (64.4)	16 (55.2)	13 (44.8)	
Abdominal	6 (13.3)	3 (50)	3 (50)	
cT Stage[3]				0.581
T1-2-3	41 (91)	25 (61)	16 (39)	
T4	4 (8.9)	3 (75)	1 (25)	
cN Stage[3]				0.336
N0	20 (44.4)	14 (70)	6 (30)	
N+	25 (55.6)	14 (56)	11 (44)	
Surgery				0.912
Yes	19 (42.2)	12 (63.2)	7 (36.8)	
No	26 (57.8)	16 (61.5)	10 (38.5)	

[1]Esophageal Squamous Cell Carcinoma; [2] Hemoglobin-Albumin-Lymphocyte-Platelet; [3] American Joint Committee on Cancer (AJCC) Eighth Edition (2017).

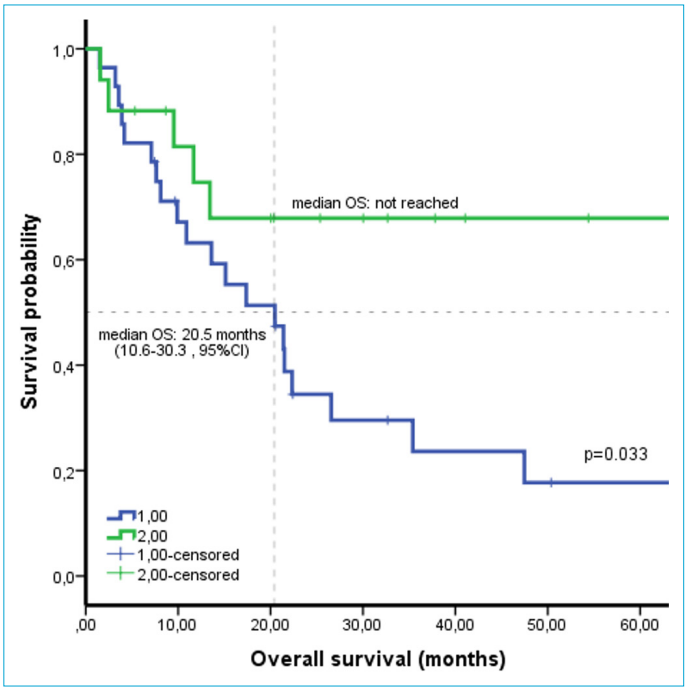

Figure 1. Overall survival (OS) of patients with HALP group 1 (<42.36) and HALP group 2 (>42.36) according to the Kaplan-Meier analysis.

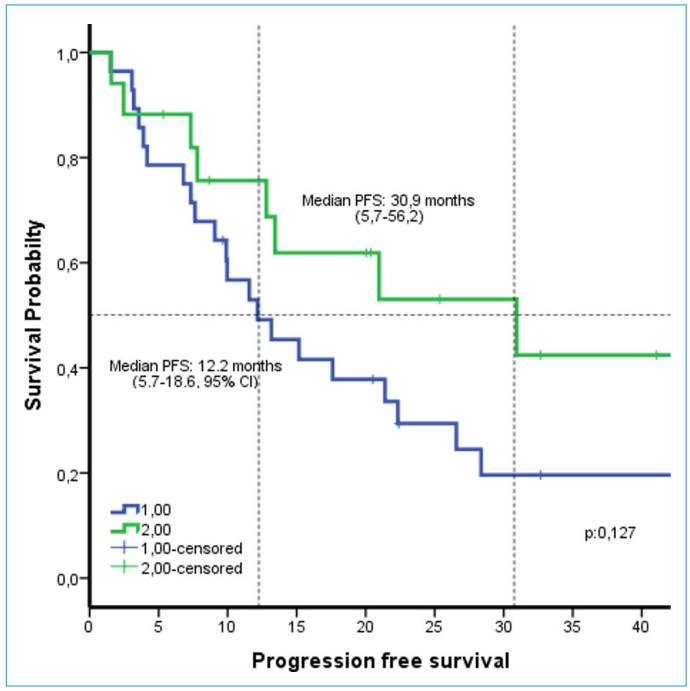

Figure 2. Progression free survival(PFS) of patients with HALP group 1(<42.36) and HALP group 2 (>42.36) according to the Kaplan-Meier analysis.

prognosis. HALP score, including hemoglobin level, albumin level, lymphocyte count, and platelet count, is an indicator of both nutritional and inflammatory status. In daily practice, hemoglobin and albumin levels, and lymphocyte and platelet counts are commonly used clinical biomarkers and the HALP score can be easily calculated in routine practices. The HALP score was generally used in patients to predict the prognosis of many types of cancers. It was used in gastric cancer, prostate cancer, pancreatic cancer, lung cancer, and ESCC.[7-10] For the first time, Chen et al. used this scoring system in patients with gastric cancer, and they found that a high HALP score had a significantly better prognosis than a low HALP score. In addition, Chen et al

Table 2. The relation between HALP* score and treatment response/survival

		HALP Score		
	All, n (%)	**Low, n=28 (62.2%)**	**High, n=17 (37.8%)**	**p**
Clinical Complete Response				0.311
Yes	15 (39.5)	8 (53.3)	7 (46.7)	
No	23 (60.5)	16 (69.6)	7 (30.4)	
Clinical Objective Response				0.875
Yes	33 (86.8)	21 (63.6)	12 (36.4)	
No	5 (13.2)	3 (60)	2 (40)	
Pathological Complete Response				0.402
Yes	9 (52.9)	5 (55.6)	4 (44.4)	
No	8 (47.1)	6 (75)	2 (25)	
Recurrence				0.058
Yes	29 (64.4)	21 (72.4)	8 (27.6)	
No	16 (35.6)	7 (43.8)	9 (56.2)	
Survival				0.006
Alive	20 (44.4)	8 (40)	12 (60)	
All cause death	25 (55.6)	20 (80)	5 (20)	

*Hemoglobin-Albumin-Lymphocyte-Platelet.

Table 3. Univariate analysis for overall survival in subgroups of patients with locally advanced ESCC[1]

	OS, HR (95% CI)	p
Gender		
Female	Reference	0.130
Male	1.85 (0.83-4.10)	
Smoking		
No	Reference	0.307
Yes	1.51 (0.68-3.37)	
Alcohol		
No	Reference	0.315
Yes	0.47(0.11-2.02)	
Tumor Site		
Cervical	Reference	0.326
Thoracal	2.21 (0.45-10.79)	0.628
Abdominal	1.43 (0.33-6.26)	
cT stage[2]		
T1-2-3	Reference	0.230
T4	2.11 (0.62-7.14)	
cN stage[2]		
N0	Reference	0.310
N+	1.51(0.67-3.38)	
Clinical Complete Response		
Yes	Reference	0.178
No	2.02 (0.72-5.62)	
Clinical Objective Response		
Yes	Reference	0.120
No	2.42 (0.79-7.39)	
Operation		
No	Reference	0.191
Yes	0.57 (0.25-1.31)	
Pathological Complete Response		
Yes	Reference	0.474
No	1.76 (0.37-8.31)	
HALP[3] Score		
Category 1[4]	Reference	0.042
Category 2[5]	0.36 (0.14-0.96)	

[1]Esophageal Squamous Cell Carcinoma; [2] American Joint Committee on Cancer (AJCC) Eighth Edition (2017); [3] Hemoglobin-Albumin-Lymphocyte-Platelet; [4]Low HALP score; [5]High HALP score.

found that clinicopathological characteristics were closely associated with the HALP score system.[12] In our study, the relationship between pre-treatment HALP score and survival in locally advanced ESCC patients was demonstrated. A study including 39 male patients with ESCC revealed that the median PFS of the high HALP group was significantly higher than the low HALP group, however, no significant difference was found in OS between the groups.[10] In our study, despite no correlation between PFS and HALP score, we found a statistically significant relationship between OS and HALP score. Similarly, another study showed that preoperative HALP score was an independent prognostic score for cancer-specific survival in patients with resectable ESCC.[13]

Each parameter in the HALP score has an important role in the prognosis of patients with cancer. Anemia is a common sign in cancer patients, especially in gastrointestinal cancers. Chronic blood loss and malnutrition are the most common causes of anemia. Besides these, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which are secreted in tumor cells, decrease hemoglobin levels.[14] Tumor-associated anemia is a major cause of hypoxia in tumor tissue, which is thought to be a factor for CT and RT resistance.[15] Hamai et al. reported that hemoglobin level is associated with the pathologic responses of tumors and OS in patients with ESCC.[16]

Albumin is the most abundant circulating protein, and serum albumin levels vary according to the degree of catabolism in the presence of cancer. Many types of cancers, especially gastrointestinal cancers, predispose patients to malnutrition, due to cancer progression and decreased absorption of nutrients or inadequate oral intake. Serum albumin level has been considered as an important indicator in the nutritional evaluation and inflammatory status of the patients.[17, 18] As was found in our study, low serum albumin levels are strongly associated with poor prognosis in cancer patients.

Systemic inflammation can cause premalignant cell proliferation and immunosuppression, resulting in the formation of microenvironments in which malignant cells can survive. Besides this, systemic inflammation stimulates angiogenesis which leads to metastatic spread. Systemic inflammatory markers such as NLR, and PLR were recently used in patients with several cancer types, and be associated with mortality and recurrence.[19] A study that included resectable ESCC patients, revealed that the HALP score was superior to other prognostic scores.[13] Similar results were also reported in another study conducted with 82 metastatic prostate cancer patients.[7] Our current study has some limitations. First, this is a retrospective study, secondly, it is a single-center with a small sample size

In conclusion, our study suggested that pretreatment low HALP score was associated with poor OS in patients with locally advanced ESCC who were treated with CRT. The measurement of the HALP score is simple, cost-effective, and easily used in routine clinical practice. Therefore, it is thought that the evaluation of pre-treatment HALP score in locally advanced ESCC patients may provide decision of the most proper treatment approaches for this patient population.

Disclosures

Ethics Committee Approval: The Clinical Research Ethics Committee of Bezmialem Vakif Universitey approved the study (2022/313).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept: Z.S.İ., M.B.; Design: Z.S.İ., M.B.; Supervision: M.Ş., H.M.T.; Materials: A.T., M.Ş., A.A.; Data Collection and/or Processing: Z.S.İ., A.İ.Y., A.A.; Analysis and/or Interpretation: M.B., M.Ş., Z.S.İ.; Literature Search: H.M.T., M.Ş., A.İ.Y.; Writing: Z.S.İ., A.T., A.İ.Y.; Critical Review: H.M.T., M.Ş.

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