

The Effect of Halp Score on the Development of Pharyngocutaneous Fistula After Laryngectomy

Larenjektomi Sonrası Faringokutanöz Fistül Gelişimi Üzerine Halp Skoru Etkisi

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Cite this article as: Baklacı D et al. The effect of halp score on the development of pharyngocutaneous fistula after laryngectomy. Med J West Black Sea. 2025;9(2): 158-165.

GRAPHICAL ABSTRACT

The HALP score was not found to be a significant predictor of pharyngocutaneous fistula development; however, hematological and nutritional evaluation remains important.

Introduction and Aim

Pharyngocutaneous fistula (PCF) is one of the most common complications after laryngectomy.

It reduces quality of life,  prolongs hospital stay.

This study investigated the relationship between HALP score and PCF development.

Medical Journal of Western Black Sea

Method

Retrospective study (2012–2024)

76 patients (47 total, 29 partial laryngectomy)

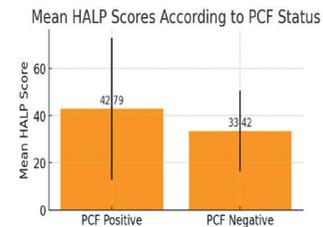
HALP score = $Hb \times Albumin \times Lymphocyte / Platelet$

PCF development was compared with HALP score.

Deniz Baklacı, Duygu Erdem, Seda Nur Saka, Gökhan Furkan Kılıç, Doğancan Eralp

Results

HALP in PCF (+): 42.79 ± 30.00
HALP in PCF (-): 33.42 ± 17.17
No significant difference found ($p > 0.05$)
PCF incidence: 51.1%
The graph below shows the means:



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ABSTRACT

Aim: Laryngeal cancers are prominent among head and neck cancers, and laryngectomy is commonly performed in advanced cases. Pharyngocutaneous fistula (PCF), a postoperative complication, negatively impacts quality of life, prolongs hospitalization, and delays treatment. The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score, calculated from hemoglobin, albumin, lymphocyte, and platelet levels, reflects immune and nutritional status.

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Received: 01.11.2024 Revision: 07.07.2025 Accepted: 08.07.2025



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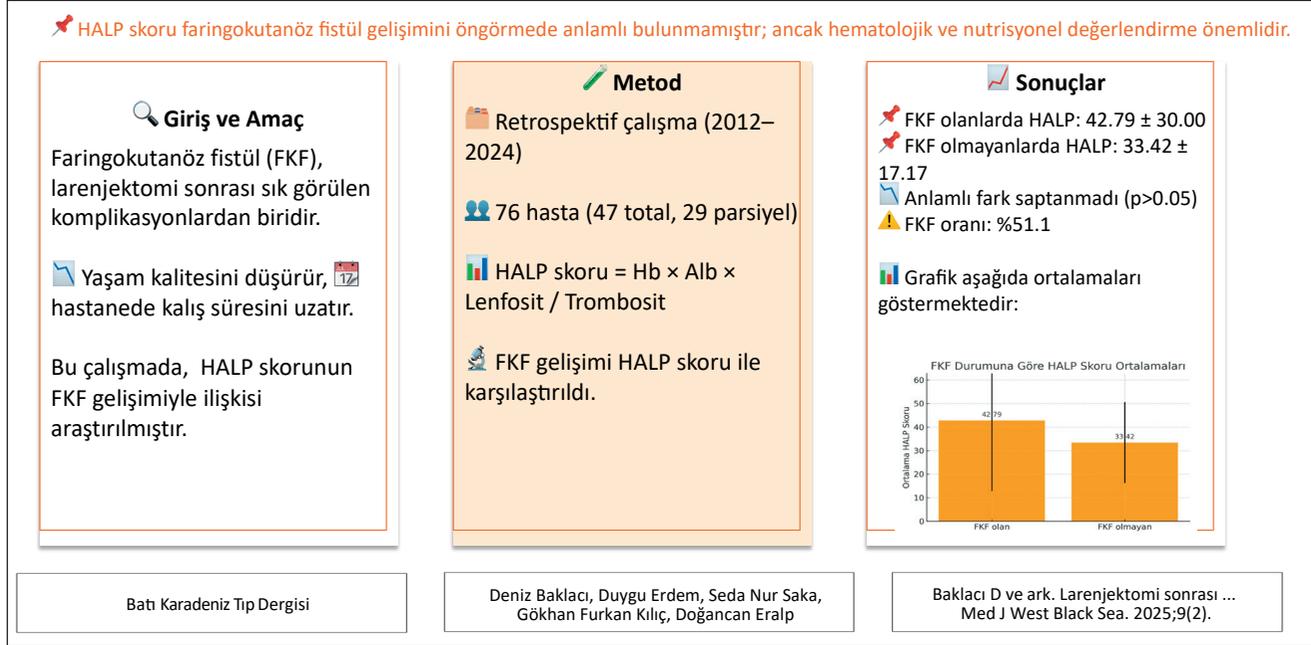
Material and Methods: This retrospective study included 76 patients who underwent surgery for laryngeal cancer between January 2012 and June 2024. Patients were grouped based on partial or total laryngectomy, and HALP scores were compared with the incidence of fistula.

Results: In the total laryngectomy group, the mean HALP score was 33.42 ± 17.17 for patients without fistula and 42.79 ± 30.00 for those with fistula. No statistically significant difference was found between the two groups ($p > 0.05$).

Conclusion: No significant relationship was found between HALP score and PCF development. However, since hemoglobin and albumin may be risk factors, larger, multicenter prospective studies are needed for a more comprehensive evaluation.

Keywords: HALP score, laryngectomy, pharyngocutaneous fistula

GRAFİKSEL ÖZET



ÖZ

Amaç: Larengeal kanserler, baş ve boyun kanserleri içinde önemli bir yer tutar ve ileri evre hastalarda genellikle larenjektomi uygulanır. Cerrahiden sonra gelişebilen farengokutanöz fistül (FKF), yaşam kalitesini düşürür, hastanede kalış süresini uzatır ve tedavi sürecini aksatır. Hemogloblin, Albumin, Lenfosit ve Platelet (HALP) skoru; hemogloblin, albümin, lenfosit ve trombosit parametrelerinin kullanıldığı, immün ve beslenme durumunu yansıtan bir biyomarkerdir.

Gereç ve Yöntemler: Ocak 2012 - Haziran 2024 tarihleri arasında kliniğimizde larenks kanseri nedeniyle opere edilen 76 hasta retrospektif olarak değerlendirildi. Hastalar, kısmi veya total larenjektomi geçirmelerine göre gruplandırıldı ve HALP skorları ile fistül gelişimi karşılaştırıldı.

Bulgular: Total larenjektomi yapılan ve fistül gelişmeyen hastaların ortalama HALP skoru 33.42 ± 17.17 , fistül gelişenlerin ise 42.79 ± 30.00 idi. Ancak gruplar arasında istatistiksel olarak anlamlı fark saptanmadı ($p > 0.05$).

Sonuç: HALP skoru ile FKF gelişimi arasında anlamlı bir ilişki bulunmadı. Ancak hemogloblin ve albümin düzeylerinin risk faktörü olabileceği göz önünde bulundurularak, bu ilişkiyi değerlendirmek için daha geniş, çok merkezli ve prospektif çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Faringokutanöz fistül, HALP skoru, larenjektomi

INTRODUCTION

Laryngeal cancer constitutes approximately 0.8% of all new cancer cases and 0.6% of all cancer-related deaths. However, the five-year survival rate has remained around 60.9% for the past few years. The survival chances of laryngeal cancer patients closely linked to the stage at diagnosis; the cure rates for early-stage T1 and T2 tumors can reach as high as 80% to 90%, while patients presenting with stage IV disease have a survival chance as low as 40% (1,2).

Advanced (stage III and IV) tumors typically require multimodal treatment. This treatment may involve a combination of radiotherapy and chemotherapy or radiotherapy following surgical intervention (3,4).

The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score is a new immune biomarker defined as hemoglobin \times albumin \times lymphocytes/platelets, first introduced by Chen et al. in 2015 to predict survival outcomes in patients with gastric cancer (5). Subsequently, the prognostic role of the HALP score has been investigated across various cancer types, with conflicting results reported (6,7).

Arikan et al. demonstrated that the HALP could be a reliable parameter for predicting postoperative pancreatic fistula development in patients undergoing pancreaticoduodenectomy for periampullary tumors (8). A study by Tarle et al. indicated that the HALP score could be an effective tool in predicting complications and outcomes such as necrosis, infection, fistula, and flap revision in microvascular free flap reconstructions of the head and neck region (9).

Pharyngocutaneous fistula (PCF) is an abnormal passage between the pharynx and the skin and is one of the most common and significant complications following total laryngectomy (10). Clinically, PCF is characterized by the presence of saliva on the skin surface after swallowing. The reported incidence of PCF in the literature varies between 2.6% and 65.5% (11). PCF is a complication that negatively impacts morbidity during the postoperative period by prolonging hospital stays, disrupting the patient's overall nutritional balance, delaying necessary adjuvant radiotherapy, and significantly increasing costs (12,13).

This study aims to investigate the effect of the HALP score on the development of PCF, a common complication in patients undergoing partial and total laryngectomy.

MATERIALS and METHODS

This study included 30 patients (29 male, 1 female) who underwent partial laryngectomy and 49 patients (47 male, 2 female) who underwent total laryngectomy due to laryngeal cancer, admitted to the department of Ear, Nose, and Throat-Head and Neck Surgery at Zonguldak Bülent Ecevit University Faculty of Medicine between January 2012 and

June 2024. Two patients for whom HALP scores could not be calculated and one patient whose fistula development could not be calculated due to mortality were excluded, and the study continued with 76 patients. Of those 76 patients, 4 were classified as stage T1, 37 as stage T2, 17 as stage T3, and 18 as stage T4. The tumor was transglottic in 56 patients, supraglottic in 13 patients, and glottic in 7 patients. In the partial laryngectomy group, we performed supracricoid laryngectomy in 13 patients, supraglottic laryngectomy in 8 patients, and vertical laryngectomy in 7 patients. In patients who underwent total laryngectomy, all laryngeal structures and a portion of the upper trachea were excised. A permanent breathing hole (tracheostoma) was created in the neck. The Connel technique was used for pharyngeal closure in all patients. Three patients who underwent partial laryngectomy and nine patients who underwent total laryngectomy had a history of radiotherapy in the preoperative period. Two patients who underwent partial laryngectomy and nineteen patients who underwent total laryngectomy had a history of tracheotomy in the preoperative period. The 30 patients included in the study were diagnosed with hypertension, 9 patients had diabetes, 11 patients had coronary artery disease, and 1 patient had hypothyroidism. PCF developed in patients between the 5th and 21st postoperative days on average. The diagnosis of PCF was made either by the presence of saliva drainage from the surgical site in the early postoperative period, food leakage from the stoma after starting oral intake or in some cases by pharyngography. The patients were divided into two groups: Those who underwent total laryngectomy and those who underwent partial laryngectomy. The clinical records of the patients were reviewed, and preoperative blood parameters were analyzed to record hemoglobin, albumin, lymphocyte, and platelet counts taken one week prior to surgery. The HALP score is calculated as $\text{HALP Score} = [\text{Hemoglobin (g/L)} \times \text{albumin (g/L)} \times \text{lymphocytes (L)}] / \text{platelets (L)}$ (14). The effect of the HALP score on the development of PCF was separately examined in patients who underwent partial and total laryngectomy. The clinical notes, patient charts and follow-up data of all patients were retrospectively reviewed.

The study received ethical approval from the ethics committee of our hospital (Date: 21.02.2024, number: 2024/05) and the study protocol was conducted in accordance with the 1964 Helsinki Declaration.

Statistical Analysis

Descriptive statistics for continuous variables included mean \pm standard deviation, median, minimum, and maximum values, while discrete variables were presented as counts and percentages. The normality of continuous data was evaluated using the Shapiro-Wilk test.

For comparisons of continuous variables between groups, the Independent Samples t-test was used for normally dis-

tributed data, while the Mann-Whitney U test was applied for non-normally distributed data.

The Chi-Square test was employed for comparisons of nominal variables (in cross tables).

The diagnostic performance of HALP values was evaluated using the area under the ROC curve (AUC).

IBM SPSS version 20 (Chicago, IL, USA) was used for analyses, and a p-value of <0.05 was considered statistically significant.

RESULTS

A total of 76 patients were included in the study, consisting of 29 patients who underwent partial laryngectomy and 47 patients who underwent total laryngectomy. PCF developed in 1 (3.4%) of the 29 patients who underwent partial laryngectomy. In the group of 47 patients who underwent total laryngectomy, PCF developed in 24 patients (51.1%). A significant difference was found between the rates of fistula development in patients who underwent total laryngectomy and those who underwent partial laryngectomy ($p < 0.001$). The rate of fistula development was found to be higher in patients who underwent total laryngectomy compared to those who underwent partial laryngectomy (Table 1).

In patients who underwent partial laryngectomy, the HALP score was calculated as mean \pm SD (44.13 \pm 14.35), median (Min-Max) 45.09 (12.61-71.63). In patients who underwent total laryngectomy, the HALP score was mean \pm SD (38.20 \pm 24.76), median (Min-Max) 37.32 (2.70-146.42). No significant difference was found between the HALP scores

of patients who underwent total laryngectomy and those who underwent partial laryngectomy ($p > 0.05$) (Table 1).

In patients who underwent total laryngectomy and had no fistula formation, the HALP score was calculated as mean \pm SD (33.42 \pm 17.17), median (Min-Max) 30.41 (2.70-57.77). In contrast, the HALP score for patients with fistulas was calculated as mean \pm SD (42.79 \pm 30.00), median (Min-Max) 38.71 (6.92-146.42) (Table 2). No significant difference was found between the HALP scores of patients with or without fistula who underwent total laryngectomy ($p > 0.05$).

The AUC calculated for HALP values in predicting fistula positivity in patients who underwent total laryngectomy was not found to be significant ($p > 0.05$) (Table 2).

A ROC analysis of the HALP score was performed for fistula positivity in patients who underwent total laryngectomy. However, in patients who underwent partial laryngectomy, ROC analysis of the HALP score could not be conducted because only one patient showed fistula positivity (Figure 1).

DISCUSSION

In general, advanced-stage laryngeal carcinomas (stage III-IV) were treated with either total laryngectomy or chemoradiotherapy. While total laryngectomy provides significant therapeutic benefits, it also carries certain risks. One of the most common side effects of total laryngectomy is the development of PCF, which increases the likelihood of wound infection. Despite various studies conducted around the world, there is still disagreement about the factors that have

Table 1: Comparisons between patients who underwent total laryngectomy and those who underwent partial laryngectomy

	Total Laryngectomy (n=47)		Partial Laryngectomy (n=29)		p value
	Mean \pm SD	Median (Min-Max)	Mean \pm SD	Median (Min-Max)	
Hemoglobin(g/L)	127.68 \pm 16.12	130 (93-157)	134.03 \pm 13.03	134 (106-155)	0.078 ^b
Albumin(g/L)	38.23 \pm 5.51	37 (26-48)	39.14 \pm 5.60	40 (28-53)	0.495 ^b
Lymphocytes	0.0017 \pm 0.008	0.0017 (0.0002-0.0041)	0.0020 \pm 0.0006	0.0021 (0.0009-0.0033)	0.073 ^c
Platelets	0.255 \pm 0.078	0.237 (0.141-0.553)	0.240 \pm 0.056	0.222 (0.144-0.356)	0.593 ^c
HALP*	38.20 \pm 24.76	37.32 (2.70-146.42)	44.13 \pm 14.35	45.09 (12.61-71.63)	0.063 ^c
	n	%	n	%	
Fistula					
Negative	23	48.9	28	96.6	<0.001 ^d
Positive	24	51.1	1	3.4	

b: Independent Samples t test, **c:** Mann Whitney U test, **d:** Chi-Square Test
*: Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score.

Table 2: Comparisons between patients with total laryngectomy who have negative fistulas and those with positive fistulas.

	Fistula Negative (n=23)	Fistula Positive (n=24)	p value
	Mean \pm SD Median (Min-Max)	Mean \pm SD Median (Min-Max)	
Hemoglobin (g/L)	128.17 \pm 13.40 129 (103-149)	127.21 \pm 18.64 131.5 (93-157)	0.840 ^b
Albumin (g/L)	37.96 \pm 5.53 37 (26-48)	38.50 \pm 5.60 38.5 (27-47)	0.740 ^b
Lymphocytes	0.0016 \pm 0.0007 0.0015 (0.0002-0.0041)	0.0019 \pm 0.009 0.0018 (0.0003-0.0039)	0.241 ^c
Platelets	0.262 \pm 0.069 0.263 (0.141-0.390)	0.248 \pm 0.086 0.235 (0.146-0.553)	0.333 ^c
HALP*	33.42 \pm 17.17 30.41 (2.70-57.77)	42.79 \pm 30.00 38.71 (6.92-146.42)	0.419 ^c
HALP*	AUC 0.569 ^d	95% CI 0.401-0.736 ^d	0.419 ^d

b: Independent Samples t test, **c:** Mann Whitney U test, **d:**The performance of HALP values in predicting fistula positivity in patients who underwent total laryngectomy.

*: Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score

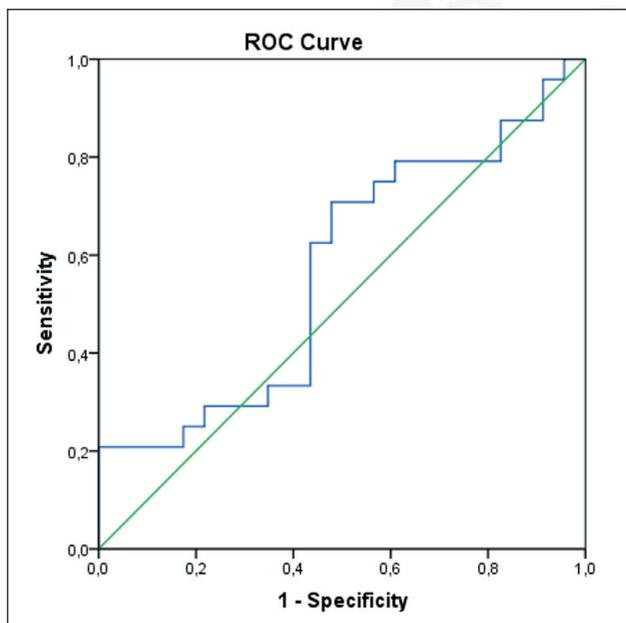


Figure 1: ROC curve of HALP values for predicting fistula positivity

the greatest impact on PCF (15). The incidence of PCF after total laryngectomy ranges from 5% to 66% (16). In our study, we found the rate of PCF in patients who underwent total laryngectomy to be 51.1%. The development of PCF is generally observed between the third and eleventh postoperative days (17).

Several risk factors have been shown to be significant for PCF in recent meta-analyses. The postoperative risk factors

reported by Paydarfar et al. and Liang et al. include anemia defined as hemoglobin <12.5 g/dL, preoperative tracheostomy, and cervical radiotherapy in the first study, while the second study identifies close surgical margins, tumor size and location, postoperative anemia, and cervical radiotherapy. These risk factors have been found to be significant in some studies and insignificant in others, making them a subject of debate (18-20). Lemaire et al. identified four main high-risk factors for PCF: Active smoking >20 pack-years, cervical radiotherapy, closure of the mucosa with simple sutures, and pharyngeal closure with a pedicled flap. They found that the risk of developing a PCF is highest when all these factors are present in the same patient. Additionally, this study analyzed postoperative C-reactive protein (CRP) levels. It was found that having a CRP level of 40 mg/L or less on the 5th postoperative day has a negative predictive value of 87% and a specificity of 24%, indicating that CRP analysis on the 5th day is useful for making early nutritional decisions (21).

Hypoalbuminemia leads to a higher incidence of PCF due to its negative effects on wound healing (17,22). According to Kılıç et al. hypoalbuminemia and hypoproteinemia showed a statistically significant relationship with the development of PCF in the preoperative period. Low prealbumin levels, high serum CRP levels, and low preoperative serum albumin/globulin ratios were statistically significant for the development of PCF (17). Redaelli et al. found that postoperative low hemoglobin levels were not a risk factor for fistula development (16). On the other hand, Morton et al. reported that low hemoglobin levels in the postoperative period played a significant role in the development of PCF (23).

In conclusion, despite various studies conducted worldwide, there is still disagreement about the factors that have the greatest impact on PCF, and research continues.

In recent years, the Hemoglobin, Albumin, Lymphocyte, Platelet Score (HALP) has emerged in the literature as a novel prognostic biomarker used to predict a variety of clinical outcomes in the context of various neoplasms. HALP is a new immunonutritional marker that integrates indicators of immune status such as platelet and lymphocyte counts, nutritional status represented by albumin, and a marker of anemia, hemoglobin.

In this study, we investigated the effect of the HALP score, introduced for the first time in 2015 by Chen et al. to predict survival outcomes in patients with gastric cancer (5), on the development of fistula in patients undergoing total and partial laryngectomy.

Preoperative low hemoglobin (anemia) is a common clinical feature in cancer patients and can lead to hypoxia (24), which may contribute to cancer progression and resistance to treatment (25). Clinical studies have shown that anemia is closely related to poor survival rates (26-29).

Albumin levels are influenced by the patient's nutritional status and metabolic demands. Inflammation and a high risk of malnutrition have been associated with low albumin (30). During an inflammatory process, while CRP tends to rise, albumin levels have been observed to decrease; the Glasgow Prognostic Score, which combines CRP and albumin, has been used in over 60 studies to predict survival and tolerability of chemotherapy in cancer (31-33). Therefore, albumin levels are a well-established indicator for prognosis in various cancers.

Lymphocytes play a role in immune surveillance, aiding in the detection and destruction of tumors; thus, a decrease in lymphocyte count is thought to play a significant role in prognosis (34).

Platelets have been shown to play a significant role in the metastatic capabilities of cancer (35). They release vascular endothelial growth factor (VEGF) which promote tumor angiogenesis along with other inflammatory mediators (36-38). It has also been demonstrated that platelets play a role in protecting tumor cells from immune detection (39).

To date, HALP has been studied in numerous research articles evaluating outcomes in various cancers; including gastric, colorectal, prostate, esophageal, pharyngeal, lung, and cervical cancers. However, the prognostic value of pre-treatment HALP scores has yet to be fully elucidated.

In a study conducted by Düzköprü et al. examining HALP and PNI (Prognostic Nutritional Index) scores in head and

neck cancers, patients were divided into two groups based on the median HALP score of 13.75, and it was found that HALP score independently predicted overall survival. However, the difference in progression-free survival between HALP score groups was not statistically significant, which was attributed to the limited number of patients and the influence of inflammatory parameters (40).

In our study, 47 patients who underwent total laryngectomy were included. PCF developed in 24 patients, while 23 did not. The threshold value for the HALP score was specifically calculated for each study; in our study, the threshold value was calculated as 33.42 for patients with positive fistula and 42.79 for those without. We found no significant relationship between the development of PCF and HALP score in patients undergoing total laryngectomy ($p > 0.05$).

Wenig et al. reported postoperative mortality, wound infection, and fistula formation rates of 2.2%, 8.8%, and 8.8%, respectively, in a series of 45 patients treated with various types of partial laryngectomy with glottic reconstruction (41). In our study, we found that fistula developed in one of the 29 patients who underwent partial laryngectomy, resulting in a fistula formation rate of 3.4%. Additionally, we compared the HALP scores of patients who underwent total laryngectomy and those who underwent partial laryngectomy. No significant difference was found between the HALP scores of patients who underwent total laryngectomy and those who underwent partial laryngectomy ($p > 0.05$).

It is important to highlight some of the limitations of our study. Firstly, the fact that our research is single-centered and retrospective may introduce potential biases and limitations. Additionally, the relatively small sample size and the heterogeneity of the patient group are among the other limitations of our study. Furthermore, the fistula rate due to salvage laryngectomies performed frequently in our center is close to the upper limit of the average, limiting our study. These factors should be considered when evaluating and interpreting the research results.

In conclusion, the HALP score is a biomarker that can be easily calculated with routine tests and can predict prognosis in many tumors. In addition to predicting cancer prognosis, it has started to be studied in different fields as well. In this study, the relationship between the HALP score and the development of PCF in patients who underwent laryngectomy was examined, but there was no correlation between HALP score and development of PCF or the course of treatment of the fistula. However, it has been previously proven that hemoglobin and albumin levels are risk factors for the development of PCF, and further multicenter and prospective studies involving more patients are needed regarding the relationship between HALP score and fistula.

Acknowledgments

None.

Author Contributions

Concept: **Deniz Baklacı**, Design: **Duygu Erdem**, Data Collection or Processing: **Seda Nur Saka**, **Doğancan Eralp**, Analysis or Interpretation: **Gökhan Furkan Kılıç**, Literature search: **Seda Nur Saka**, **Gökhan Furkan Kılıç**, Writing: **Deniz Baklacı**, **Seda Nur Saka**, **Gökhan Furkan Kılıç**, Approval: **Duygu Erdem**.

Conflicts of Interest

The authors have no conflict of interest to declare.

Financial Support

This study received no financial support.

Ethical Approval

The study was approved by the Clinical Researches Ethics Committee of Zonguldak Bülent Ecevit University Faculty of Medicine (Date: 21.02.2024, number: 2024/05).

Review Process

Extremely and externally peer-reviewed.

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