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Association Between Preoperative Albumin-to-Alkaline Phosphatase Ratio and Pharyngocutaneous Fistula After Total Laryngectomy

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ABSTRACT

Objective: Pharyngocutaneous fistula (PCF) is an important complication after total laryngectomy, associated with delayed wound healing, prolonged hospitalization, and increased costs. Serum albumin reflects nutritional and immune status, whereas alkaline phosphatase reflects systemic inflammation and hepatic function. Albumin-to-alkaline phosphatase ratio (AAPR) may therefore represent a simple preoperative marker of nutritional and inflammatory status.

Methods: This retrospective cohort study included 82 patients who underwent primary total laryngectomy with simultaneous bilateral level II-IV neck dissection between 2016 and 2023. Preoperative serum albumin and alkaline phosphatase levels were recorded, and AAPR was calculated. Pharyngocutaneous fistula development was the primary outcome. The optimal AAPR cut-off associated with PCF was determined using receiver operating characteristic (ROC) analysis. Factors associated with PCF were analyzed using univariable and multivariable logistic regression.

Results: Pharyngocutaneous fistula occurred in 19 patients (23.1%). Preoperative AAPR was significantly lower in patients with PCF ($P = .001$). Receiver operating characteristic analysis demonstrated an area under the curve of 0.745. The exploratory AAPR cut-off value selected using the Youden index was 0.48, with 84% sensitivity and 60% specificity. Low AAPR was associated with PCF in univariable analysis ($P < .05$) but was not an independent predictor in multivariable analysis ($P = .353$). Advanced T stage remained independently associated with PCF ($P = .048$).

Conclusions: Preoperative AAPR was lower in patients who developed PCF and showed moderate discriminatory ability. However, AAPR did not remain an independent predictor after adjustment for T stage. Therefore, AAPR should be interpreted as an exploratory marker rather than a standalone predictor of PCF. Larger prospective studies are required.

Keywords: Albumin-to-alkaline phosphatase ratio, laryngeal squamous cell carcinoma, nutritional biomarkers, pharyngocutaneous fistula, total laryngectomy

Introduction

Laryngeal cancer is among the most common malignancies of the upper aerodigestive tract.[1] More than 90% of laryngeal tumors originate from the mucosal lining, and the most common histological subtype is well-differentiated squamous cell carcinoma.[2] Although multiple risk factors contribute to the development of laryngeal cancer, tobacco and alcohol consumption are the most significant etiological factors. A strong association between tobacco use and the development of laryngeal cancer has been well established.[3]

Approximately 60% of patients present with advanced-stage disease (stage III or IV) at the time of diagnosis.[4] Depending on tumor stage and patient-related factors, treatment options include surgery, radiotherapy (RT), or chemoradiotherapy (CRT). In patients with advanced-stage laryngeal cancer, total laryngectomy has been reported to provide a survival advantage compared to chemoradiotherapy.[5] However, total laryngectomy is a procedure in which preoperative and postoperative management is often more challenging than the surgical intervention itself. Preoperative blood parameters significantly influence postoperative healing and long-term

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outcomes. Among postoperative complications, pharyngocutaneous fistula (PCF) is 1 of the most important, as it delays wound healing and increases both the length of hospital stay and overall treatment costs.[6]

Pharyngocutaneous fistula is a serious complication characterized by dehiscence of the surgically closed pharyngeal mucosa, resulting in the formation of a pathological communication between the pharynx and the skin.[7] It is 1 of the most common complications following total laryngectomy and pharyngolaryngectomy and has a substantial negative impact on patient morbidity. Factors predisposing to fistula formation have been categorized as patient-related, disease-related, and treatment-related factors.[8] Nevertheless, there is still no clear consensus in the literature regarding the most decisive risk factors for the development of PCF.[8]

Serum albumin (ALB) is an important indicator of nutritional status and immune function, whereas serum alkaline phosphatase (ALP) levels are associated with systemic inflammation and liver function. These parameters have been shown to be correlated with prognosis in cancer patients. The prognostic value of the albumin-to-alkaline phosphatase ratio (AAPR) was first described in 2015 in patients with hepatocellular carcinoma.[9] In head and neck cancers, albumin-based biomarkers have been reported to be useful in predicting survival and perioperative outcomes.[10] However, no studies to date have investigated the relationship between AAPR and the development of PCF.

The aim of this study was to investigate the association between preoperative AAPR and postoperative PCF development in patients with laryngeal cancer undergoing primary total laryngectomy. This study also aimed to explore whether AAPR may provide additional information as a simple marker of nutritional and inflammatory status in preoperative risk assessment.

Methods

Study Design and Patient Selection

This retrospective cohort study was conducted at a tertiary referral center, and approval was obtained from the Institutional Ethics Committee of University of Health Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital prior to the study (approval date: December 12, 2024; approval number: 2024-11/180).

Main Points

- Pharyngocutaneous fistula occurred in 23.1% of patients undergoing primary total laryngectomy.
- Patients who developed pharyngocutaneous fistula had significantly lower preoperative albumin-to-alkaline phosphatase ratio (AAPR) values.
- An AAPR cut-off value of 0.48 showed moderate discriminatory performance in this retrospective cohort.
- Low AAPR was associated with pharyngocutaneous fistula in univariable analysis; however, advanced T stage was the only variable independently associated with pharyngocutaneous fistula (PCF) in the multivariable model.

Because of the retrospective design of the study and the use of anonymized patient data, the requirement for informed consent was waived by the Institutional Ethics Committee. Medical records of patients diagnosed with laryngeal squamous cell carcinoma who underwent primary total laryngectomy with bilateral level II–IV neck dissection at the clinic between January 2016 and August 2023 were retrospectively reviewed. Patients with incomplete clinical, pathological, biochemical, or follow-up data were excluded. After application of the eligibility criteria, 82 patients with complete preoperative laboratory and clinical data were included in the final analysis. Patients with documented preoperative anemia or uncontrolled diabetes mellitus were excluded. All patients included in the study were active smokers at the time of diagnosis. Data regarding alcohol consumption were not included in the analysis due to the lack of standardized quantitative records. However, none of the included patients had a documented alcohol use disorder; the cohort consisted only of patients who reported either no alcohol consumption or social drinking. Neopharyngeal reconstruction was performed by primary manual I-shaped vertical closure in all included patients. No regional or free flap reconstruction, stapling device, tissue adhesive, or other surgical sealant was used. All procedures were performed by surgeons from the same head and neck surgery team using a consistent institutional surgical approach.

Inclusion and Exclusion Criteria

All patients included in the study met the following criteria:

- Histopathologically confirmed diagnosis of laryngeal squamous cell carcinoma,
- Underwent primary total laryngectomy,
- Active tobacco use at the time of diagnosis.

Patients with the following characteristics were excluded from the study:

- History of radiotherapy or chemoradiotherapy,
- Patients who underwent salvage surgery,
- Previous surgical treatment for laryngeal cancer,
- Presence of synchronous malignancies,
- Preoperative anemia,
- Uncontrolled diabetes mellitus.

None of the patients included in the study underwent salvage laryngectomy.

Biochemical Assessment

Preoperative serum albumin (g/L) and alkaline phosphatase (U/L) levels obtained within 15 days before surgery were recorded. The AAPR was calculated by dividing the serum albumin level by the serum alkaline phosphatase level, as shown below:

$$\text{AAPR} = \frac{\text{Serum Albumin (g/L)}}{\text{Serum Alkaline Phosphatase (U/L)}}$$

Outcome Measure

The primary outcome of the study was the development of postoperative PCF following total laryngectomy. Pharyngocutaneous fistula was defined as clinically evident salivary leakage from the cervical wound site during

postoperative hospitalization, confirmed by physical examination and/or imaging modalities.

Statistical Analysis

Statistical analyses were performed using Student's *t*-test, Mann–Whitney *U*-test, and chi-square or Fisher's exact test, as appropriate. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. A *P* value of < .05 was considered statistically significant.

The discriminatory performance of AAPR for PCF development was evaluated using receiver operating characteristic (ROC) curve analysis. The exploratory optimal cut-off value was selected by maximizing the Youden index, calculated as sensitivity + specificity − 1. Because the cut-off value was derived from the same retrospective cohort, it was considered exploratory and was not interpreted as an externally validated clinical threshold. For the dichotomized analysis, AAPR < 0.48 was coded as the exposure category, whereas AAPR ≥ 0.48 was used as the reference category. Accordingly, odds ratios greater than 1 indicated increased odds of PCF among patients with low AAPR. Multivariable logistic regression analysis was performed to evaluate whether AAPR was independently associated with PCF after adjustment for tumor stage. Due to the limited number of PCF events (n = 19), the number of covariates included in the multivariable model was deliberately restricted to reduce the risk of model overfitting and unstable estimates. Albumin-to-alkaline phosphatase ratio and T stage were selected based on their clinical relevance and univariable associations. Other potentially relevant patient-, disease-, and treatment-related variables could not be included simultaneously because of the limited event number.

Results

A total of 82 patients were included in the study, with a mean age of 62.73 ± 8.82 years. Only 2 patients were female. According to pathological evaluation based on the American Joint Committee on Cancer Eighth Edition tumor–node–metastasis staging system, 55 patients had T4 tumors and 27 patients had T3 tumors. Demographic and clinical characteristics of the patients are shown in Table 1.

Biochemical parameters according to PCF status are compared in Table 2.

Table 1. Demographic and Clinical Characteristics of the Patients

Variable	Patients (n = 82)
Age, years, mean ± SD	62.73 ± 8.82
Sex, n (%)	
Male	80 (97.6)
Female	2 (2.4)
T Stage, n (%)	
T3	27 (32.9)
T4a	55 (67.1)
PCF, n (%)	19 (23.1)

PCF, pharyngocutaneous fistula.

Univariable logistic regression results for PCF development are presented in Table 3.

A multivariable logistic regression model including AAPR and T stage was constructed. In this model, low AAPR (<0.48) was not independently associated with PCF after adjustment for T stage (odds ratio [OR] = 3.729, 95% CI = 0.232-60.003, *P* = .353), whereas advanced T stage was the only variable independently associated with PCF in the multivariable model (OR = 4.817, 95% CI = 1.014-22.896, *P* = .048).

The discriminatory performance of AAPR for PCF was evaluated using ROC curve analysis (Figure 1). The analysis demonstrated an AUC of 0.745, indicating moderate discriminatory ability. Based on the maximum Youden index, the exploratory AAPR cut-off value providing the best balance between sensitivity and specificity was 0.48, with a sensitivity of 84% and a specificity of 60%. This threshold should be interpreted cautiously because it was derived retrospectively and was not tested in an independent validation cohort. The distribution of PCF according to the AAPR cut-off value is shown in Table 4. In the univariable logistic regression analysis based on the exploratory cut-off value, patients with AAPR < 0.48 had significantly higher odds of developing PCF than those with AAPR ≥ 0.48 (OR = 4.255, 95% CI = 1.361-13.333, *P* = .013).

Discussion

In this study, the preoperative AAPR was associated with PCF in univariable analysis but did not remain an independent predictor after multivariable adjustment. This is the first study to investigate the association between AAPR and PCF development in patients undergoing total laryngectomy. In patients who developed PCF, serum albumin levels were lower, alkaline phosphatase levels were higher, and consequently, AAPR values were markedly reduced. Furthermore, univariable logistic regression analysis demonstrated that albumin, ALP, and particularly AAPR were significantly associated with PCF development. Receiver operating characteristic analysis demonstrated moderate discriminatory ability, with an AUC of 0.745. The exploratory AAPR cut-off value of 0.48, selected using the Youden index, yielded a sensitivity of 84% and a specificity of 60%. However, given the retrospective design, limited number of events, and lack of external validation, this finding should be considered hypothesis-generating.

Table 2. Comparison of Biochemical Parameters According to the Development of Pharyngocutaneous Fistula

Parameter	PCF (−)	PCF (+)	*P*
Albumin, g/L, mean ± SD	40.56 ± 4.01	37.21 ± 4.57	.03*
ALP, U/L, median (min–max)	78.50 (38.9-147.0)	95.40 (60.20-163.20)	.03**
AAPR, median (min–max)	0.52 (0.248-1.149)	0.40 (0.253-0.701)	.001**

AAPR, albumin-to-alkaline phosphatase ratio; ALP, alkaline phosphatase; PCF, pharyngocutaneous fistula.
* Student's *t*-test.
** Mann–Whitney *U*-test.

Table 3. Univariable Logistic Regression Analysis for the Development of Pharyngocutaneous Fistula

Variable	*P*	OR	95% CI
Albumin	.005	0.828	0.725-0.945
ALP	.04	1.021	1.001-1.041
AAPR < 0.48 vs ≥ 0.48	.013	4.255	1.361-13.333

AAPR, albumin-to-alkaline phosphatase ratio; ALP, alkaline phosphatase; OR, odds ratio.
AAPR ≥ 0.48 was used as the reference category. The exploratory AAPR cut-off value of 0.48 was selected by maximising the Youden index in receiver operating characteristic (ROC) analysis (AUC = 0.745).

Predisposing factors can be categorized into 3 main groups: patient-related, disease-related, and treatment-related factors.[11] Patient-related factors include sex, age, smoking status, alcohol consumption, diabetes, cardiovascular disease, gastroesophageal reflux disease, decreased preoperative hemoglobin, albumin, and calcium levels, prior surgical treatment, previous radiotherapy or chemoradiotherapy, and tumor recurrence.[11,12] Disease-related factors include tumor stage, lymph node involvement, and pharyngeal invasion.[13,14]

Another study identified risk factors significantly associated with PCF development, including advanced age, postoperative anemia, diabetes mellitus, tumor location in the supraglottic or subglottic region, prior radiotherapy, previous tracheostomy, timing of surgery (salvage procedure), extended total laryngectomy (including pharyngectomy), and postoperative hypoproteinemia. In contrast, primary tracheoesophageal puncture was found to reduce the risk of PCF.[14]

Several studies have investigated the role of serum biomarkers in PCF due to their ease of accessibility. Among these, markers such as the prognostic nutritional index (PNI), systemic immune-inflammation index (SII), and hemoglobin, albumin, lymphocyte, platelet (HALP) have been evaluated in relation to PCF risk.[15] Numerous studies have reported that ALB, ALP, and AAPR are associated with complications, prognosis, and recurrence in cancer patients.[16] Albumin is considered a marker of nutritional status and systemic inflammation.[17] Relatively low ALB levels or hypoalbuminemia in cancer patients can be attributed to factors such as disease-induced stress response, reduced protein intake, and concomitant infections. These conditions may negatively affect both nutritional status and treatment response.[18]

Alkaline phosphatase is an enzyme that dephosphorylates various molecules, including nucleotides, proteins, and alkaloids, and has emerged as an increasingly important prognostic factor in various carcinoma types.[16] The prognostic role of ALP has been documented in multiple studies, which have shown that elevated ALP is an adverse factor and may also indicate cancer recurrence and distant metastasis.[16] Overall, pre-treatment

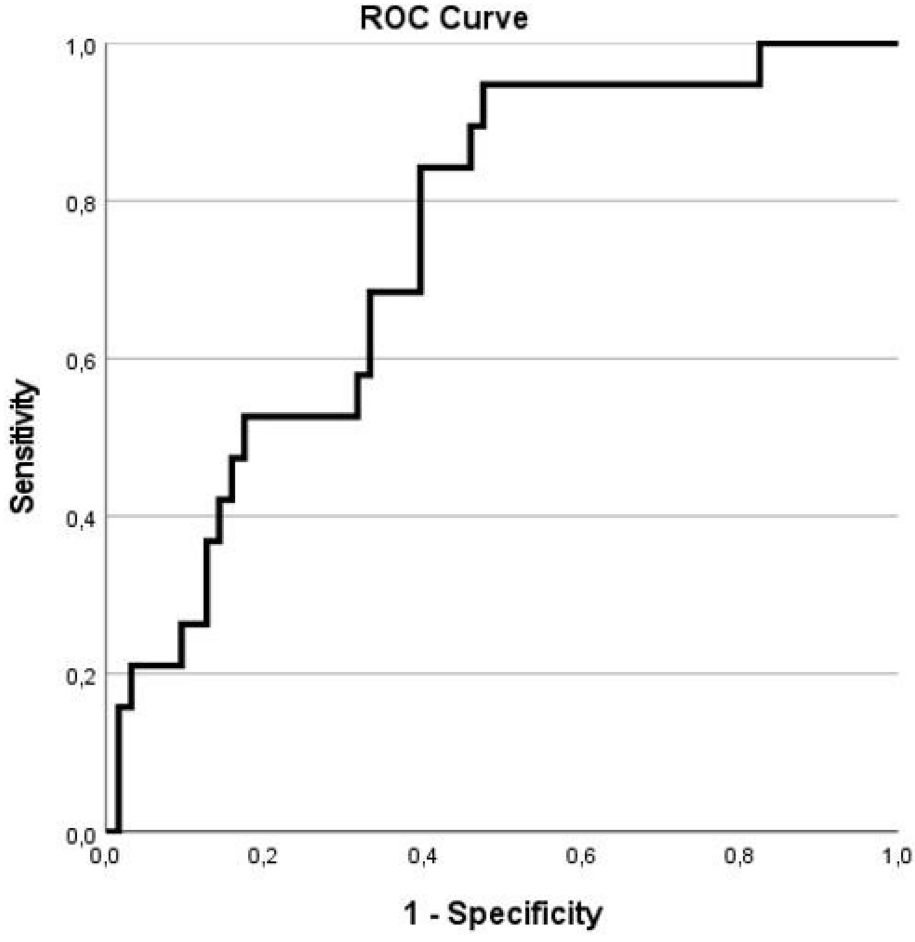

Figure 1. Receiver operating characteristic curve showing the discriminatory performance of preoperative albumin-to-alkaline phosphatase ratio for pharyngocutaneous fistula development (AUC = 0.745).

Table 4. Distribution of Pharyngocutaneous Fistula According to the Cut-off Value

AAPR	PCF (−)	PCF (+)	*P*
≥0.48	38	5	.017*
<0.48	25	14	

AAPR, albumin-to-alkaline phosphatase ratio; PCF, pharyngocutaneous fistula.
* Fisher's exact test.

AAPR may reflect systemic inflammatory status and nutritional condition. This novel biomarker has also been associated with poor prognosis in head and neck cancers.[19]

These widely available markers may provide additional clinical information in selected settings. A low AAPR value likely represents the combined effects of malnutrition and systemic inflammation, both of which may impair wound healing and tissue regeneration. However, PCF is primarily a local wound-healing complication influenced by mechanical, anatomical, and surgical factors, including pharyngeal closure tension, local tissue perfusion, infection, and postoperative care. Therefore, AAPR should not be interpreted as a direct mechanistic marker of pharyngeal breakdown. Rather, a low AAPR may act as an indirect marker of impaired nutritional reserve, systemic inflammation, and advanced disease burden, all of which may contribute to poor wound healing.

The ROC analysis identified an exploratory AAPR cut-off value of 0.48, with a sensitivity of 84% and a specificity of 60%. This suggests that lower AAPR values may be associated with an increased risk of PCF. However, the overall discriminatory performance was moderate (AUC = 0.745), indicating that AAPR alone is unlikely to be sufficient as a standalone predictor. In addition, this threshold was derived from the same retrospective dataset and was not validated in an independent cohort. Therefore, AAPR may be considered only as a complementary exploratory parameter rather than a definitive predictor, and the cut-off value should not be directly applied to clinical decision-making without external validation.

This study has several limitations. First, the retrospective single-center design may limit the generalizability of the findings and may have introduced selection bias, particularly because patients with incomplete clinical, pathological, biochemical, or follow-up data were excluded. Second, the sample size was relatively small, and only 19 patients developed pharyngocutaneous fistula. Therefore, the multivariable model was intentionally restricted to a limited number of variables to reduce the risk of overfitting. Nevertheless, the adjusted estimate for low AAPR had a very wide confidence interval, indicating substantial imprecision and model instability related to the limited number of PCF events and sparse observations across the AAPR and T-stage categories. Importantly, the direction of the association remained consistent between the univariable and multivariable analyses after low AAPR (<0.48) was uniformly defined as the exposure category. Third, although AAPR was associated with PCF in univariable analysis, it did not remain an independent predictor after adjustment for T stage. Thus, AAPR should not be interpreted as a standalone or specific predictive biomarker for PCF, but rather as an exploratory marker that may reflect impaired nutritional reserve, systemic inflammation, and advanced disease burden. Fourth, operative duration and intraoperative blood loss could not be reliably evaluated because these variables were not consistently documented in the retrospective records. Postoperative hemoglobin changes, timing of oral feeding, surgeon-related variation, and perioperative protocol differences could also not be fully assessed. Therefore, residual confounding by surgical and postoperative factors cannot be excluded. Although none of the included patients had a documented alcohol use disorder, alcohol consumption could not be quantitatively analyzed because standardized information on the amount and frequency of alcohol intake was unavailable. Therefore, residual confounding related to differences between social drinkers and non-drinkers cannot be excluded. Although albumin and alkaline phosphatase measurements were obtained within 15 days before surgery, AAPR is a dynamic biomarker that may vary according to nutritional status, systemic inflammation, body mass index, hepatic function, and perioperative nutritional interventions. Detailed data on these potential determinants, including preoperative nutritional support and postoperative feeding protocols, were not consistently available and could not be incorporated into the analysis. Fifth, the study period extended from 2016 to 2023, during which perioperative protocols, antibiotic strategies, postoperative care, and surgical practice may have changed. Because year of surgery was not included in the model, temporal changes may also have contributed to residual confounding. Finally, the AAPR cut-off value of 0.48 was derived from the same retrospective cohort and was not validated in an independent dataset. Therefore, this threshold should be considered exploratory and should not be directly applied to clinical decision-making without external validation. Larger prospective multicenter studies are required to determine whether AAPR provides clinically meaningful incremental value beyond established patient-related, disease-related, and surgical risk factors.

In conclusion, lower preoperative AAPR was associated with PCF development in univariable analysis and demonstrated moderate discriminatory performance in this retrospective cohort. However, AAPR did not remain an independent predictor after adjustment for T stage. These findings suggest that AAPR may reflect poor nutritional and inflammatory status rather than directly predicting local pharyngeal wound breakdown. Therefore, AAPR should be considered a hypothesis-generating, complementary marker, and its clinical value requires external validation in larger prospective cohorts.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: This study used ChatGPT (OpenAI) solely for language editing and grammatical correction during the preparation of the manuscript. The final version was thoroughly reviewed and approved by all authors, who take full responsibility for its content.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of University of Health Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Approval no.: 2024-11/180; Date: December 12, 2024).

Informed Consent: Informed consent was waived due to the retrospective nature of the study.

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