

# Predictors of fistula after laryngectomy: a 10-year review

## Original Article

### Authors

**Pedro Marques Gomes**

Unidade Local de Saúde de Matosinhos – Hospital Pedro Hispano, Portugal

**Diogo Cunha Cabral**

Unidade Local de Saúde de Matosinhos – Hospital Pedro Hispano, Portugal

**Nuno Oliveira**

Unidade Local de Saúde de Matosinhos – Hospital Pedro Hispano, Portugal

**Delfim Duarte**

Unidade Local de Saúde de Matosinhos – Hospital Pedro Hispano, Portugal

**Paula Azevedo**

Unidade Local de Saúde de Matosinhos – Hospital Pedro Hispano, Portugal

**Correspondence:**

Pedro Marques Gomes  
pedrommarquesgomes@hotmail.com

Article received on March 6, 2025.

Accepted for publication on June 20, 2025.

### Abstract

**Introduction:** Total laryngectomy (TL) is a surgical procedure used to treat advanced laryngeal cancer. Although effective, it is associated with several postoperative complications, one of the most important being pharyngocutaneous fistula (PCF). The incidence of this complication varies from 8.7% to 27%, depending on factors such as surgical technique and patient characteristics. The development of PCF can prolong hospital stay, increase treatment costs and compromise patient recovery.

**Objectives:** The study aimed to identify the predictors associated with the development of PCF in patients undergoing TL and pharyngolaryngectomy, contributing to the implementation of more effective preventive and therapeutic strategies.

**Material and Methods:** A retrospective and analytical study was performed, based on data from patients who underwent TL and pharyngolaryngectomy between 2013 and 2023 in a single hospital. Pre-, peri- and postoperative factors were analysed, including age, smoking, alcohol consumption, nutritional status, surgical technique and postoperative laboratory parameters. Statistical analysis included univariate tests and binary logistic regression to identify independent risk factors.

**Results:** The sample included 66 patients with a mean age of 62.14 years. The incidence of CFS was significantly associated with pharyngeal tumour involvement (OR = 23.1;  $p = 0.010$ ). In univariate analysis, lower levels of albuminemia ( $p = 0.012$ ), total proteinemia ( $p = 0.045$ ) and haemoglobinemia ( $p = 0.023$ ) were also associated with PCF, but did not remain significant in logistic regression. Other factors such as smoking, alcoholism, history of cancer treatment and closure technique were not statistically significant.

**Conclusions:** Pharyngeal tumour involvement was identified as the main independent risk factor for the development of PCF. Nutritional and haematological factors showed an association in univariate analysis, but their impact seems to be secondary. Preoperative optimisation of nutritional status and selection of the most appropriate surgical technique may reduce complications and improve clinical outcomes for patients.

**Keywords:** Laryngeal cancer, total laryngectomy, pharyngocutaneous fistula, postoperative complications, predictors.

Introduction

Total laryngectomy (TL) is commonly used for the surgical management of advanced laryngeal carcinoma. Although it is effective in controlling local disease progression, TL is associated with several postoperative complications that can substantially impact patient recovery. Among these, pharyngocutaneous fistula (PCF) is one of the most frequent and clinically significant complications<sup>1</sup>. International studies have reported that the incidence of PCF following TL ranges between 8.7–27%, depending on factors such as the surgical technique and patient-specific characteristics<sup>2</sup>. A systematic review identified multiple risk factors for the development of PCF, including preoperative radiotherapy, prior tracheostomy, malnutrition, and existing comorbidities<sup>3</sup>. PCF is associated with a longer hospital stay, increased treatment costs, higher risk of infection, and delayed rehabilitation<sup>4</sup>. These consequences can negatively affect both the quality of life and prognosis of patients undergoing TL<sup>5</sup>. In this context, identifying predictive factors for PCF is essential for developing more effective preventive strategies and therapeutic interventions.

Objectives

To analyze the relationship of PCF with clinical, demographic, and laboratory parameters of patients undergoing TL or pharyngolaryngectomy, with the aim of optimizing the perioperative approach and reducing complications.

Materials and Methods

This retrospective, analytical, and single-center study was conducted using data from a single hospital. All patients who underwent TL or pharyngolaryngectomy between January 2013 and December 2023 were included. The only exclusion criterion was the lack of information regarding the presence or absence of PCF. Risk factors were classified as preoperative, perioperative, or postoperative (Table 1). Preoperative risk factors were associated with both the patient and tumor. Patient-related factors included age, smoking habits (< 10 or ≥ 10 pack-years), alcohol consumption (< 60 g/day or ≥ 60 g/day), and body mass index (BMI). Tumor-related factors included prior radiotherapy, chemotherapy, or chemoradiotherapy; tumor stage according to the tumor-node-metastasis (TNM) classification; presence of preoperative

Table 1 Risk factors for PCF
<b>Preoperative</b>
Patient-related Age Smoking habits Alcohol consumption BMI Tumor-related Previous CT/RT/CTRT TNM staging Tracheostomy Primary or salvage surgery
<b>Perioperative</b>
Surgical margins Pharyngeal tumor involvement Type of closure
<b>Postoperative</b>
Serum albumin level Total serum protein level Serum hemoglobin level

PCF, pharyngocutaneous fistula; CT, chemotherapy; RT, radiotherapy; CTRT, chemoradiotherapy; BMI, body mass index.

tracheostomy; and whether the surgery was performed as a primary treatment or salvage procedure. Perioperative risk factors included the status of the surgical margins, categorized as clear (R0), microscopically involved or < 3 mm (R1), or macroscopically invaded (R2); pharyngeal tumor involvement; and the type of pharyngeal closure (manual suturing with separate stitches or mechanical closure using staples). Postoperative risk factors were assessed during the first week after surgery and included serum albumin, total serum protein, and serum hemoglobin levels. Statistical analysis was conducted using the SPSS® software, version 29 (IBM Corp., Armonk, NY, USA). Descriptive statistics were initially used to characterize the sample, including means, standard deviations, and proportions of the assessed variables. Univariate analysis was subsequently conducted to identify the associations among the variables. The Chi-square or Fisher's exact test was used for categorical variables. The Student's t-test or Mann–Whitney test was used for continuous variables, depending on the data distribution. Multivariate analysis was performed using binary logistic regression to identify the independent factors associated with PCF, with

the results expressed as odds ratios (OR) with 95% confidence intervals (CI95%). Statistical significance was set as  $p < 0.05$ .

Results

The final sample included 66 patients who underwent surgery between 2013 and 2023. The mean age was 62.14 years ( $\pm 9.48$ ), and the mean BMI was 24.59 kg/m<sup>2</sup> ( $\pm 4.21$ ). Postoperative laboratory parameters showed mean values of 3.34 g/dL for serum albumin, 5.73 g/dL for total protein, and 10.82 g/dL for hemoglobin. Regarding the preoperative factors, 93.1% of the patients had a significant history of smoking ( $\geq 10$  pack-years) and 51.5% reported high alcohol consumption ( $\geq 60$  g/day). Additionally, 43.9% of the patients had undergone prior tracheostomy, and salvage surgery was performed in 13.6% cases. Regarding the perioperative factors, the majority of patients (80.3%) had clear surgical margins (R0). Pharyngeal tumor involvement (oropharynx/hypopharynx) was observed in 21.2% of cases. Pharyngeal closure was performed manually in 22.7% patients and mechanically in 75.8% patients. All these data are detailed in Tables 2 and 3.

Table 2 Clinical and demographic characteristics	
Continuous variables	
Age	
Mean $\pm$ standard deviation	62,14 $\pm$ 9,48
Minimum	43
Maximum	88
BMI (Body Mass Index)	
Mean $\pm$ standard deviation	24,59 $\pm$ 4,21
Minimum	16,50
Maximum	35,00
Postoperative albumin level	
Mean $\pm$ standard deviation	3,34 $\pm$ 0,55
Minimum	2,20
Maximum	4,70
Postoperative total protein level	
Mean $\pm$ standard deviation	5,73 $\pm$ 0,81
Minimum	3,40
Maximum	7,40
Postoperative hemoglobin level	
Mean $\pm$ standard deviation	10,82 $\pm$ 1,43
Minimum	7,20
Maximum	14,00

**Table 3**  
Clinical and demographic characteristics

Categorical variables	N (%)
<b>Smoking habits</b>	
< 10 pack-years	4 (6,9)
≥ 10 pack-years	62 (93,1)
<b>Alcohol consumption</b>	
< 60 g/day	32 (48,5)
≥ 60 g/day	34 (51,5)
<b>Previous CT/RT/CTRT</b>	3 (4,5)
<b>Pathological TNM (pTNM) staging</b>	
<b>T</b>	
T2	10 (15,2)
T3	33 (50,0)
T4a	23 (34,8)
<b>N</b>	
N0	35 (53,0)
N1	9 (13,6)
N2	15 (22,8)
N3	7 (10,6)
<b>M</b>	
M0	66 (100)
<b>Staging</b>	
II	5 (7,6)
III	25 (37,9)
IV	36 (54,5)
<b>Tracheostomy</b>	29 (43,9)
<b>Primary or salvage surgery</b>	
Primary	57 (86,4)
Salvage	9 (13,6)
<b>Surgical margins</b>	
R0	53 (80,3)
R1/R2	13 (19,7)
<b>Pharyngeal involvement</b>	14 (21,2)
<b>Type of surgery</b>	
TL	52 (78,8)
Total pharyngolaryngectomy	14 (21,2)
<b>Type of closure</b>	
Manual	15 (22,7)
Mechanical	50 (75,8)

CT, chemotherapy; RT, radiotherapy; TL, total laryngectomy

Univariate analysis identified several factors that were significantly associated with PCF (table 4 and 5):

- Pharyngeal involvement was observed in 50.0% of cases that developed PCF, compared to 21.2% of those without PCF ( $p = 0.038$ ).
- Postoperative serum albumin ( $p = 0.012$ ).
- Total protein ( $p = 0.045$ ).
- Hemoglobin ( $p = 0.023$ ) levels showed a negative correlation.

Other parameters, such as smoking habits, alcohol consumption, prior chemotherapy and/or radiotherapy, tumor stage, preoperative tracheostomy, salvage surgery, surgical margins, and type of pharyngeal closure, demonstrated no statistically significant associations with PCF.

In the multivariate analysis, binary logistic regression was used to identify the independent risk factors for PCF (table 6).

**Table 4**  
Factors associated with PCF in univariate analysis

Variable	PCF (%)	p
Sex (m/f)	27,7 vs 0,0	,727
Smoking habits (< 10 vs ≥ 10 packs-year)	50,0 vs 25,8	,298
Alcohol consumption (< 60 g/day vs ≥ 60 g/day)	27,8 vs 15,8	,314
Previous CT/RT/CTRT (y/n)	66,7 vs 25,4	,178
Staging (II/III vs IV)	30,0 vs 22,9	,514
Tracheostomy (y/n)	20,7 vs 32,4	,288
Surgery (primary/salvage)	28,1 vs 22,2	,533
Margins (R0/R1+2)	25,4 vs 41,7	,178
Pharyngeal involvement (y/n)	<b>50,0 vs 21,2</b>	<b>,038</b>
Closure (manual/mechanical)	40,0 vs 22,0	.146

PCF, pharyngocutaneous fistula; CT, chemotherapy; RT, radiotherapy; CTRT, chemoradiotherapy.

**Table 5**  
Factors associated with PCF in univariate analysis

Variable	PCF (r)	p
Age	-,096	,445
BMI	-,090	,474
Postoperative albumin level	<b>-,368</b>	<b>,012</b>
Postoperative total protein level	<b>-,310</b>	<b>,045</b>
Postoperative hemoglobin level	<b>-,279</b>	<b>,023</b>

PCF, pharyngocutaneous fistula; BMI, body mass index.

**Table 6**  
Factors associated with PCF in multivariate logistic regression analysis

Variable	OR	CI	p
Pharyngeal involvement	23,095	2.114-252.287	<b>,010</b>
Postoperative albumin level	,068	,387-1.262	,132
Postoperative total protein level	,601	,112-3.212	,551
Postoperative hemoglobin level	,699	,387-1.262	,234

PCF, pharyngocutaneous fistula; OR, odds ratio; CI, confidence interval

Pharyngeal tumor involvement was the only factor significantly associated with fistula formation (OR = 23.095, 95% CI: 2.114–252.287,  $p = 0.010$ ), indicating that patients with pharyngeal invasion had a 23-fold increased risk of developing PCF compared to those without tumor involvement.

Although serum albumin, total protein, and hemoglobin levels were associated with PCF in the univariate analysis, these

variables showed no statistical significance in multivariate logistic regression. Nevertheless, the coefficients for these laboratory parameters indicated a trend; lower albumin and total protein levels were associated with an increased risk of PCF.

## Discussion

PCF is one of the most common and challenging complications of TL. It negatively affects patient recovery, prolongs hospital stay, increases healthcare costs, and contributes to significant psychological distress.

Despite advances in surgical techniques and perioperative care, the incidence of postoperative complications remains high. Therefore, the identification of risk factors and implementation of prevention strategies is essential.

This study analyzed the predictive factors for PCF in a cohort of 66 patients who underwent TL. Our results indicated that pharyngeal tumor involvement was the only factor independently associated with PCF (OR = 23.095, 95% CI: 2.114–252.287,  $p=0.010$ ), indicating that the extent of resection and need for pharyngeal reconstruction may compromise anastomotic integrity, thereby increasing the risk of fistula formation. Univariate analysis revealed that lower postoperative serum albumin, total protein, and hemoglobin levels were significantly associated with PCF. However, these variables did not reach statistical significance in the multivariate logistic regression, suggesting that although nutritional status and hematologic reserve may support healing, pharyngeal tumor involvement remains the key determinant for the development of fistulas. The pathophysiology underlying the relationship between pharyngeal tumor involvement and PCF may be related to the extent of surgical resection required in these cases. Pharyngeal tumor invasion may require a more extensive resection, which can compromise the viability of the remaining tissue available for pharyngeal anastomosis. Additionally, tumors in this region are frequently associated with increased inflammation and fibrosis, which can impair healing and contribute to suture dehiscence. Regarding the nutritional status, serum albumin is a well-established marker used to assess the protein reserves and tissue healing capacity. Reduced serum albumin and total protein levels reflect a deficient

nutritional state, which may impair collagen deposition and tissue repair postoperatively<sup>6</sup>. Similarly, hemoglobin plays a vital role in tissue oxygenation, and low levels may impair cellular regeneration and increase the risk of necrosis at the suture line<sup>6</sup>. Although these variables did not retain statistical significance in the multivariate analysis, their association with PCF highlights the importance of optimizing the nutritional and hematologic parameters preoperatively.

Our findings align with those of previous studies that identified similar factors associated with the development of PCF following TL or pharyngolaryngectomy. Rao et al.<sup>6</sup> conducted a comprehensive meta-analysis to evaluate the predictors of PCF across 14 studies involving 2,446 patients who underwent TL. They found that reduced preoperative serum hemoglobin (OR 3.590,  $p < 0.001$ ) and albumin (OR 2.833,  $p < 0.001$ ) levels were significantly associated with PCF. These findings reinforce the need to enhance the patient's nutritional and hematologic status in the preoperative period. Furthermore, the same study identified hypopharyngeal involvement as a significant risk factor, supporting our observation that the extent of resection and need for pharyngeal reconstruction may compromise anastomotic integrity and predispose patients to fistula formation. Similarly, a systematic review and meta-analysis by Kim et al.<sup>2</sup> confirmed the association between PCF and postoperative anemia (OR 2.29,  $p < 0.001$ ) and low serum protein level (OR 9.98,  $p < 0.001$ ). Low serum protein demonstrated the highest predictive accuracy for PCF, with a specificity of 90% and area under the curve (AUC) of 0.84. These findings underscore the critical role of nutritional status in anastomotic healing and support our recommendation for adequate nutritional management throughout the preoperative, intraoperative, and postoperative periods.

In contrast, a study by Wei et al.<sup>7</sup> involving 124 patients who underwent TL identified prior radiotherapy as a key factor in the development of PCF, which increases the

incidence and complicates its management. Although radiotherapy was not independently associated with PCF in our univariate and multivariate analyses, the impact of radiotherapy-induced fibrosis and chronic tissue inflammation on pharyngeal anastomotic integrity cannot be overlooked.

Moreover, a review by Mäkitie et al.<sup>8</sup> emphasized the importance of a multidisciplinary approach to prevent PCF, and that intraoperative technical factors and postoperative care are essential to minimize complications. The authors also stated that the choice of the pharyngeal closure technique (manual vs. mechanical) remains controversial and requires an individualized assessment for each patient. This observation aligns with our findings, which showed no statistically significant association between the type of pharyngeal closure and occurrence of PCF.

Our results have significant clinical implications and emphasize the need for a personalized approach to reduce the risk of PCF following TL. The identification of pharyngeal tumor involvement as an independent risk factor highlights the importance of thorough preoperative assessment to guide the selection of surgical techniques that minimize anastomotic tension and promote optimal healing. Furthermore, the observed associations of PCF with nutritional and hematologic parameters indicate that optimizing these factors preoperatively may help in reducing the risk of postoperative complications. The implementation of nutritional support protocols and iron supplementation may help to improve the surgical outcomes and reduce the incidence of PCF.

This study has some limitations, including its retrospective and single-center design, which may limit the generalizability of the results. Additionally, the relatively small sample size may have reduced the ability to detect statistically significant associations with certain risk factors. Future multicenter, prospective studies are required to validate our findings and explore novel strategies

for PCF prevention. Although 19.7% of the patients presented with R1 or R2 margins, no statistically significant association between surgical margins and PCF was observed. This finding should be interpreted with caution due to potential biases and sample size limitations. Finally, the fact that pharyngeal closure was not performed by the same surgeon in all cases introduces a potential source of variability that may have influenced the results.

## Conclusion

Pharyngeal tumor involvement was identified as the primary independent risk factor for PCF following TL. Although nutritional and hematologic factors showed an association in univariate analysis, their impact appears to be secondary. Optimizing preoperative preparation and employing appropriate surgical strategies are crucial for reducing complications.

## Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

## Data Confidentiality

The authors declare having followed the protocols used at their working center regarding patient data publication.

## Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and the 2013 Helsinki Declaration of The World Medical Association.

## Funding Sources

This work did not receive any contribution, funding, or scholarship.

## Availability of scientific data

There are no datasets available, or publicity related to this work.



## References

1. Chotipanich A, Wongmanee S. Incidence of pharyngocutaneous fistula after total laryngectomy and its relationship with the shapes of mucosa closure: a meta-analysis. *Cureus*. 2022 Sep 6;14(9):e28822. doi: 10.7759/cureus.28822.
2. Kim DH, Kim SW, Hwang SH. Predictive value of risk factors for pharyngocutaneous fistula after total laryngectomy. *Laryngoscope*. 2023 Apr;133(4):742-754. doi: 10.1002/lary.30278.
3. Wang M, Xun Y, Wang K, Lu L, Yu A, Guan B. et al. Risk factors of pharyngocutaneous fistula after total laryngectomy: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. 2020 Feb;277(2):585-599. doi: 10.1007/s00405-019-05718-9.
4. Dedivitis RA, Aires FT, Cernea CR, Brandão LG. Pharyngocutaneous fistula after total laryngectomy: systematic review of risk factors. *Head Neck*. 2015 Nov;37(11):1691-7. doi: 10.1002/hed.23804.
5. Liang JW, Li ZD, Li SC, Fang FQ, Zhao YJ, Li YG. Pharyngocutaneous fistula after total laryngectomy: A systematic review and meta-analysis of risk factors. *Auris Nasus Larynx*. 2015 Oct;42(5):353-9. doi: 10.1016/j.anl.2015.04.002.
6. Rao KN, Arora RD, Singh A, Nagarkar NM, Aggarwal A. *Pharyngocutaneous fistula following primary total laryngectomy: a meta-analysis*. *Indian J Surg Oncol*. 2022 Dec;13(4):797-808. doi: 10.1007/s13193-022-01581-z.
7. Wei Wl, Lam KH, Wong J, Ong GB. *Pharyngocutaneous fistula complicating total laryngectomy*. *Aust N Z J Surg*. 1980 Aug;50(4):366-9. doi: 10.1111/j.1445-2197.1980.tb04141.x.
8. Mäkitie AA, Irish J, Gullane PJ. *Pharyngocutaneous fistula*. *Curr Opin Otolaryngol Head Neck Surg*. 2003 Apr;11(2):78-84. doi: 10.1097/00020840-200304000-00003.