Indian Journal of Surgical Oncology (December 2022) 13(4):797–808
https://doi.org/10.1007/s13193-022-01581-z

REVIEW ARTICLE

Pharyngocutaneous Fistula Following Primary Total Laryngectomy: a Meta-analysis

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Received: 14 March 2022 / Accepted: 28 June 2022 / Published online: 5 July 2022

Abstract

Pharyngocutaneous fistula (PCF) is the most common complication which significantly increases morbidity. High-level evidence is lacking that determines the PCF rates in the primary laryngectomy. The main objective of this study was to systematically identify the factors leading to the PCF formation in primary laryngectomy. Human studies reporting at least one risk factor for developing PCF in patients undergoing primary total laryngectomy for laryngeal cancer were included. PubMed, EMBASE, and Cochrane databases were searched for the data extraction. Risk of bias assessment tool for non-randomized trial tool was used. Cochrane's Q test and Higgin's I^2-heterogeneity was applied. The Mantel–Haenszel and DerSimonian Laird method was employed. Odds ratio was calculated for each risk factor, a P-value < 0.05 was considered as statistically significant. PROSPERO registration CRD42021248382. The meta-analysis comprised a total of 2446 patients in 14 included non-randomized studies. The among the analyzed risk factors—comorbidities (OR 2.781, R: 1.892–4.088, $P < 0.001$), site of tumor (OR 4.485, R: 3.003–6.699, $P < 0.001$), low pre-operative hemoglobin (OR 3.590, R: 2.130–6.050, $P < 0.001$), low pre-operative albumin (OR 2.833, R: 1.596–5.031, $P < 0.001$), utilization of surgical staplers (OR 0.172, R: 0.064–0.460, $P < 0.001$) (protective effect), positive mucosal margin (OR 4.92 R: 1.90–12.75, $P = 0.001$). The risk factors for PCF in patients undergoing primary TL included comorbidities, hypopharyngeal involvement, pre-operative hemoglobin and albumin, stapler usage, and positive mucosal margin.
Level of Evidence - III

Keywords Laryngeal cancer · Total laryngectomy · Pharyngocutaneous fistula · Complications · Risk factors

Introduction

Laryngeal cancer is a common cancer in the world [1]. Since the last decade, there is a trend towards non-surgical treatment. However, in advanced cancers with large volume tumors, cartilage destruction, compromised laryngeal function, and recurrent or residual disease, surgery remains the treatment of choice [2].

Pharyngocutaneous fistula (PCF) is the most common complication following total laryngectomy, which significantly increases morbidity. PCF prolongs hospital stay, nasogastric feeding, delays adjuvant therapy, and could involve additional surgery for controlling vessel blow-outs or reconstructing the pharynx [3]. With technological evolution, newer solutions emerge that need to be explored to seek alternative methods. The focus of pharyngocutaneous fistula studies have been in the salvage settings; it is very well established that radiation, anemia, and hypoalbuminemia have a role in development of PCF.

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Various factors affecting PCF such as suture material and method of pharyngeal closure have always been suspected but never shown to be significant. High-level evidence is lacking that determines the PCF rates in the primary laryngectomy. Here we intend to investigate the existing data to assess the risk factors predisposing to pharyngocutaneous fistula in patient undergoing primary total laryngectomy for laryngeal cancer.

Methodology

Search Strategy

Based on the AMSTAR 2 guidelines, at least two databases must be included in the search strategy to get adequate literature coverage [4]. We have included PubMed, EMBASE, and Cochrane databases to get a comprehensive coverage of published literature [5]. The published literature in English between 1970 and 2020 was considered.

Search Syntax

"Laryngeal cancer," "Hypopharyngeal cancer," "Total laryngectomy," "Primary laryngectomy," "Laryngectomy," "Pharyngocutaneous fistula," "Salivary fistula," "Salivary leak," "Pharyngeal leak," "Complications," "Outcomes." Boolean operators (NOT, AND, OR) were used in succession to obtain the results. The data was last retrieved on 10 April 2021.

Data Screening and Selection

The retrieved articles were initially screened independently by two investigators KNR and AS, based to type of article, title, and abstract. The eligible articles were pooled; a thorough full-text analysis and references in the relevant articles were further assessed by hand-searching (Fig. 1). The articles were selected by K. N. R., A. A., and A. S.; any disagreement on inclusion of articles was resolved by the senior authors R. D. A. and N. M. N.

Inclusion Criteria

1. Primary laryngectomy/laryngopharyngectomy for laryngeal and hypopharyngeal cancer
2. Laryngeal or hypopharyngeal cancers with total laryngectomy/laryngopharyngectomy (with or without neck dissection) as a primary modality of therapy
3. Original articles published in peer-reviewed journals.
4. Study must report at least one risk factor for pharyngocutaneous fistula.

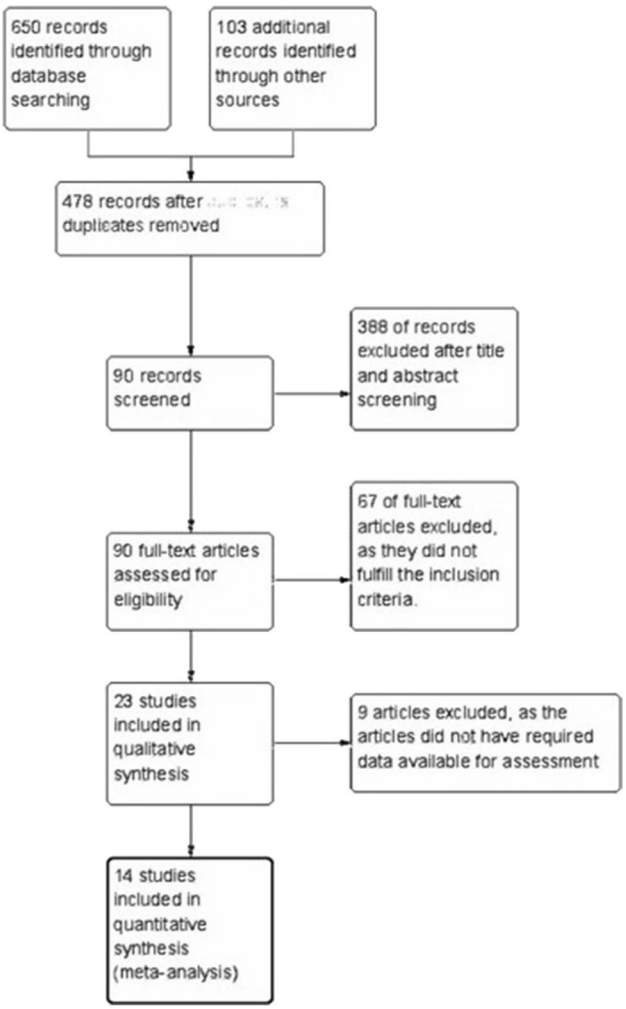

Fig. 1 Study flow diagram

Exclusion Criteria

1. Non-human studies
2. Laryngectomy/laryngopharyngectomy for non-oncological reason
3. Neoadjuvant chemotherapy/radiation therapy prior to surgery
4. Any previous oncological treatment
5. Recurrent or second primary tumors
6. Not reported – reoperative outcomes
7. Review articles, meeting abstracts, case reports, editorial letters, and other forms of publication
8. Incomplete data or insufficient information
9. Overlapping study populations, shared dataset

Data Extraction

All included articles were independently hand screened by two authors K. N. R. and A. S. The following study characteristics were recorded: first author, year of publication, country of origin, sample size (treatment naïve primary total laryngectomy for malignancy), type of study, pharyngocutaneous fistula rate (among primary laryngectomy), age, sex, comorbidities, smoking, alcohol consumption, subsite, T staging, N staging, pre-operative hemoglobin, pre-operative albumin, type of pharyngeal closure (vertical/T type and horizontal closure), stapler use, suture material use, tracheoesophageal prosthesis insertion, mucosal margin, and previous tracheostomy data were searched and documented (Table 1).

Quality Assessment

Level of Evidence

The level of evidence of the eligible studies was performed independently by two authors, as per the Oxford Centre for Evidence- Based Medicine (OCEBM) criteria.

Methodology Quality

Methodological quality was assessed by two authors, the Newcastle–Ottawa Scale was used for quality assessment of the included studies. The score ranged from 0 to 9. The articles with score > 5 was selected for meta-analysis.

Risk of Bias Assessment

Risk of bias assessment tool for non-randomized trial tool from AMSTAR guidelines was used to determine the bias [4]. The following domains were assessed—selection bias, confounding variables, intervention measurement, detection bias, attrition, reporting, and other bias. The studies were graded as low risk, unclear risk, and high risk using QUADAS-2 tool on RevMan v.5.4 (Cochrane collaboration, Copenhagen, Denmark) (Figs. 2 and 3).

Statistical Analysis

Cochrane's Q test and Higgin's I^2-heterogeneity of the included studies by using OpenMeta and STATA software. A P-value for heterogeneity (Ph) > 0.1 and $I^2 < 50\%$ indicated nonsignificant heterogeneity, and therefore, the fixed-effects model (Mantel–Haenszel method) was applied. Otherwise, the random effects model (DerSimonian Laird method) was employed. Odds ratio was calculated for each risk factor; a P-value < 0.05 was considered as statistically significant.

Reporting and Registration

The meta-analysis was registered in International prospective register of systematic reviews (PROSPERO), registration no CRD42021248382. This work has been reported in concordance with the PRISMA [6] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and

Table 1 Characteristics of included studies

Sl No	Author	Year of publication	Country	Sample size	Type of study	PCF	%	Level of evidence	Newcastle–Ottawa Scale
1	Thompson	2020	UK	114	Retrospective	7	6.14	3b	6
2	Nitassi	2016	Morocco	136	Retrospective	37	27.21	3b	6
3	Aydin	2014	Turkey	47	Prospective	14	29.79	3b	7
4	Stankovic	2012	Serbia	316	Retrospective	37	11.71	3b	5
5	Calli	2011	Turkey	182	Prospective	27	14.84	3b	5
6	Tsou	2010	China	112	Retrospective	24	21.43	3b	7
7	Goncalves	2009	Brazil	60	Prospective	13	21.67	3b	5
8	Akduman	2008	Turkey	17	Retrospective	6	35.29	3b	6
9	Wakisaka	2008	Japan	40	Retrospective	7	17.50	3b	5
10	Galli	2005	Italy	190	Retrospective	25	13.16	3b	6
11	Markou	2004	Greece	291	Retrospective	36	12.37	3b	7
12	Cavalot	2000	Italy	265	Retrospective	22	8.30	3b	6
13	Herranz	2000	Spain	471	Retrospective	99	21.02	3b	5
14	Papazoglou	1994	Greece	205	Retrospective	10	4.88	3b	5
	Total			2446		364	14.88		

PCF, pharyngocutaneous fistula

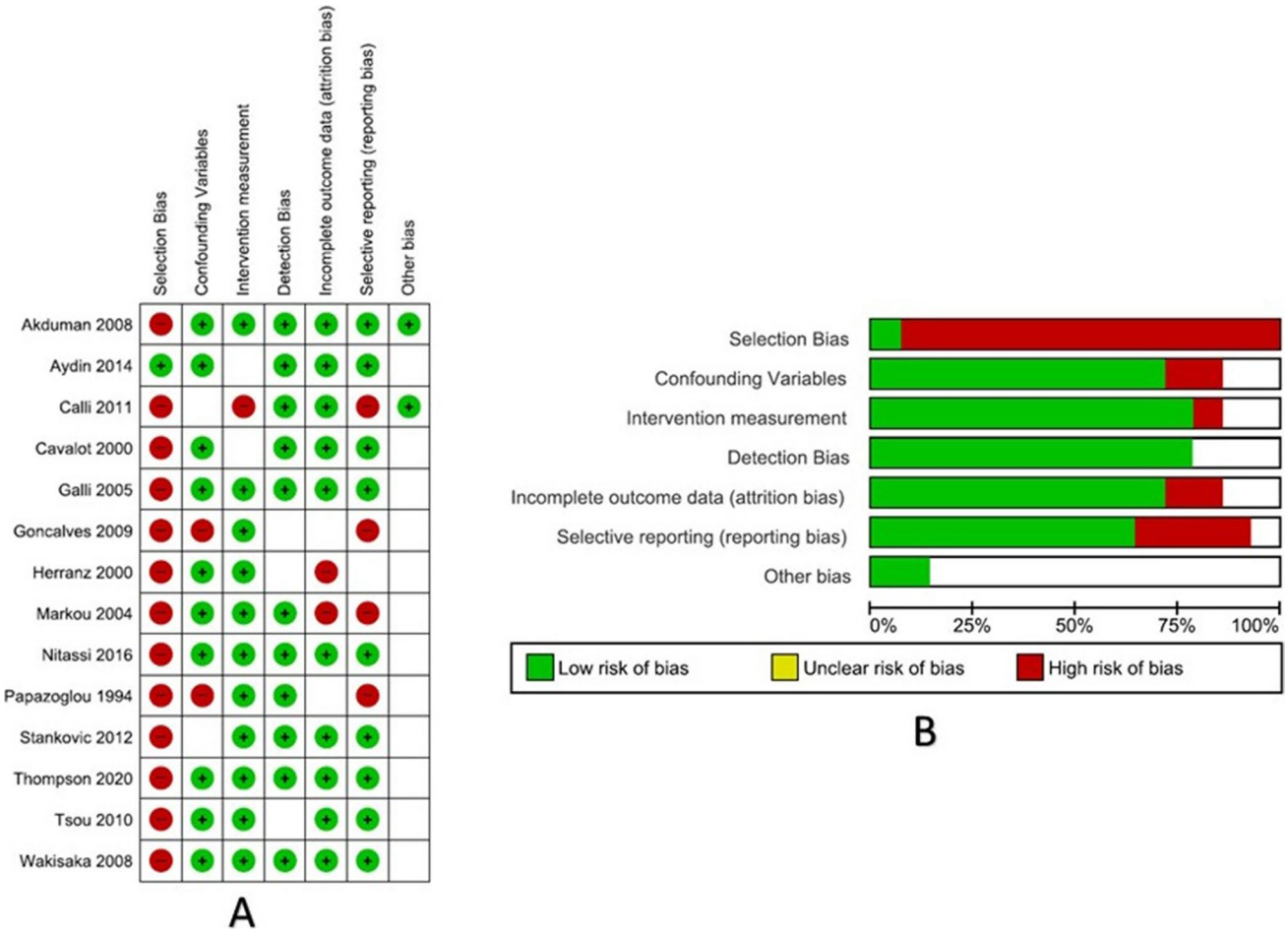

Fig. 2 **A** Risk of bias summary; **B** risk of bias graph

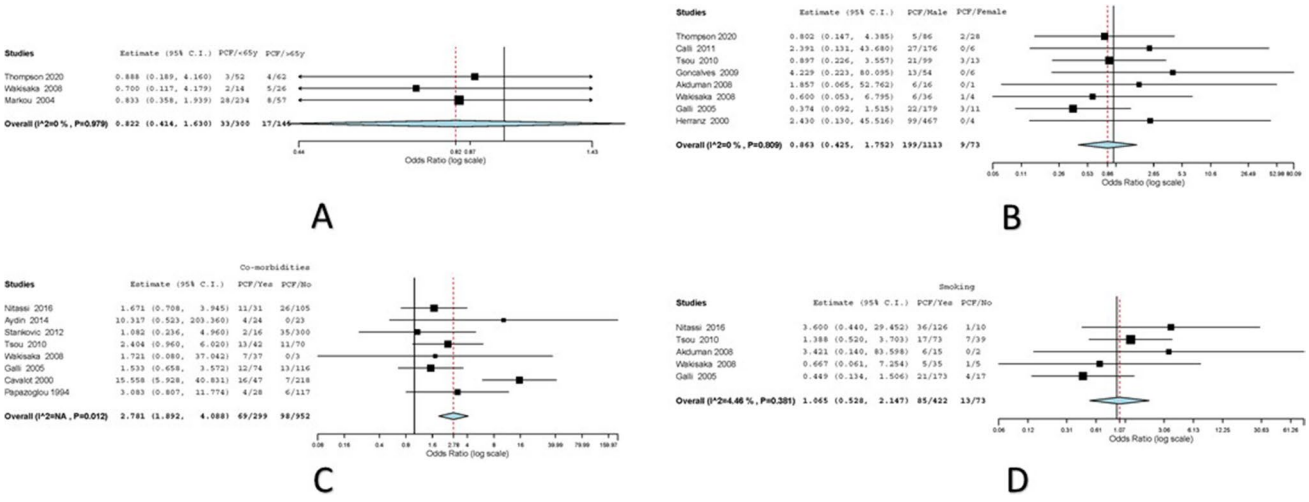

Fig. 3 **A** Forest plot for age as risk factor for PCF; **B** forest plot for gender as risk factor for PCF; **C** forest plot for comorbidities as risk factor for PCF; **D** forest plot for smoking as risk factor for PCF

AMSTAR (Assessing the methodological quality of systematic reviews) guidelines.

Results

Literature Retrieval and Data Extraction

The initial literature search using the predefined search syntax identified a total of 753 papers. Of these, 478 remained after deleting 275 duplicates. Upon title and abstract screening, 388 articles were removed due to nonconformity with our study. After full-text analysis of the remaining 90 articles, 67 papers were rejected due to lack of necessary information needed for analysis, not meeting the criteria for inclusion, or coinciding with exclusion criteria. Finally, 14 studies were considered eligible and chosen for meta-analysis.

Quality of Included Studies

The main characteristics of the included studies are summarized in Table 1. Overall, the meta-analysis included a total of 2446 patients in 14 included studies. Eligible studies were either a prospective (3) or retrospective (11) cohort study design; none of the studies was randomized controlled trial. The studies were level 3b evidence as per the OCEBM levels of evidence guidelines. The Newcastle–Ottawa score ranged from 5 to 7 (Table 1). Based on the RoBANS risk of Bias assessment, the included studies had highest risk of selection bias with least risk of intervention or detection bias (Fig. 3).

Overall Rate of PCF

Among the 2446 patients undergoing primary total laryngectomy, 346 patients had pharyngocutaneous fistula (14.88%). We systematically evaluated 16 risk factors to identify the factors significantly associated with PCF. Table 2 shows the main results of the meta-analysis.

Age

Three studies had reported the effects of age on development of PCF in 445 laryngectomies [7–9]. Variations were attributed to heterogeneity in the included studies ($I^2 = 0\%$, Cochran $Q = 0.041$, Het. P value $= 0.979$). In age < 65 years, numbers of total laryngectomy (TL) performed were 300; 33/300 (11%) developed PCF. Among patients who were > 65 years, 145 TLs were performed with 17/145 (11.72%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 0.822 (0.414–1.630) with $P = 0.575$ on random effects model (Fig. 3).

Sex

Eight studies had reported the effect of gender on PCF development among 1186 patients [7, 8, 10–15]. Variations were attributed to heterogeneity in the included studies ($I^2 = 0\%$, Cochran $Q = 3.74$, Het. P value $= 0.809$). One thousand one hundred thirteen males had undergone TL; 119/1113 (17.88%) developed PCF. Only 73 female TL were reported among the pooled dataset; 9/73 (12.3%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 0.863 (0.425–1.752) with $P = 0.684$ on random effects model (Fig. 3).

Comorbidities

Many articles had described various comorbidities as a factor leading to PCF, diabetes, hypertension, and cardiac illness were most reported. Eight articles among the included studies reported on comorbidities as a factor among 1251 patients in developing post-operative PCF [8, 11, 14, 16–20]. Not many variations were attributed to heterogeneity in the included studies (Cochran $Q = 17.920$, Het. P value $= 0.012$). Two hundred ninety-nine patients had comorbidities; 69/299 (23.08%) developed PCF. Ninety-eight out of nine hundred fifty-two (10.29%) patients without comorbidities developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 2.781 (1.892–4.088) with $P \leq 0.001$ on fixed-effects model (Fig. 3).

Tobacco Smoking

Five studies had reported the effect of smoking on PCF development among 495 patients [8, 11, 13, 14, 16]. Variations were attributed to heterogeneity in the included studies ($I^2 = 4.45\%$, Cochran $Q = 4.18$, Het. P value $= 0.38$). Four hundred forty-two previous or active tobacco smokers had undergone TL; 85/422 (20.14%) developed PCF. Only 73 patients had no history of tobacco smoking in the pooled dataset; 13/73 (17.8%) developed PCF. The Overall (odds ratio) OR values with the corresponding 95% CI were 1.065 (0.528–2.147) with $P = 0.86$ on Random effects model (Fig. 3).

Alcohol Consumption

Five studies had reported the effect of smoking on PCF development among 495 patients [13,14,16,17,19. Variations were attributed to heterogeneity in the included studies ($I^2 = 0$, Cochran $Q = 2.44$, Het. P value $= 0.654$). Two hundred seventy-five previous or active tobacco smokers had undergone TL; 46/275 (16.73%) developed PCF. Two hundred twenty-seven patients had no history of alcohol consumption in the pooled dataset; 60/227 (17.8%) developed

Table 2 Summary of results from the meta-analysis

Risk factor		Number of studies reporting	Number of laryngectomies	Number of patients with PCF	PCF %	Cochran Q value	Odds ratio	Statistical test	*P* value
Age	< 65 years	3	300	33	11.00%	0.041	0.822 (0.414–1.630)	BREF	0.575
	> 65 years		145	17	11.72%				
Sex	Male	8	1113	199	17.88%	3.745	0.863 (0.425–1.752)	BREF	0.684
	Female		73	9	12.33%				
Comorbidities	Yes	8	299	69	23.08%	17.92	2.781 (1.892–4.088)	BFEM	< 0.001
	No		952	98	10.29%				
Smoking	Yes	5	422	85	20.14%	4.187	1.065 (0.528–2.147)	BREF	0.86
	No		73	13	17.80%				
Alcohol	Yes	5	275	46	16.73%	2.447	0.765 (0.471–1.243)	BREF	0.279
	No		227	60	26.43%				
Site	Larynx	3	569	76	13.36%	0.266	4.485 (3.003–6.699)	BREF	< 0.001
	Hypopharynx		166	67	40.36%				
T stage	T1 and T2	8	131	8	6.11%	3.62	0.769 (0.370–1.598)	BREF	0.481
	T3 and T4		1054	140	13.28%				
N stage	N0	3	70	13	18.57%	0.044	0.794 (0.345–1.828)	BREF	0.588
	N +		333	45	13.51%				
Pre-operative hemoglobin	< 12	4	174	40	22.99%	2.809	3.590 (2.130–6.050)	BREF	< 0.001
	> 12		455	48	10.55%				
Pre-operative albumin	< 4	3	81	32	39.51%	10.999	2.833 (1.596–5.031)	BFEM	< 0.001
	> 4		207	36	17.39%				
Type of closure	Vertical/T type	2	504	112	22.22%	3.548	0.762 (0.412–1.408)	BFEM	0.385
	Horizontal		55	16	29.09%				
Stapler use	Yes	2	91	5	5.49%	0.257	0.172 (0.064–0.460)	BREF	< 0.001
	No		151	35	23.18%				
Suture material	Vicryl	3	600	105	17.50%	3.08	0.781 (0.428–1.425)	BREF	0.42
	Others		326	39	11.96%				
TEP insertion	Yes	3	322	46	14.29%	0.694	0.880 (0.594–1.305)	BREF	0.526
	No		554	96	17.33%				
Mucosal margin	Positive	1	22	8	36.36%	NA	4.92 (1.90–12.75)	BFEM	0.001
	Negative		269	28	10.41%				
Pre-operative tracheostomy	Yes	6	163	33	20.25%	11.757	0.714 (0.456–1.118)	BFEM	0.141
	No		832	158	18.99%				

PCF, Pharyngocutaneous fistula; *BREF*, binary random effects model; *BFEM*, binary fixed-effects model; *TEP*, tracheo-esophageal prosthesis; *NA*, not applicable; red colored, statistically significant

PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 0.765 (0.471–1.147) with $P = 0.86$ on random effects model (Fig. 4).

Site

Three studies had reported the effect of site of tumor on PCF development among 735 patients [7, 15, 16]. Variations were attributed to heterogeneity in the included studies ($I^2 = 0$, Cochran $Q = 0.266$, Het. P value = 0.876). Five hundred sixty-nine patients with laryngeal involvement underwent TL; 76/569 (13.36%) developed PCF. One hundred sixty-six patients with hypopharyngeal involvement had undergone TL in the pooled dataset; 67/166 (40.36%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 4.485 (3.003–6.699) with $P \leq 0.001$ on random effects model (Fig. 4).

T Stage

Eight studies had reported the effect of the tumor stage on PCF development among 1185 patients [7–9, 11, 12,

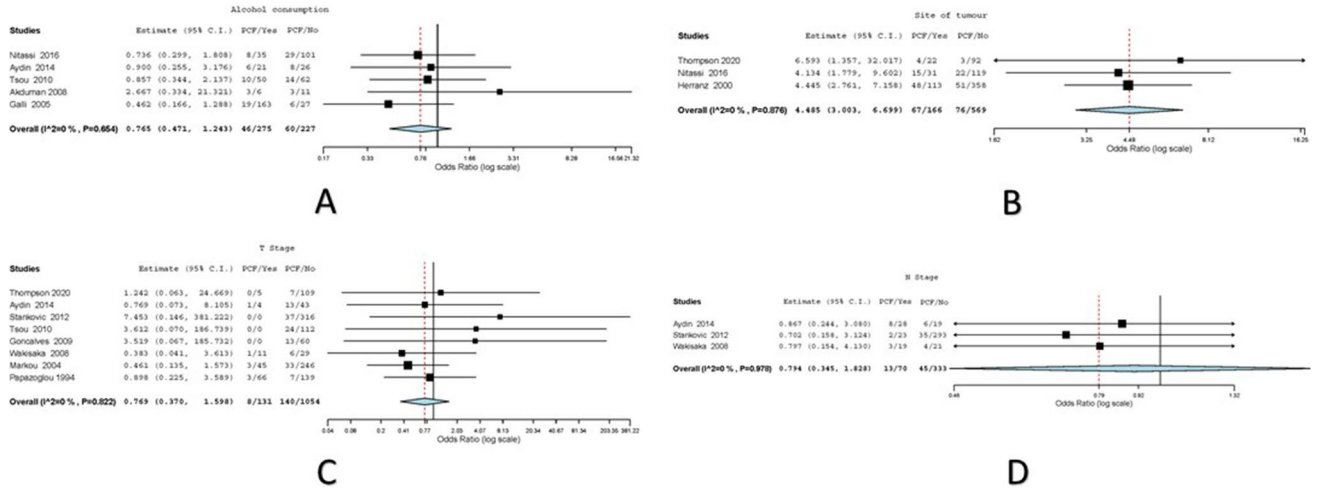

Fig. 4 **A** Forest plot for alcohol as risk factor for PCF; **B** forest plot for site as risk factor for PCF; **C** forest plot for the T stage as risk factor for PCF; **D** forest plot for the N stage as risk factor for PCF

17, 18, 20]. Variations were attributed to heterogeneity in the included studies ($I^2 = 0$, Cochran $Q = 3.62$, Het. P value = 0.822). One hundred thirty-one patients with T1 and T2 tumor had undergone TL; 8/131 (6.11%) developed PCF. One thousand fifty-four patients with T3 and T4 tumor had undergone TL in the pooled dataset; 140/1054 (13.28%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 0.769 (0.37–1.598) with $P = 0.481$ on random effects model (Fig. 4).

N Stage

Three studies had reported the effect of nodal involvement on PCF development among 403 patients [8, 17, 18]. Variations were attributed to heterogeneity in the included studies ($I^2 = 0$, Cochran $Q = 0.044$, Het. P value = 0.978). Seventy patients with N0 nodal involvement had undergone TL; 13/70 (18.57%) developed PCF. Three hundred thirty-three patients with N + nodal involvement had undergone TL in the pooled dataset; 45/333 (13.51%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 0.794 (0.345–1.828) with $P = 0.588$ on random effects model (Fig. 4).

Pre-operative Hemoglobin

Four studies had reported the effect of pre-operative hemoglobin on PCF development among 629 patients [7, 11, 16, 19]. Variations were attributed to heterogeneity in the included studies ($I^2 = 0$, Cochran $Q = 2.809$, Het. P value = 0.422). One hundred seventy-four patients with hemoglobin < 12 had undergone TL; 40/174 (22.99%) developed PCF. Four hundred fifty-five patients with hemoglobin > 12 had undergone TL in the pooled dataset; 48/455 (10.55%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 3.590 (2.130–6.050) with $P \leq 0.001$ on random effects model (Fig. 5).

Pre-operative Albumin

Three studies had reported the effect of pre-operative albumin on PCF development among 288 patients [8, 11, 16]. Variations were attributed to heterogeneity in the included studies (Cochran $Q = 10.999$, Het. P value = 0.004). Eighty-one patients with albumin < 4 had undergone TL; 32/81 (39.51%) developed PCF. Two hundred seven patients with albumin > 4 had undergone TL in the pooled dataset, 36/207 (17.39%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 2.833 (1.596–5.031) with $P \leq 0.001$ on random effects model (Fig. 5).

Type of Closure

Only two studies had reported the effect of type of closure on PCF development among 559 patients [15, 16]. Variations were attributed to heterogeneity in the included studies (Cochran $Q = 3.548$, Het. P value = 0.06). Five hundred four patients had undergone TL with vertical/T type closure; 112/504 (22.22%) developed PCF. Fifty-five patients had undergone TL with horizontal closure; 16/55 (29.09%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 0.762 (0.412–1.408) with $P = 0.385$ on random effects model (Fig. 5).

Stapler Use

Two studies had reported the effect of stapler use on PCF development among 242 patients [10, 12]. Variations were

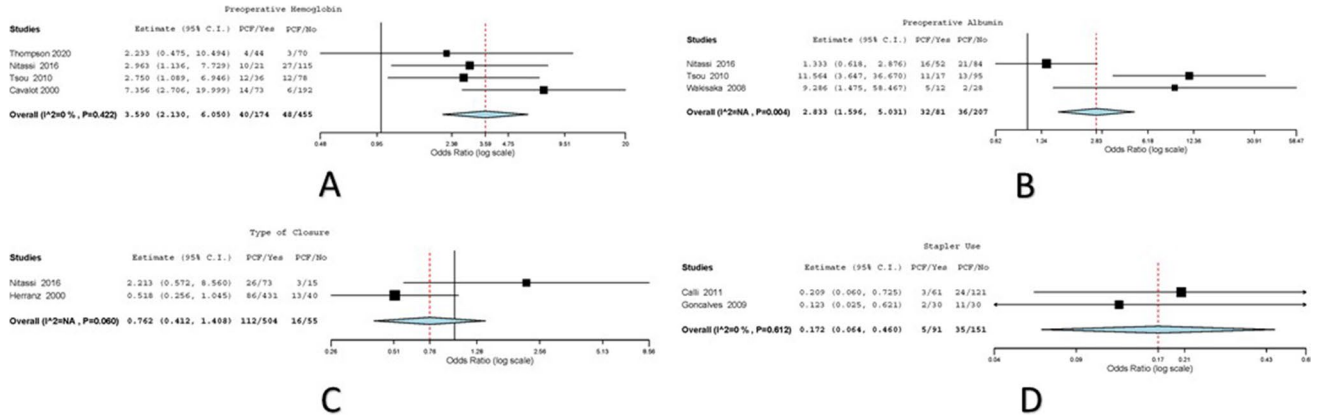

Fig. 5 **A** Forest plot for pre-operative hemoglobin as risk factor for PCF; **B** forest plot for pre-operative albumin as risk factor for PCF; **C** forest plot for type of closure as risk factor for PCF; **D** forest plot for stapler use as risk factor for PCF

attributed to heterogeneity in the included studies ($I^2 = 0$, Cochran $Q = 0.257$, Het. P value $= 0.612$). Ninety-one patients had undergone TL with use of staplers; 5/91 (5.49%) developed PCF. One hundred fifty-one patients had undergone TL without use of staplers; 35/151 (23.18%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 0.172 (0.064–0.46) with $P \leq 0.001$ on random effects model (Fig. 5).

Suture Material

Three studies had reported the effect of different suture materials on PCF development among 926 patients [14, 15, 19]. Variations were attributed to heterogeneity in the included studies ($I^2 = 35.256$, Cochran $Q = 3.089$, Het. P value $= 0.213$). Six hundred patients had undergone TL with use of vicryl; 105/600 (17.5%) developed PCF. Three hundred twenty-six patients had undergone TL with use of other suture materials; 39/326 (11.96%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 0.781 (0.428–1.425) with $P = 0.42$ on random effects model (Fig. 6).

TEP Insertion

Three studies had reported the effect of TEP insertion on PCF development among 876 patients [7, 9, 15]. Variations were attributed to heterogeneity in the included studies ($I^2 = 0$, Cochran $Q = 0.694$, Het. P value $= 0.707$). Three hundred twenty-two patients had undergone TL with TEP insertion; 46/322 (14.29%) developed PCF. Five hundred fifty-four patients had undergone TL without insertion of TEP; 96/554 (17.33%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 0.88 (0.594–1.305) with $P = 0.526$ on random effects model (Fig. 6).

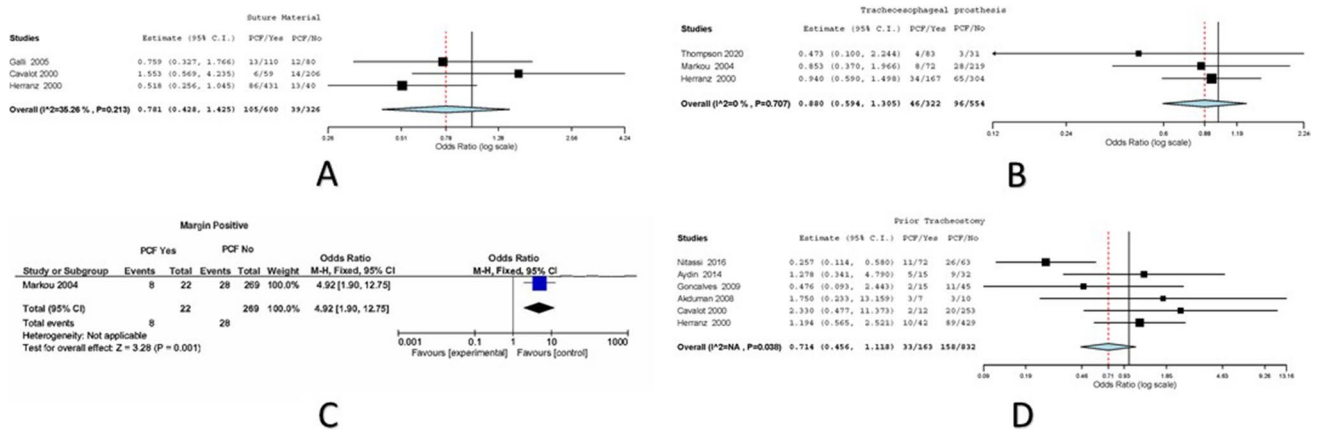

Fig. 6 **A** Forest plot for suture material as risk factor for PCF; **B** forest plot for TEP insertion as risk factor for PCF; **C** forest plot for mucosal margin as risk factor for PCF; **D** forest plot for pre-operative tracheostomy as risk factor for PCF

Mucosal Margin

One study reported the effect of mucosal margins on PCF development among 292 patients [9]. Variations were attributed to heterogeneity in the included studies. Twenty-two patients had undergone TL with positive mucosal margins; 8/22 (36.36%) developed PCF. Two hundred sixty-nine patients had undergone TL without use of staplers; 28/269 (10.41%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 4.92 (1.9–12.75) with $P \leq 0.001$ on random effects model (Fig. 6).

Pre-operative Tracheostomy

Six studies had reported the effect of pre-operative tracheostomy on PCF development among 995 patients [12, 13, 15–17, 19]. Variations were attributed to heterogeneity in the included studies. One hundred sixty-three patients had undergone TL with pre-operative tracheostomy; 33/163 (20.25%) developed PCF. Eight hundred thirty-two patients had undergone TL without pre-operative tracheostomy; 158/832 (18.99%) developed PCF. The overall (odds ratio) OR values with the corresponding 95% CI were 0.714 (0.456–1.118) with $P = 0.141$ on random effects model (Fig. 6).

Discussion

In last two decades, the laryngeal cancer treatment had a paradigm shift from the surgical treatment to non-surgical therapy based on some well-performed trials [21–24]. Functional organ preservation may not be feasible in certain intermediate and advanced cases; hence, a primary total laryngectomy is still an initial treatment in such cases, especially in patients who do not want or are physically unable to undergo the ordeal of chemoradiation and follow-up, which may benefit from TL as a primary treatment option. Alternative treatment options, such as combined therapy with concurrent chemoradiotherapy and salvage surgery (including its morbidity), could be too costly for in certain patient subset. Total laryngectomy is commonly used primary treatment in many developing nations including India and Brazil, mainly due to cost concerns [25, 26]. There has been multiple level I and II evidence generated in the past decade pertaining to the risk factors leading to the development of pharyngocutaneous fistula following salvage laryngectomy [27–32], but none of them has addressed it for primary total laryngectomy alone.

In our study, we did not find the age to be the risk factor for the development of PCF in patients undergoing primary TL. A recent meta-analysis by Wang and colleagues, which included patients undergoing salvage and primary TL, showed that the age of patient to be a significant risk factor leading to development of PCF [32]. Similarly, there was no statistically significant difference in the PCF rates among males and females.

Multiple studies have suggested that comorbidities such as diabetes mellitus, pulmonary disorders, cardiopathy, and hypothyroidism may contribute to the occurrence of PCF. Unfortunately, pinpointing the exact comorbidity leading to development of PCF is difficult to assess due to heterogeneity and lack of consensus in data collection and reporting. In our meta-analysis, we found that having an associated comorbidity significantly impacted towards the development of PCF. An Italian paper in 2008 demonstrated that diabetes mellitus lead to increased risk of development of PCF [33]. Just having a comorbidity does not mean that the individual will develop a PCF; it is vital to understand that all comorbidities must be well controlled, and patient must be optimized before surgery to reduce the risk of PCF.

It is very difficult to ascertain the role of tobacco smoking and alcohol consumption on the development of PCF; the previous history of habits alone may not be sufficient to determine the causal relationship. We emphasize the clinicians to note the major variables pertaining to tobacco smoking and alcohol consumption; this may help to determine time-dose–response relationship. Based on the current available data, a tangible conclusion cannot be derived due to inadequacy of variables to demonstrate the effect in primary TL. Due to this discrepancy in data reporting, there is a controversy in discerning the role of habits on development of PCF, with studies showing both causal [32–34] and noncausal [35, 36] effects.

The subsite of the tumor plays a vital role in determining the extent of surgical resection. Involvement of the hypopharynx usually entails the removal of pharyngeal mucosa along with the Larynx. Primary closure of pharyngeal mucosa can be attempted if the width of the unstretched and non-devascularized pharyngeal mucosa is over 3.5 cm [37]; else, this may lead to neopharyngeal stenosis or neopharyngeal breakdown if augmentation pharyngoplasty is not performed [32, 37, 38]. The hypopharyngeal involvement leads to higher chances of PCF; this corroborates with our study. Further subsite stratification was not feasible due to non-uniformity in reporting.

Higher T stage of the disease leads to higher chances of PCF in combined salvage and primary laryngectomy dataset [32]; higher T stage was not seen as an independent risk factor for the development of PCF in patients undergoing primary TL. Further individual subset analysis of each T stage is necessary especially between T3 and T4a and by stage matching it to the latest AJCC staging system. The N stage of the disease has not been shown to be risk factor to the development of PCF in both salvage and in primary TL [27, 29, 31, 32].

The nutritional status of the patient is determined by pre-operative hemoglobin and albumin levels as surrogate markers [39]. This directly affects the ability of the body to handle surgical stress and wound healing. Our results are in line with the meta-analysis conducted by the Brazilian group [27]. Ensuring adequate nutritional status of the patient is of utmost essential to prevent the development of PCF.

The effect of type of pharyngeal closure has been hypothesized to be a factor in PCF development but has never been proven, mainly due to overlapping surgical techniques, non-standardized nomenclature, and reporting. Only two studies were included in his analysis based on the inclusion and exclusion criteria; in our study, we did not find any statistically significant difference PCF rates among different types of pharyngeal closure. The trifurcation in the T-shaped closure could theoretically increase the risk of fistula development, according to some studies [16, 40]. On the other hand, other studies have found that vertical closure increases the risk of a fistula [41, 42]. In some defect shapes, the T-shaped closure is thought to cause less tension than the vertical closure. However, horizontal closure may not be appropriate for vertically extended pharyngeal defects.

There has been a recent increase in the trend to use staplers for the creation of neopharynx. Only two studies were included in our analysis; both the studies showed a statistically significant difference in the development of PCF [10, 12]. This result is compounded by a recent meta-analysis from Taiwan, which shows a reduction of operative time and reduced complications following the use of staplers [43]. We must highlight that the use of staplers for creating neopharynx requires considerable expertise and may lead to non-satisfactory results if the staplers are not applied in a designated manner. There is a considerable selection, and reporting bias found among the included studies as seen in surgical technique articles [44]. The result of PCF reduction with stapler use must be further strengthened with well-controlled randomized studies.

Different suture materials like catgut, silk, polydioxanone, polyglycolic acid (monofilament and braided), and polypropylene have been used for pharyngeal closure [45–47]. The sutures are usually chosen based on the surgeon's comfort and experience with it. Also, the techniques of pharyngeal mucosal approximation by various techniques were simple continuous interlocking sutures [45], interrupted sutures with extraluminal or intraluminal knots, Connell [48], Lembert [49], and Gambee [50]. The literature lacks information of leak rates with these different suturing techniques and materials. In our analysis, suture materials did not have a bearing on the development of PCF. A well-controlled blinded study must be conducted among the surgeons of various expertise by keeping certain patient parameters constant to accurately determine the effect of suture materials on development of PCF.

Rehabilitation following total laryngectomy is crucial to restore the functionality. TEP is now a standard of care for speech rehabilitation due to its in speech intelligibility, better acquisition, and fluency. Patients do not require a second surgery for speech acquisition when primary TEP is inserted. Furthermore, after a laryngectomy, patients can begin speech therapy within 2 weeks. In our study, preforming a primary TEP following a primary TL showed no statistically increase in the PCF rates. In a systematic review by Neto and colleagues, inserting a primary TEP during the TL and total laryngopharyngectomy leads to increase in the peri-TEP leak, wound infection, and stomal stenosis [51]. This study has also included patients undergoing primary TL, salvage procedures, and augmentation pharyngoplasty. A primary TEP is now a standard of care if there is no contraindication.

The presence of positive infiltrated margins may explain the reason for PCF occurring more frequently, mainly due to poor healing process occurring locally at the surgical wound. The presence of tumor cells can alter or obstruct the healing process and wound closure. In addition, the surgeon's attempts to avoid positive margins by further and deeper pharyngeal mucosal excision into healthy tissue may result in insufficient tissue to perform the pharyngoplasty, resulting in tension wound closure which is predisposed to complications.

Our study did not find any difference in the PCF rates among the previously tracheostomized patents and non-tracheostomized patients undergoing primary TL. The tracheostoma is and exteriorized tracheal wound, which is almost always contaminated and colonized with respiratory flora. In a paper by Asher and colleagues, they hypothesized that the duration of tracheostomy has an effect on the post-operative complications including PCF formation, mainly due to migration of tracheostoma wound from clean contaminated to contaminated wound with the increase in duration. This data was not analyzed due to non-availability of the parameters among the included articles.

Our meta-analysis, however, has some limitations. In the few articles included, and the research was insufficient, in articles needing clarification, the missing data was sought from the respective corresponding authors. Some studies had fewer cases, and the negative results may not have been published. All of these factors could have contributed to the bias, as it cannot be completely ruled out. In the future, more high-quality studies will be needed to confirm these findings.

Conclusion

In conclusion, PCF after total laryngectomy is caused by a multitude of factors. The risk factors for PCF are currently debatable, and many studies are required to determine the most important risk factor. In this meta-analysis, we

were able to determine the risk factors for PCF in patients undergoing primary TL, which included comorbidities, hypopharyngeal involvement, pre-operative hemoglobin and albumin, stapler usage, and positive mucosal margin. In clinical practice, our study provides important evidence-based medical evidence for the prevention and reduction of the development of PCF for primary TL.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13193-022-01581-z.

Author Contribution All authors have contributed equally towards the development of the manuscript.

Data Availability Data is available with the corresponding author.

Declarations

Provenance and Peer review Not commissioned, externally peer-reviewed.

Conflict of Interest The authors declare no competing interests.

References

1. Bobdey S, Jain A, Balasubramanium G (2015) Epidemiological review of laryngeal cancer: an Indian perspective. Indian J Med Paediatr Oncol Off J Indian Soc Med Paediatr Oncol 36(3):154–160
2. Ahn S-H, Hong HJ, Kwon SY, Kwon KH, Roh J-L, Ryu J et al (2017) Guidelines for the surgical management of laryngeal cancer: Korean Society of Thyroid-Head and Neck Surgery. Clin Exp Otorhinolaryngol 10(1):1–43
3. Molteni G, Sacchetto A, Sacchetto L, Marchioni D (2020) Optimal management of post-laryngectomy pharyngocutaneous fistula . Open Access Surg 13:11–25
4. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J et al (2017) AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 358:j4008
5. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH (2017) Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. Syst Rev 6(1):245
6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg 88:105906
7. Thompson CSG, Asimakopoulos P, Evans A, Vernham G, Hay AJ, Nixon IJ (2020) Complications and predisposing factors from a decade of total laryngectomy. J Laryngol Otol 134(3):256–262
8. Wakisaka N, Murono S, Kondo S, Furukawa M, Yoshizaki T (2008) Post-operative pharyngocutaneous fistula after laryngectomy. Auris Nasus Larynx 35(2):203–208
9. Markou KD, Vlachtsis KC, Nikolaou AC, Petridis DG, Kouloulas AI, Daniilidis IC (2004) Incidence and predisposing factors of pharyngocutaneous fistula formation after total laryngectomy. Is there a relationship with tumor recurrence? Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg 261(2):61–7
10. Calli C, Pinar E, Oncel S (2011) Pharyngocutaneous fistula after total laryngectomy: less common with mechanical stapler closure. Ann Otol Rhinol Laryngol 120(5):339–344
11. Tsou Y-A, Hua C-H, Lin M-H, Tseng H-C, Tsai M-H, Shaha A (2010) Comparison of pharyngocutaneous fistula between patients followed by primary laryngopharyngectomy and salvage laryngopharyngectomy for advanced hypopharyngeal cancer. Head Neck 32(11):1494–1500
12. Gonçalves AJ, de Souza J a L, Menezes MB, Kavabata NK, Suehara AB, Lehn CN (2009) Pharyngocutaneous fistulae following total laryngectomy comparison between manual and mechanical sutures. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg 266(11):1793–8
13. Akduman D, Naiboğlu B, Uslu C, Oysu C, Tek A, Sürmeli M et al (2008) Pharyngocutaneous fistula after total laryngectomy: incidence, predisposing factors, and treatment. Kulak Burun Bogaz Ihtis Derg KBB J Ear Nose Throat 18(6):349–354
14. Galli J, Valenza V, Parrilla C, Galla S, Marchese MR, Castaldi P et al (2009) Pharyngocutaneous fistula onset after total laryngectomy: scintigraphic analysis. Acta Otorhinolaryngol Ital Organo Uff Della Soc Ital Otorinolaringol E Chir Cerv-facc 29(5):242–244
15. Herranz J, Sarandeses A, Fernández MF, Barro CV, Vidal JM, Gavilán J (2000) Complications after total laryngectomy in non-radiated laryngeal and hypopharyngeal carcinomas. Otolaryngol-Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg 122(6):892–898
16. Nitassi S, Belayachi J, Chihab M, Rkain I, Benayad J, Benbouzid MA et al (2016) Evaluation of post laryngectomy pharyngocutaneous fistula risk factors. Iran J Otorhinolaryngol 28(85):141–147
17. Aydin S, Taskin U, Orhan I, Altas B, Ege SS, Yucebas K et al (2014) The impact of pharyngeal repair time and suture frequency on the development of pharyngocutaneous fistula after total laryngectomy. J Craniofac Surg 25(3):775–779
18. Stanković M, Milisavljević D, Stojanov D, Zivić M, Zivaljević S, Stanković I et al (2012) Influential factors, complications and survival rate of primary and salvage total laryngectomy for advanced laryngeal cancer. Coll Antropol 36(Suppl 2):7–12
19. Cavalot AL, Gervasio CF, Nazionale G, Albera R, Bussi M, Staffieri A et al (2000) Pharyngocutaneous fistula as a complication of total laryngectomy: review of the literature and analysis of case records. Otolaryngol-Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg 123(5):587–592
20. Papazoglou G, Doundoulakis G, Terzakis G, Dokianakis G (1994) Pharyngocutaneous fistula after total laryngectomy: incidence, cause, and treatment. Ann Otol Rhinol Laryngol 103(10):801–805
21. Department of Veterans Affairs Laryngeal Cancer Study Group, Wolf GT, Fisher SG, Hong WK, Hillman R, Spaulding M et al (1991) Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 324(24):1685–90
22. Wolf GT, Forastiere A, Ang K, Brockstein B, Conley B, Goepfert H et al (1999) Workshop report: organ preservation strategies in advanced head and neck cancer–current status and future directions. Head Neck 21(8):689–693
23. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W et al (2003) Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 349(22):2091–2098
24. Pointreau Y, Garaud P, Chapet S, Sire C, Tuchais C, Tortochaux J et al (2009) Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 101(7):498–506
25. Silver CE, Beitler JJ, Shaha AR, Rinaldo A, Ferlito A (2009) Current trends in initial management of laryngeal cancer:

the declining use of open surgery. Eur Arch Otorhinolaryngol 266(9):1333–1352
26. Terrell JE, Fisher SG, Wolf GT, for the Veterans Affairs Laryngeal Cancer Study Group (1998) Long-term quality of life after treatment of laryngeal cancer. Arch Otolaryngol Neck Surg 124(9):964–71
27. Dedivitis RA, Aires FT, Cernea CR, Brandão LG (2015) Pharyngocutaneous fistula after total laryngectomy: systematic review of risk factors. Head Neck 37(11):1691–1697
28. Hasan Z, Dwivedi RC, Gunaratne DA, Virk SA, Palme CE, Riffat F (2017) Systematic review and meta-analysis of the complications of salvage total laryngectomy. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol 43(1):42–51
29. Liang J-W, Li Z-D, Li S-C, Fang F-Q, Zhao Y-J, Li Y-G (2015) Pharyngocutaneous fistula after total laryngectomy: a systematic review and meta-analysis of risk factors. Auris Nasus Larynx 42(5):353–359
30. Paleri V, Drinnan M, van den Brekel MWM, Hinni ML, Bradley PJ, Wolf GT et al (2014) Vascularized tissue to reduce fistula following salvage total laryngectomy: a systematic review. Laryngoscope 124(8):1848–1853
31. Sayles M, Grant DG (2014) Preventing pharyngo-cutaneous fistula in total laryngectomy: a systematic review and meta-analysis. Laryngoscope 124(5):1150–1163
32. Wang M, Xun Y, Wang K, Lu L, Yu A, Guan B et al (2020) Risk factors of pharyngocutaneous fistula after total laryngectomy: a systematic review and meta-analysis. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg 277(2):585–599
33. Boscolo-Rizzo P, De Cillis G, Marchiori C, Carpenè S, Da Mosto MC (2008) Multivariate analysis of risk factors for pharyngocutaneous fistula after total laryngectomy. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg 265(8):929–936
34. Aslıer NGY, Doğan E, Aslıer M, İkiz AÖ (2016) Pharyngocutaneous fistula after total laryngectomy: risk factors with emphasis on previous radiotherapy and heavy smoking. Turk Arch Otorhinolaryngol 54(3):91–98
35 Patel UA, Moore BA, Wax M, Rosenthal E, Sweeny L, Militsakh ON et al (2013) Impact of pharyngeal closure technique on fistula after salvage laryngectomy. JAMA Otolaryngol- Head Neck Surg 139(11):1156–62
36. Erdag MA, Arslanoglu S, Onal K, Songu M, Tuylu AO (2013) Pharyngocutaneous fistula following total laryngectomy: multivariate analysis of risk factors. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg 270(1):173–179
37. Hui Y, Wei WI, Yuen PW, Lam LK, Ho WK (1996) Primary closure of pharyngeal remnant after total laryngectomy and partial pharyngectomy: how much residual mucosa is sufficient? Laryngoscope 106(4):490–494
38. Chotipanich A (2021) Total laryngectomy: a review of surgical techniques. Cureus [Internet]. [cited 2021 Oct 13]. Available from: https://www.cureus.com/articles/69113-total-laryngectomy-a-review-of-surgical-techniques
39. Corona LP, de Oliveira Duarte YA, Lebrão ML (2018) Markers of nutritional status and mortality in older adults: the role of anemia and hypoalbuminemia. Geriatr Gerontol Int 18(1):177–182
40. Deniz M, Ciftci Z, Gultekin E (2015) Pharyngoesophageal suturing technique may decrease the incidence of pharyngocutaneous fistula following total laryngectomy. Surg Res Pract 2015:363640
41. Walton B, Vellucci J, Patel PB, Jennings K, McCammon S, Underbrink MP (2018) Post-Laryngectomy stricture and pharyngocutaneous fistula: review of techniques in primary pharyngeal reconstruction in laryngectomy. Clin Otolaryngol Off J ENT-UK Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg 43(1):109–116
42. van der Kamp MF, Rinkel RNPM, Eerenstein SEJ (2017) The influence of closure technique in total laryngectomy on the development of a pseudo-diverticulum and dysphagia. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg 274(4):1967–1973
43. Lee Y-C, Fang T-J, Kuo I-C, Tsai Y-T, Hsin L-J (2021) Stapler closure versus manual closure in total laryngectomy for laryngeal cancer: a systematic review and meta-analysis. Clin Otolaryngol Off J ENT-UK Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg 46(4):692–698
44. Paradis C (2008) Bias in surgical research. Ann Surg 248(2):180–188
45. Haksever M, Akduman D, Aslan S, Solmaz F, Ozmen S (2015) Modified continuous mucosal Connell suture for the pharyngeal closure after total laryngectomy: zipper suture. Clin Exp Otorhinolaryngol 8(3):281–288
46. Altissimi G, Frenguelli A (2007) Linear stapler closure of the pharynx during total laryngectomy: a 15-year experience (from closed technique to semi-closed technique). Acta Otorhinolaryngol Ital 27(3):118–122
47. Soylu L, Kıroğlu M, Aydoğan B, Çetik F, Kıroğlu F, Akçalı Ç et al (1998) Pharyngocutaneous fistula following laryngectomy. Head Neck J Sci Spec Head Neck 20(1):22–25
48. Huddleston HT, Dunnihoo DR (1998) Connell Suture. J Gynecol Surg 14(3):149–149
49. Hardy KJ (1990) A View of the development of intestinal suture. Part Ii. Principles and Techniques. Aust N Z J Surg 60(5):377–84
50 Hirata K, Konishi T, Ueda Y, Kurosaki S, Tomisaki I, Nasu K et al (2000) Healing in the intestinal anastomosis–comparison of the Albert-Lembert and Gambee methods. J UOEH 22(1):1–6
51. BarraunaNeto JC, Dedivitis RA, Aires FT, Pfann RZ, Matos LL, Cernea CR (2017) Comparison between primary and secondary tracheoesophageal puncture prosthesis: a systematic review. ORL 79(4):222–229