Am J Transl Res 2023;15(4):2281-2290
www.ajtr.org /ISSN:1943-8141/AJTR0148929

Review Article

Meta-analysis of risk factors associated with pharyngocutaneous fistulas following total laryngectomy

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Received January 4, 2023; Accepted February 12, 2023; Epub April 15, 2023; Published April 30, 2023

Abstract: Background: To investigate the risk factors for pharyngocutaneous fistulas following total laryngectomy. Methods: PubMed, Web of Science, CNKI, Medline and Wanfang database were utilized to conduct a systematic literature research. Further, sensitivity and publication bias were analyzed to comprehensively estimate the risk factors associated with pharyngocutaneous fistulas following total laryngectomy. Results: Of the 112 studies identified, 25 were included in this analysis. The results showed that age (OR = 0.21, 95% CI 0.11-0.39, P<0.00001), smoking (OR = 3, 95% CI 1.54-5.84, P<0.00001), T-stage (OR = 0.3, 95% CI 0.22-0.4, P<0.00001), previous radiotherapy (OR = 0.31, 95% CI 0.23-0.44, P<0.000001) and preoperative albumin (OR = 0.28, 95% CI 0.16-0.47, P<0.00001) were risk factors associated with pharyngocutaneous fistulas. Conclusions: This review is a comprehensive analysis of the risk factors associated with pharyngocutaneous fistulas following total laryngectomy. Age, smoking, T-stage, previous radiotherapy and preoperative albumin were found to be the risk factors.

Keywords: Pharyngocutaneous fistulas, total laryngectomy, risk factors, meta-analysis

Introduction

Laryngeal cancer is a common malignant tumor of otorhinolaryngology with an incidence of 7.9%-35% in malignant otorhinolaryngological tumors, ranking third after head and neck malignant tumors [1]. According to WHO statistics, the male-female ratio of laryngeal cancer patients in China is 10.5:1, and it is more common in men over 40 years old [2]. At present, patients with laryngeal cancer usually take multidisciplinary comprehensive treatments, which are surgical treatment supplemented with radiotherapy and chemotherapy [3, 4]. Complications after total laryngectomy are common in clinical practice and sometimes unavoidable, including incision bleeding or infection, pharyngeal fistula formation, tracheostomy stenosis, pneumonia, atelectasis, pharyngeal stenosis and so on [5-8].

Pharyngeal fistula, as one of the most common complications after total laryngectomy, is mainly manifested by the failure in normal healing of the pharyngeal anastomosis and the accumulation of saliva under the skin, giving bacteria a certain breeding condition [9]. Pharyngeal fistula usually occurs 6-15 days after the surgery [10]. In patients undergoing total laryngectomy, pharyngeal fistula can lead to abnormal mucous membrane in the operation area. Long term stimulation of saliva or food will impact on the healing of the anastomosis. If the fistula is located at the tracheostomy orifice, it will affect the healing of the fistula orifice [11]. Moreover, patients with pharyngeal fistula need to change their dressing after surgery for a long time, which requires close care from their families. This not only prolongs the hospital stay, but also creates pressure on the physical and mental health of patients and their familie members [12].

To reduce the incidence of pharyngeal fistula after total laryngectomy, a large number of studies were conducted to assess the risk factors

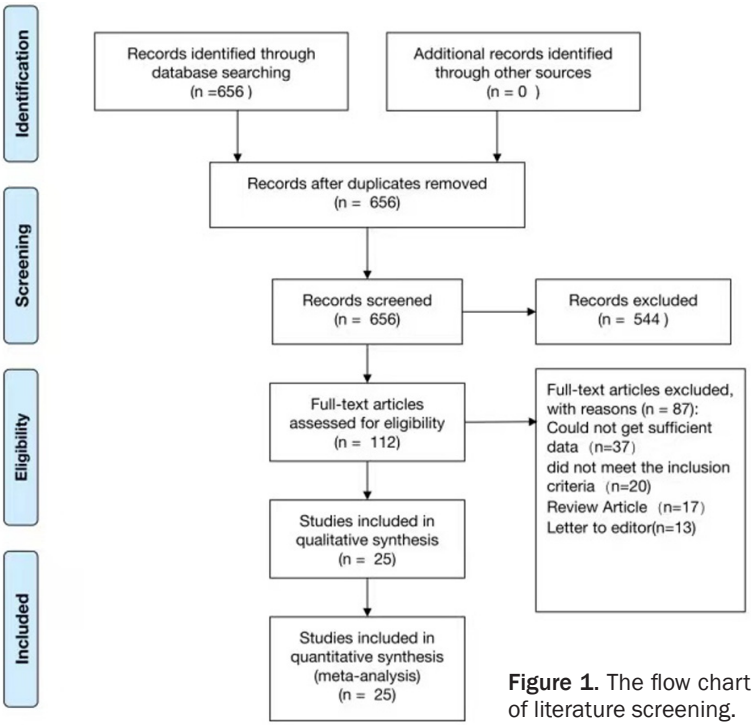

Figure 1. The flow chart of literature screening.

of pharyngeal fistula [15-39]. Although some risk factors have been reported, the number of samples in a single study is small and less persuasive, and the incidence of pharyngeal fistula differs largely in different reports. The recognition of some risk factors is still controversial, and more high-quality research work is needed to confirm these findings and to find other potential risk factors.

Currently, a number of single research had shown risk factors associated with pharyngocutaneous fistulas following total laryngectomy. However, those results were largely different and less persuasive. Thus, we conducted a meta-analysis to comprehensively analyze the risk factors associated with pharyngocutaneous fistulas following total laryngectomy.

Methods

Searching strategy

This study was performed according to the Cochrane Handbook for Systematic Reviews of Interventions [13]. This review abided by published guidelines according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement [14].

We searched the publication no later than September 2022 in the following electronic databases: Cochrane Library, PubMed, web of science, CNKI, VIP, Medline, ISI Web of Science, CBMdisc and Wanfang. No limit was set on language. The search keywords were ("Total laryngectomy" or "laryngeal neoplasms") and ("pharyngocutaneous fistulas" or "cutaneous fistula").

Inclusion and exclusion criteria

The inclusion criteria for the selected studies were as follows: a) Studies met the requirement of total laryngectomy for primary laryngeal cancer and hypopharyngeal cancer; b) Studies reported at least one risk factor; c) Retrospective study or prospective research.

The exclusion criteria were as follows: a) Animal research, b) Case reports; c) The outcome indicators cannot be extracted or calculated; d) The data were repeatedly published.

Data extraction and quality assessment

Two researchers (Zhenhe Huang and Yunxiang Cai) screened the studies respectively, in accordance with the inclusion and exclusion criteria. When there was a difference, a third researcher was consulted for final determination. The flow chart of literature screening is shown in **Figure 1**. The bias risk assessment tool in Cochrane Handbook for systematic review of interventions (version 5.1.0) was used to evaluate the quality of the included studies. The results of the quality assessment are shown in **Figure 2**.

Statistical analysis

The Review Manager Software (RevMan, version 5.2 from the Cochrane Collaboration) was used for meta analysis. The calculation rate and 95% confidence interval were used to calculate the combined effect amount, confidence

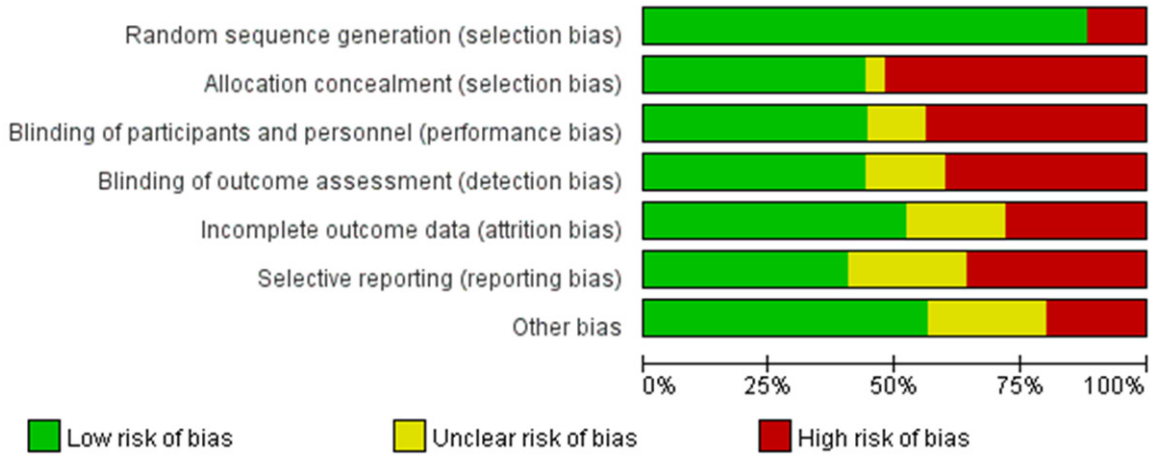

Figure 2. The risk of bias of included in the meta-analysis.

interval and heterogeneity test statistics (P). If $I^2 \leq 50\%$, fixed effect model was applied for quantitative assess, and $I^2 > 50\%$, random effect models used.

Ethical approval

Ethical approval was not necessary because our study is a meta-analysis, and which belongs to a form of secondary analysis.

Results

Flow chart of study selection

A total of 656 studies were identified in the initial literature search. A flow diagram of the study selection process is shown in **Figure 1**. After screening, 25 studies [15-39] were included in this meta-analysis.

Characteristics of included studies

The characteristics of included studies are summarized in **Table 1**. Among the 25 studies eligible for the meta-analysis, a total of 6396 subjects were enrolled. Among them, 3086 subjects suffered from pharyngocutaneous fistulas. Two studies were conducted in eastern countries. The duration of therapy ranged from 5 to 180 months. Randomization was performed according to a computer-generated random list or by means of a randomly generated number pattern in the majority of the trials [15-39]. In conclusion, the quality of these studies was moderate to high (**Figure 2**).

Pooled analysis

Nine studies [16, 19, 26, 28, 30, 32, 33, 38] provided data on smoking, including 1793 patients. The results showed that smoking status significantly affected the incidence of pharyngocutaneous fistulas. Smoking patients were more likely to develop pharyngocutaneous fistulas (OR = 3, 95% CI 1.54-5.84, P<0.00001) (**Figure 3**).

Thirteen studies [15, 18-21, 24, 26, 28, 29, 35-37] provided data on age and pharyngocutaneous fistulas rate. The pharyngocutaneous fistulas rate in patients over 60 years old was higher than that in those ≤60 years old (OR = 0.21, 95% CI 0.11-0.39, P<0.00001) (**Figure 4**).

All 25 studies [15-39] provided data on T-stage and pharyngocutaneous fistulas rate. The pharyngocutaneous fistulas rate was significantly different between the T1/T2 group and the T3/T4 group (OR = 0.3, 95% CI 0.22-0.4, P<0.00001) (**Figure 5**). Patients at a T-stage of T3/T4 were more likely to develop pharyngocutaneous fistulas.

Twenty-two studies [15-19, 22-30, 32-39] provided data on previous radiotherapy treatments and pharyngocutaneous fistulas rate. The pharyngocutaneous fistulas rate was higher in patients with previous radiotherapy than in those without (OR = 0.31, 95% CI 0.23-0.44, P<0.000001) (**Figure 6**).

Table 1. Characteristics of the 25 studies in the meta-analysis

Author	Country	Year	Size EG/CG	Age (EG vs. CG) Mean ± SD	Therapy (months)
Maleki 2021 [15]	Iran	2021	15/20	62.07±10.08/63.83±7.22	5
Aires FT 2018 [16]	Brazil	2018	70/71	52.4±11.3/54.98±9.78	72
Busoni 2015 [17]	Italy	2015	86/86	N/A	180
Dedivitis 2007 [18]	Brazil	2007	7/48	N/A	96
Lemaire 2021 [19]	France	2021	328/128	N/A	120
Zou 2021 [20]	China	2021	50/200	55.43±10.67/58.76±13.45	24
Yücel 2020 [21]	Turkey	2020	20/66	62.5±9.9/57.6±12	180
Sumarroca 2019 [22]	Spain	2019	50/50	60.8±7.8/62.7±8.9	180
Benson 2015 [23]	USA	2015	17/42	N/A	132
Akduman 2008 [24]	Turkey	2008	32/293	67.8±9.8 vs. 66.7±8.5	120
Furuta 2008 [25]	Japan	2008	14/86	63.8±11.5 vs. 63.8±11.3	96
Dirven 2009 [26]	Australia	2009	33/152	61.1±1.2 vs. 63.2±1.4	84
Goncalves 2009 [27]	Brazil	2009	13/60	52.7±8.3 vs. 52.8±8.5	60
Patel & Keni 2009 [28]	USA	2009	11/43	60.9±1.6 vs. 61.2±2.1	36
Tsou 2010 [29]	USA	2010	52/160	44.23±11.35/45.23±12.1	84
Calli 2011 [30]	Turkey	2011	27/182	44(21-68)/61(39-75)	43
White 2012 [31]	USA	2012	55/259	53.8±8/58.6±9.5	24
Basheeth 2013 [32]	Ireland	2013	19/74	49.52±12.27/51.87±11.41	72
Patel 2013 [33]	USA	2013	94/359	Unclear	42
Aydin 2014 [34]	Turkey	2014	14/47	72±13/62±16	36
Sayles 2014 [35]	UK	2014	50/171	Unclear	48
Timmermans 2014 [36]	Netherlands	2014	57/217	Unclear	48
Sifrer 2016 [37]	Slovenia	2016	48/158	36.2±9.5/45.3±9.3	36
Aslier 2016 [38]	Turkey	2016	37/183	48.72±1.57/44.58±1.02	60
Hone 2017 [39]	UK	2017	45/199	Unclear	72

Note: EG/CG: Experimental group/Control group.

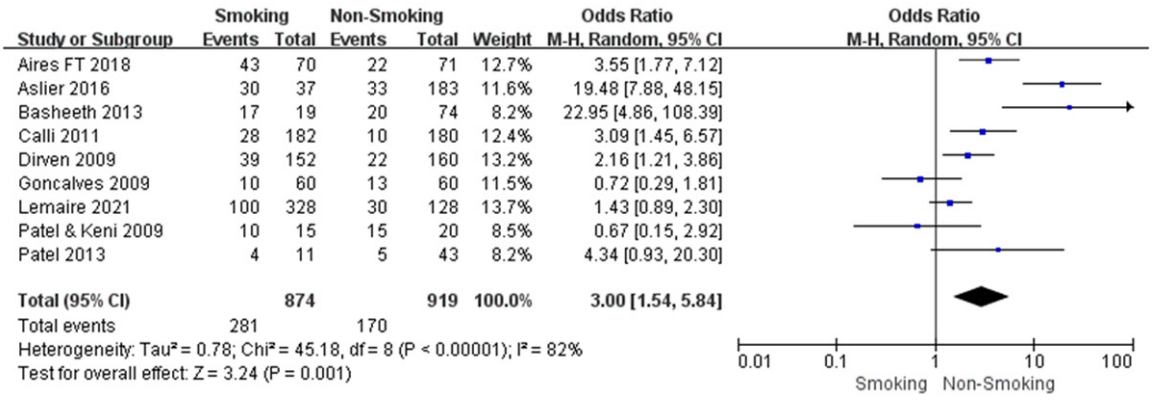

Figure 3. Forest plot for the meta-analysis of smoking and pharyngocutaneous fistulas rate.

Thirteen studies [15, 17-19, 23, 25-28, 30, 32, 33, 39] provided data on preoperative albumin and pharyngocutaneous fistulas rate. The pharyngocutaneous fistulas rate was higher in the low albumin level group than that in the normal albumin level group (OR = 0.28, 95% CI 0.16-0.47, P<0.000001) (**Figure 7**). Patients with low albumin level were more likely to develop pharyngocutaneous fistulas.

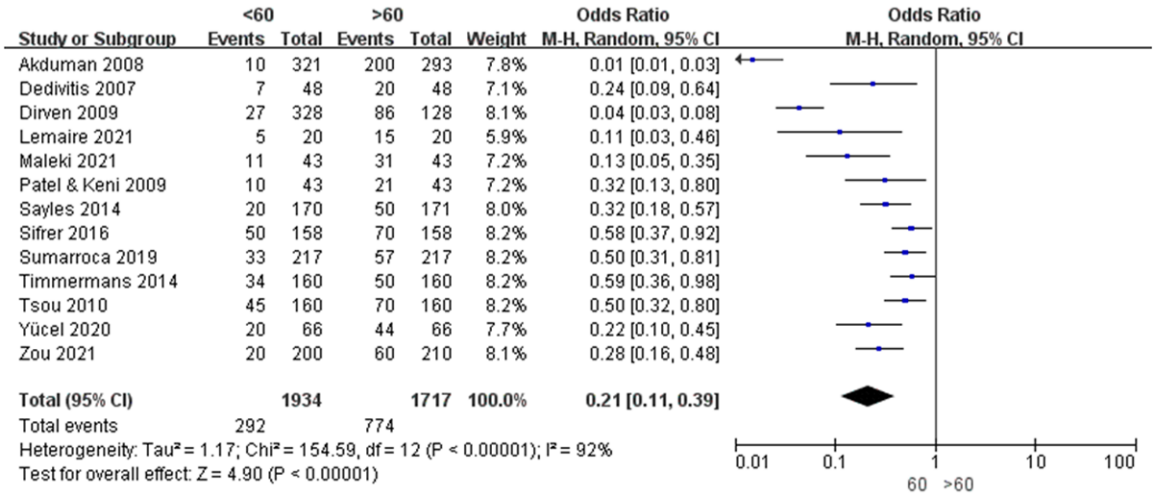

Figure 4. Forest plot for the meta-analysis of age and pharyngocutaneous fistulas rate.

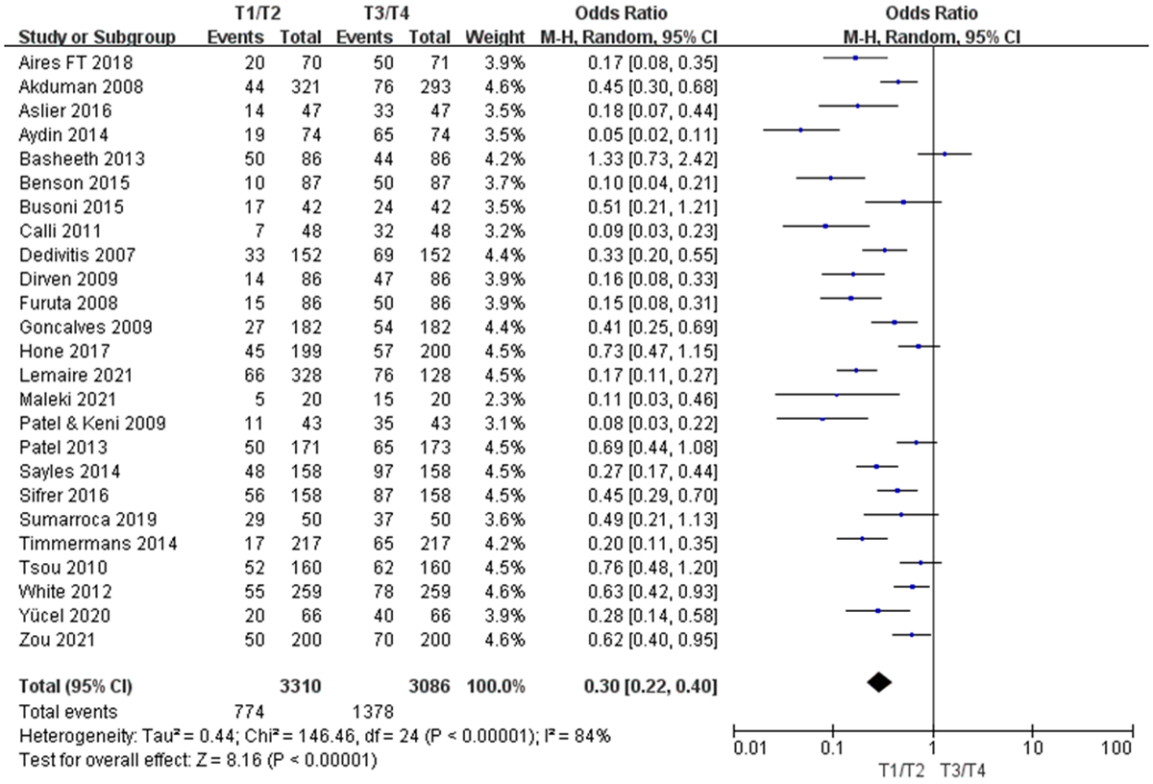

Figure 5. Forest plot for the meta-analysis of T-stage and pharyngocutaneous fistulas rate.

Sensitivity analysis and publication bias

Sensitivity analysis revealed that removal of any one study from the analysis did not subvert the results of the pooled analysis (SMD = 0.5, 95% CI = [0.29, 0.71, P<0.00001). Furthermore, we constructed funnel plots to evaluate publication bias. The funnel plots (**Figure 8**) showed no publication bias.

Discussion

In the clinical treatment of patients with laryngeal cancer, total laryngectomy is a common

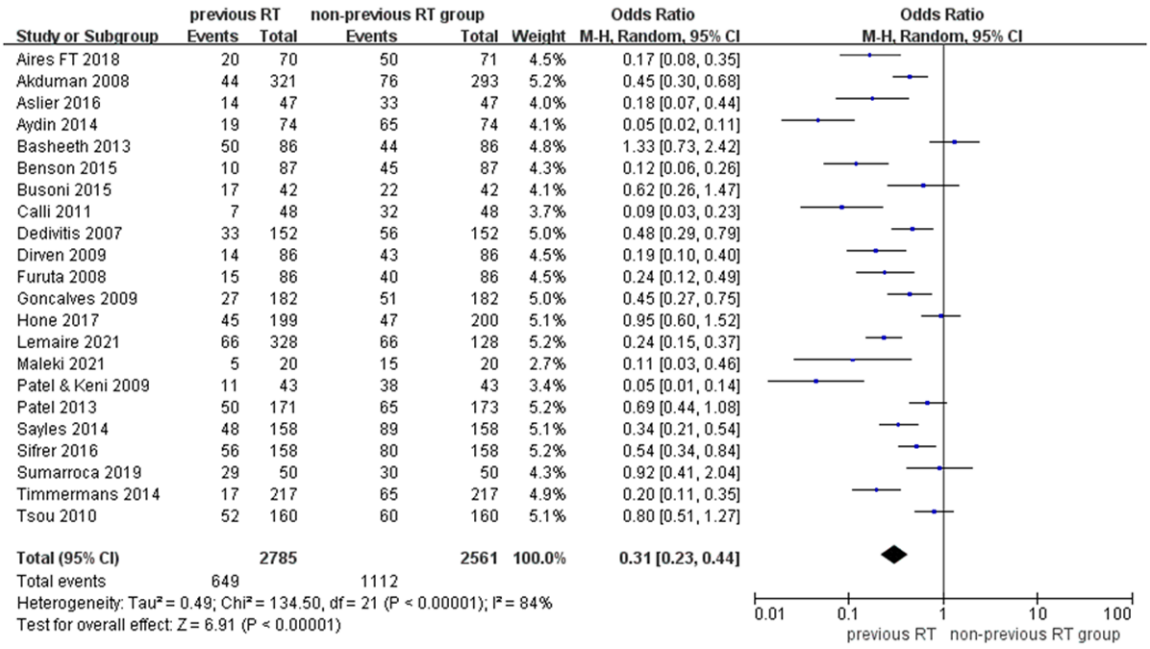

Figure 6. Forest plot for the meta-analysis of previous radiotherapy treatments and pharyngocutaneous fistulas rate.

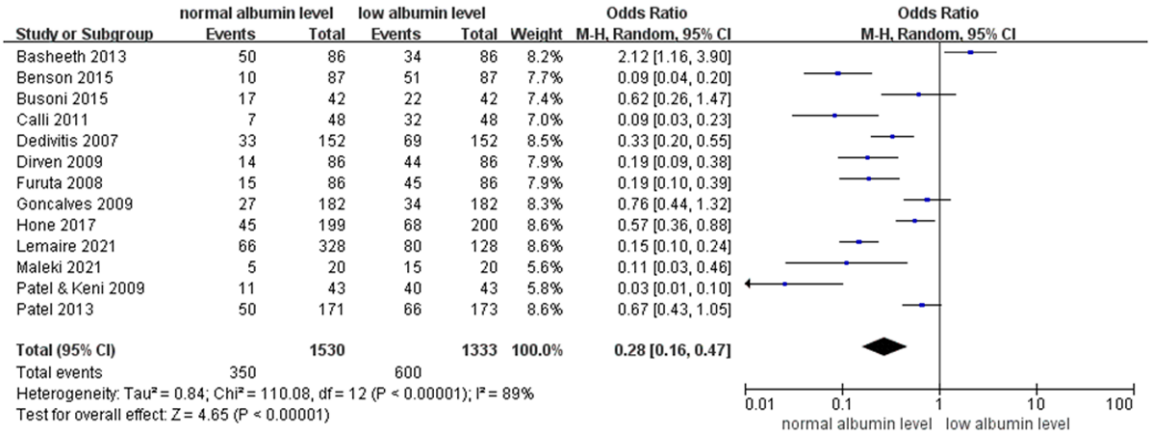

Figure 7. Forest plot for the meta-analysis of preoperative albumin and pharyngocutaneous fistulas rate.

method, and pharyngocutaneous fistula is one of the common postoperative complications. According to relevant statistics [40], the incidence of pharyngocutaneous fistulas after total laryngectomy is 13.67% to 39.08%. In this meta analysis, the results suggested that age, smoking, T-stage, previous radiotherapy and preoperative albumin were risk factors for pharyngocutaneous fistulas.

Many studies have shown that surgery combined with radiotherapy is the main treatment to improve the prognosis of patients with laryngeal cancer. For patients at an advanced stage, preoperative radiotherapy can effectively inhibit the tumor growth, shrink the tumor body and facilitate surgical resection [41]. For tumors with a wide range of invasion, preoperative radiotherapy can effectively reduce the tumor volume and the scope of resection to increase the chances of surgery for patients at an advanced stage, further preserving the function and improving the quality of life. Yoshizaki et al. [42] believed that the incidence of postoperative pharyngocutaneous fistulas in patients receiving preoperative radiotherapy was higher

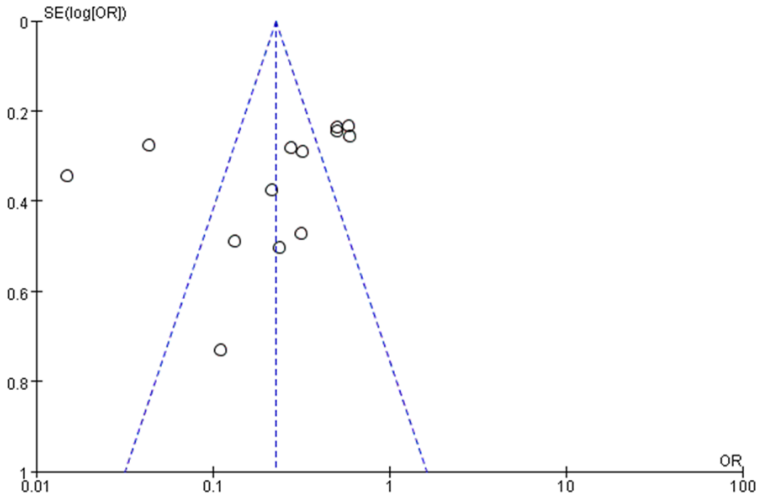

Figure 8. The funnel plots.

than that in patients without preoperative radiotherapy, with a statistically significant difference. In addition, the shorter the interval between surgery and preoperative radiotherapy, the higher the incidence of postoperative pharyngocutaneous fistulas. The greater the preoperative radiotherapy dose, the greater the probability of postoperative pharyngocutaneous fistulas. Its occurrence may be due to the fact that preoperative radiotherapy can destroy the microvascular circulation in the surgical area, resulting in blood supply disorders in local tissues. In addition, local tissue sclerosis, edema and tissue fibrosis after radiotherapy lead to decreased tissue repair ability and prolonged wound healing time after surgery [43]. Some scholars also believed that the dose of preoperative preventive radiotherapy should not exceed 40 Gy, and large dose of radiotherapy could increase the incidence of postoperative pharyngocutaneous fistulas [44, 45]. This is consistent with the results of this study.

Tumor stage is a commonly acknowledged related factor of pharyngocutaneous fistulas. Milisavljevic et al. [46] indicated in their study that patients with high tumor stage have a higher probability of pharyngocutaneous fistulas after surgery. The patients at T3 and T4 stages have a large range of lesions, which need to be removed during surgery. Therefore, there are few normal point membranes left after tumor resection, and the suture tension is relatively large. Generally, if the defect was large after tumor resection, the transfer of skin flap repair could reduce the occurrence of pharyngocutaneous fistulas [47]. According to the statistics of the research results of this group, T stage is a relevant factor of postoperative pharyngocutaneous fistulas, and T stage is an independent risk factor of postoperative pharyngocutaneous fistulas.

Preoperative hemoglobin and albumin levels reflect the nutritional status of the body. Some scholars have verified that postoperative hemoglobin and albumin were the risk factors for pharyngocutaneous fistulas [48-50]. This is consistent with our results ($P<0.01$). Preoperative comprehensive assessment of the patient's overall nutritional status and improvement of the perioperative nutritional support can reduce the incidence of postoperative pharyngocutaneous fistulas. Wang et al. [51] reported that enteral and parenteral nutrition support for 7 consecutive days before surgery could reduce the incidence of pharyngocutaneous fistulas.

The primary limitation of current meta-analysis is the limited number of studies analyzed. We only included 25 studies, which were not randomized controlled trial. In addition, we did not analyze the severity of pharyngocutaneous fistulas in subgroup. Moreover, other measurements such as obesity, drinking status and other lifestyle factors should be considered confounding factors, because the results of our study were based on unadjusted estimates. Finally, this review included small sample-size, single-center studies with clinical heterogeneity and variable patient backgrounds, which could result in low statistical power and inconsistent results. Therefore, large sample-size clinical trials should be carried out to further verify the risk factors associated with pharyngocutaneous fistulas after total laryngectomy.

In conclusion, this review is a comprehensive analysis of the risk factors associated with pharyngocutaneous fistulas following total laryngectomy. It showed that age, smoking, T-stage, previous radiotherapy and preoperative albu-

min were risk factors for pharyngocutaneous fistulas after total laryngectomy.

Disclosure of conflict of interest

None.

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