Presentation, Management, and Hearing Outcomes of Labyrinthine Fistula Secondary to Cholesteatoma: A Systematic Review and Meta-analysis

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Objective: The current study systematically reviewed the literature to compare auditory outcomes of patients treated for labyrinthine fistula (LF) based on characteristics of disease and surgical management.
Databases Reviewed: PubMed, Scopus, Web of Science.
Methods: Original series (at least five cases) published from 2000 reporting management and hearing results of LF secondary to cholesteatoma were included. Proportion and odds-ratio (OR) meta-analyses were conducted through inverse variance random-effects models based on logit transformation.
Results: The prevalence of LF is estimated to be 7% (95% confidence interval [CI], 5–9%). Fistulae involving the lateral semicircular canal (90%; 95% CI, 87–93%) and larger than 2 mm (53%; 95% CI, 43–64%) were common, whereas membranous involvement was less frequent (20%; 95% CI, 12–30%). Complete removal of the cholesteatoma matrix overlying the LF was mostly applied. Bone conduction (BC) preservation was frequently achieved (81%; 95% CI, 76–85%); new-onset postoperative anacusis was rarely reported (5%; 95% CI, 4–8%). A higher chance of BC preservation was associated with sparing the perilymphatic space (OR, 4.67; 95% CI, 1.26–17.37) or membranous labyrinth (OR, 4.56; 95% CI, 2.33–8.93), exclusive lateral semicircular canal involvement (OR, 3.52; 95% CI, 1.32–9.38), smaller size (<2 mm; OR, 3.03; 95% CI, 1.24–7.40), and intravenous steroid infusion (OR, 7.87; 95% CI, 2.34–26.42).
Conclusion: LF occurs in a significant proportion of patients with cholesteatoma. In the past two decades, complete removal of the cholesteatoma matrix followed by immediate sealing has been favored, supported by the high proportion of BC preservation. Hearing preservation depends primarily on characteristics of the LF, and specific surgical strategies should be pursued. Intraoperative and postoperative intravenous steroid infusion is recommended.
Key Words: Cholesteatoma—Fistula—Hearing, bone conduction—Labyrinth, bony—Labyrinth, membranous—Labyrinth, vestibule—Mastoidectomy—Semicircular canals—Sensorineural hearing loss—Tympanoplasty.

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INTRODUCTION

Labyrinthine fistula (LF) is an intratemporal complication of acquired cholesteatoma. The lateral semicircular canal (LSCC) is generally the most frequently involved subsite. Despite thorough clinical examination and modern imaging techniques, definitive preoperative diagnosis of LF is not always possible, and the classic signs and symptoms related to LF are highly variable and neither sensitive nor specific. Numerous classifications have been proposed to describe the extent of LF, mainly according to size (1–3) and bony and membranous labyrinth involvement (4–6).

The management of LF secondary to cholesteatoma is controversial. The main points of discussion include indication for open mastoid cavity and for complete removal of the cholesteatoma matrix to achieve the best balance of radicality, auditory outcome, and best long-term control. Over the years, new strategies have emerged (7–9), and the protective role of intravenous (i.v.) steroid infusion has been advocated (6,10,11). The purpose of this study is to compare auditory outcomes of patients treated for LF based on characteristics of disease and surgical management. In addition, the study systematically examines the most relevant clinical features of LF at presentation, as well as intraoperative characteristics and related surgical strategies used.

MATERIALS AND METHODS

Article Collection

A systematic review of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and

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Meta-Analyses statement (12) and the position paper by McRackan et al. (13). The search was conducted on PubMed, Scopus, and Web of Science online databases, and updated to October 18, 2021. The following query "labyrinthine OR (horizontal OR lateral AND (semicircular canal)) AND (dehiscence OR fistula OR erosion) AND cholesteatoma" was used to collect all the articles describing LF secondary to cholesteatoma. In addition, the references of both the original series included in this study and the literature reviews on the topic found through the literature search were carefully screened. Two authors (M.A. and M.T.) independently screened the titles and abstracts of the studies included, discarding articles according to specific inclusion and exclusion criteria (Fig. 1). Discrepancies were clarified by discussion between authors and consultation with a senior otologic surgeon (T.S.).

Eligibility Criteria

The participants, interventions, comparisons, outcomes, timings, and study design (PICOTS) model was adopted (Supplementary Table 1, http://links.lww.com/MAO/B515) (14). Studies were included according to the following criteria: (*a*) original series reporting data on the treatment of LF secondary to cholesteatoma, (*b*) at least five consecutive cases, (*c*) published after 2000, and (*d*) availability of preoperative and postoperative hearing performance, minimally reporting change in the average bone conduction (BC), proportion of patients with unchanged/improved hearing or new-onset postoperative anacusis. Exclusion criteria were as follows: (*a*) case reports, (*b*) non-English language studies, and (*c*) studies reporting data exclusively on cochlear fistula. Moreover, articles were screened for duplicated original data from the same center; the largest and most recent publication was always considered.

Quality Assessment

The quality assessment of each study included was independently estimated by two authors (M.A. and M.T.) through the Newcastle–Ottawa Scale adapted for cross-sectional, cohort, and case–control studies (15). In case of discrepancies, a definitive evaluation was reached by discussion and consultation with a senior author (A.D.).

Data Collection and Statistical Analysis

The most relevant characteristics on study design, population (country, period of observation, sex, and mean age), preoperative radiological accuracy, clinical presentation, surgery, LF extension and location, surgical management, and auditory outcomes were collected in a dedicated database.

If not explicitly stated, depth of fistula was defined according to Dornhoffer and Milewski (6) or Palva and Ramsay (5) classifications, as follows (Fig. 2):

- blue line, intact endosteum (Dornhoffer type I, Palva stages I and II);

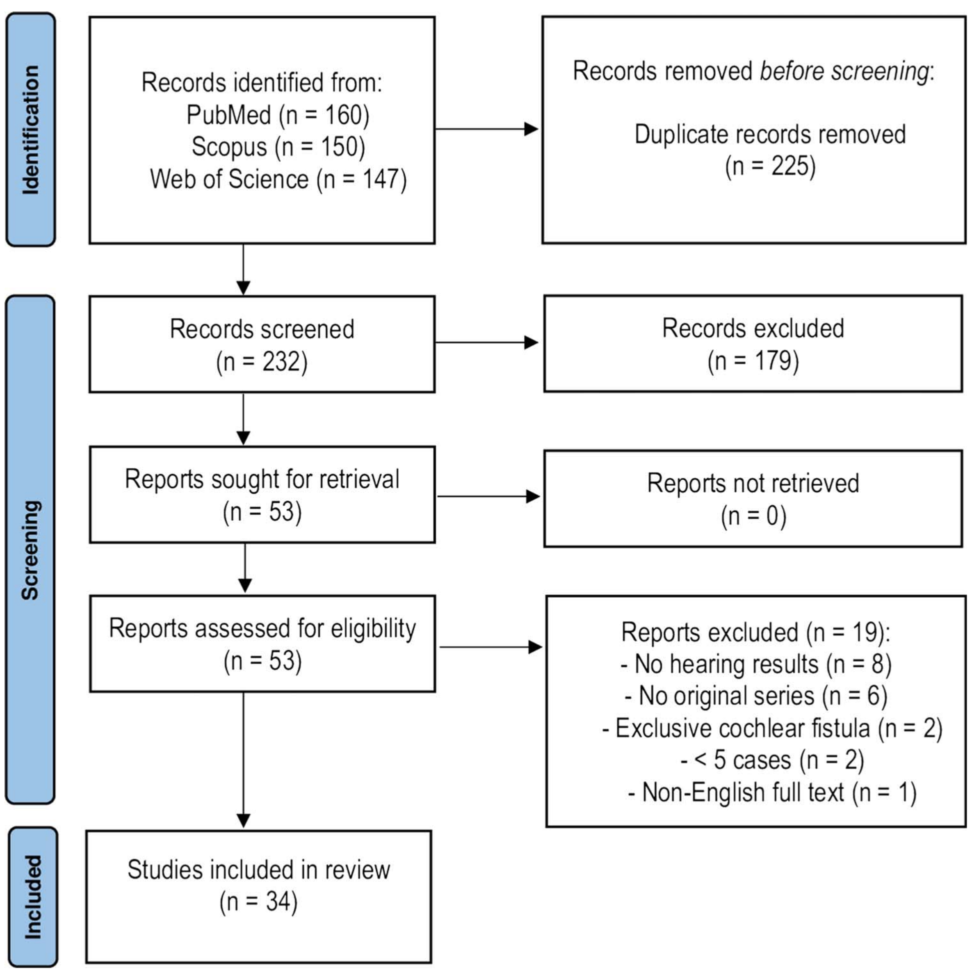

FIG. 1. PRISMA flowchart. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Dornhoffer and Milewski classification		
Type I	*Blue line*	Erosion of the bony labyrinth with intact endosteum
Type II	*Bony fistula*	Erosion of the endosteum with open perilymphatic space
		- type IIa, perilymphatic space left undisturbed
		- type IIb, perilymphatic space disturbed by active suctioning before recognition of the fistula or ingrowth of cholesteatoma
Type III	*Membranous fistula*	Involvement or destruction of the membranous labyrinth

Palva and Ramsay classification		
Type I	*Blue line*	Partial erosion of the bony labyrinth
Type II	*Blue line*	Complete erosion of the bony labyrinth with intact endosteum
Type III	*Bony fistula*	Erosion of the endosteum, removal of the matrix determines the opening of the perilymphatic space
Type IV	*Membranous fistula*	Encasement of the membranous canal

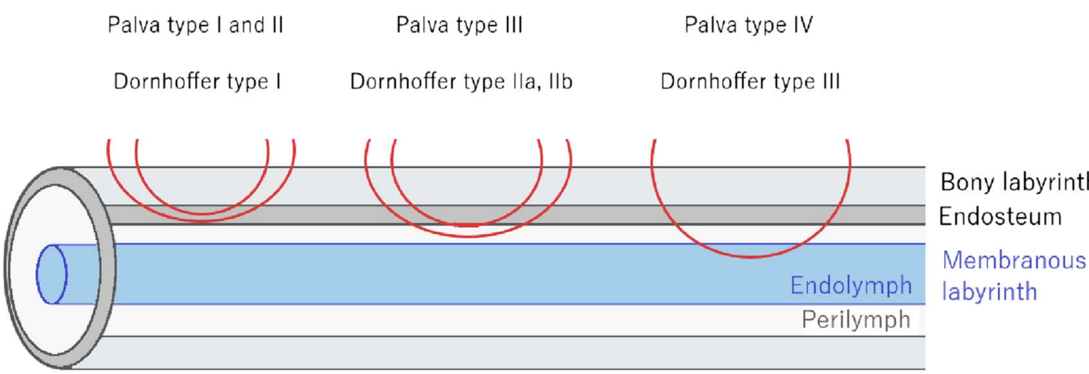

FIG. 2. Dornhoffer and Milewski, and Palva and Ramsay classifications of fistula extension to bony and membranous labyrinth.

- bony fistula, erosion of bony labyrinth endosteum (Dornhoffer type II, Palva stage III); and
- membranous fistula, involvement of membranous labyrinth (Dornhoffer type III, Palva stage i.v.).

Studies reporting details on Dornhoffer subclassification into types IIa and IIb were included to summarize the effect of disturbed perilymphatic space on hearing outcome.

Large fistulae were defined according to either two or three mm cutoffs (1–3).

Postoperative hearing preservation/improvement was defined as maintaining a BC within 10 dB compared with preoperative values by all studies, except for three studies using 5- and 20-dB cutoffs (16–18).

The primary outcome was to determine the prevalence of LF and to quantify the effect on hearing preservation and the odds of postoperative anacusis according to fistula characteristics (extension to perilymphatic space and membranous labyrinth, involvement of subsites other than LSCC, size) and management (intraoperative steroid infusion). When considering the outcomes of hearing preservation improvement, patients with preoperative anacusis were excluded.

The secondary outcome was to calculate the pooled proportion of the most relevant preoperative and postoperative features, namely, sex, computed tomographic scan accuracy, clinical presentation (dizziness-vertigo, tinnitus, otorrhea, otalgia, hypoacusis, concurrent facial palsy, positive fistula sign), membranous labyrinth involvement, fistula location, size, and preoperative and postoperative hearing performance. Moreover, a review of the different intraoperative strategies was conducted.

Proportion and odds-ratio (OR) meta-analyses were conducted through inverse variance random-effects models based on logit transformation and presented as Forest plots. The pooled proportion and OR estimates and corresponding 95% confidence intervals (CIs) were calculated according to the random-effects models of DerSimonian and Laird (19). For each study, proportions, and OR are depicted as gray squares, and relative 95% CI as horizontal lines. The weight of each study on the overall effect estimate is reported and represented by the square size. The pooled proportions and OR estimates with relative 95% CI are depicted as black diamonds at the bottom of the Forest plot. Heterogeneity between studies was assessed with Higgins I^2 and τ^2 tests, defined as low if I^2 was less than 25%, moderate if between 25 and 50%, and substantial if greater than 50% (20). Publication bias was assessed through funnel plot and Egger's test (21,22).

Statistical analysis was performed with R (version 4.1.2; R foundation for Statistical Computing, Vienna, Austria): packages "meta" and "metafor." Statistical significance was defined as $p < 0.05$.

RESULTS

Article Collection and Quality Assessment

The bibliographic search returned 457 titles: 160 from PubMed, 150 from Scopus, and 147 from Web of Science. A total of 232 records screened through title and abstract evaluation after duplicates removal (n = 225). Fifty-three full-text articles were assessed for eligibility. Nineteen articles were excluded because they did not report auditory findings (n = 8), reported data not from original series (n = 6) or on fewer than five patients (n = 2), exclusively described patients with cochlear fistulas (n = 2), or had the full text not in English (n = 1). Thirty-four articles met the inclusion criteria and were considered appropriate for the current systematic review (Table 1). Further details are available in the flowchart reported in Figure 1.

According to the Newcastle–Ottawa Scale, the overall quality of the included studies was good (median value of 7.2; range, 6–8). Details are reported in Supplementary Table 2, http://links.lww.com/MAO/B515. Most studies were retrospective unicentric series. A prospective or combined retrospective and prospective data collection was conducted in only three studies (8.8%) (7,16,30), whereas (5.9%) multicenter experience was reported in two studies (10,34).

Study Population, Preoperative Radiological, and Clinical Evaluation

The number of operations for cholesteatoma during the period of observation was reported by most studies (2,7,9,10,17,18,23–36,38,40–42,45–47). Overall, on 13,554 operations for cholesteatoma, the pooled prevalence of LF was 7% (95% CI, 5–7%; I^2 = 89%). Among 947 patients affected by LF, a slight male prevalence was observed (pooled proportion, 55%; 95% CI, 51–59%; I^2 = 41%). Mean and median ages at diagnosis were quite heterogeneous, reported to be in the fourth decade by 7 studies (17,24,29,32,39,46,47), in the fifth by 9 (7,9,16,23,25,28,38,41,45), and in the sixth by 10 (10,11,26,27,31,33–35,37,43).

Most studies reported data on the accuracy of imaging, with a pooled proportion of preoperative LF detection of 82% (95% CI, 69–91%; I^2 = 82%). Data on clinical presentation showed a pooled proportion of reported dizziness-vertigo of 54% (95% CI, 48–60%; I^2 = 53%), tinnitus of 29% (95% CI, 18–44%; I^2 = 82%), and otalgia of 29% (95% CI, 18–43%; I^2 = 74%). Hearing loss was reported by almost all patients (95%; 95% CI, 90–98%; I^2 = 75%). Clinical evaluation showed a pooled proportion of otorrhea of 75% (95% CI, 67–82%; I^2 = 63%), positive fistula test of 29% (95% CI, 21–38%;

TABLE 1. *Most relevant study and patients-related details of each study included in the systematic review*

Study Characteristics						Population Characteristics				
Author	Publication Year	Country	Study Design	Period of Observation	Primary/ Recurrent	Overall No. of Operations	No. of Patients with Fistula	No. of Ears Operated	Male	Age at Surgery (yr), Mean (Range), yr
Soda-Merhy and Betancourt-Suárez (17)	2000	Mexico	R U	1985–1997	Both	360	27	27	11	37.3
Manolidis (2)	2000	United Stated	R U	N.S.	Both	111	23	25	N.S.	N.S.
Gersdorff et al. (23)	2000	Belgium	R U	1986–1996	Primary	769	54	54	30	40.8 (6–83)
Kvestad et al. (24)	2001	Norway	R U	1986–1999	N.S.	631	20	20	10	37
Ahmad and East (25)	2002	United Kingdom	R U	1987–1999	N.S.	382	25	25	12	45.2 (10–81)
Magliulo et al. (16)	2008	Italy	P U	1996–2006	N.S.	N.S.	14	14	5	44.5 (28–66)
Quaranta et al. (26)	2009	Italy	R U	2001–2007	Primary	361	46	46	19	54.6 (16–86)
Ueda et al. (27)	2009	Japan	R U	1995–2005	N.S.	561	31	31	17	56
Chen et al. (28)	2010	China	R U	2003–2007	N.S.	600	22	22	12	46.7 (27–68)
Sari et al. (29)	2010	Turkey	R U	1988–2007	N.S.	582	33	33	17	37.2
Faramarzi et al. (30)	2010	Iran	P U	2003–2008	Primary	462	24	24	N.S.	N.S.
Yamamoto et al. (31)	2010	Japan	R U	2001–2009	N.S.	197	22	22	10	56.7 (12–86)
Stephenson and Saliba (32)	2011	Canada	R U	2004–2009	N.S.	317	28	28	16	38 (7–76)
Gocea et al. (11)	2011	Spain	R U	1997–2008	N.S.	N.S.	31	31	16	50.3 (20–74)
Moon et al. (33)	2011	Korea	R U	1991–2007	N.S.	778	38	38	27	51.6
Ghiasi (18)	2011	Iran	R U	2003–2008	Both	108	16	16	10	27.18
Ikeda et al. (34)	2012	Japan	R M	1998–2009	Both	589	47	47	19	53.5 (13–83)
Albu et al. (10)	2013	Italy	R M	1990–2010	Both	1,587	97	97	50	52.4
Katsura et al. (35)	2013	Japan	R U	1996–2010	N.S.	1,197	14	14	6	58 (50–72)
Jang et al. (36)	2013	Korea	R U	2005–2012	N.S.	720	17	17	8	(21–76)
Cho et al. (37)	2014	Korea	R U	2005–2011	N.S.	N.S.	23	23	10	55.6 (37–67)
Meyer et al. (38)	2015	France	R U	1993–2013	Both	695	42	42	29	40.8 (4–76)
Bo et al. (39)	2015	China	R U	2008–2013	N.S.	N.S.	35	35	17	37.03 (8–75)
Dispenza (40)	2015	Italy	R U	2011–2014	Primary	57	8	8	N.S.	N.S.
Geerse et al. (41)	2017	The Netherlands	R U	2002–2015	Both	690	44	45	25	49 (16–76)
Sagar et al. (42)	2017	India	R U	2011–2015	Primary	81	14	14	N.S.	N.S.
Rah et al. (43)	2018	Korea	R U	2010–2016	N.S.	N.S.	43	43	31	55.7 (23–79)
Baylan et al. (44)	2018	Turkey	R U	2013–2017	N.S.	N.S.	23	23	23	11
Rosito et al. (45)	2018	Brazil	R U	2000–2016	Primary	333	9	8	5	44.40
Basu and Hamilton (8)	2019	United Kingdom	R U	2005–2017	N.S.	N.S.	36	36	N.S.	N.S.
Misale et al. (46)	2019	India	R U	2014–2016	Both	275	30	30	25	34 (18–72)
Balci et al. (47)	2019	Turkey	R U	2008–2014	N.S.	188	32	32	22	37.1 (17–56)
Bartochowska et al. (7)	2021	Poland	P, R U	2015–2020	Both	465	38	38	18	47
Thangavelu et al. (9)	2021	Germany	R U	2013–2019	N.S.	458	20	20	13	45

BC, bone conduction; N.S., not specified; P, prospective; R, retrospective.

I^2 = 72%), and concurrent facial palsy of 9% (95% CI, 7–13%; I^2 = 25%). Publication bias was frequently observed. Forest and funnel plots are reported in Supplementary Figures 1–10, http://links.lww.com/MAO/B515.

Characteristics of LFs and Surgical Management

Although rather variable, canal wall down (CWD) or radical mastoidectomy were the most common procedures performed in most studies (2,9,10,16–18,24–32,34–40,42, 43,47), with a pooled proportion of 88% (95% CI, 79–94%; I^2 = 81%). LFs were most frequently located on the LSCC, with a pooled proportion of 90% (95% CI, 87–93%; I^2 = 46%). The occurrence of multiple fistulas involving LSCC and other labyrinthine subsites was described in 11% of cases (95% CI, 8–14%; I^2 = 25%). Membranous labyrinth involvement (Dornhoffer type III, Palva stage i.v.) was encountered in 20% of cases (95% CI, 12–30%; I^2 = 75%); 53% of fistulae were larger than 2 mm (95% CI, 43–64%; I^2 = 68%), and 23% were larger than 3 mm (95% CI, 17–31%; I^2 = 34%). Publication bias was frequently observed. Forest and funnel plots are reported in Supplementary Figures 11–15, http:// links.lww.com/MAO/B515.

Among studies included, 24 (70.6%) reported that the matrix was completely removed in all patients. In five studies (17,23,26,29,34), complete removal was pursued in more than 90% of cases, whereas in three studies (24,40,45), a lower rate of patients with complete matrix eradication was observed (Table 1). Most studies (79.4%) (7,9–11,16–18, 23–25,27–31,33–39,43–47) reported details on the intraoperative strategies for LF management. In these, careful matrix removal at the end of the surgical procedure was immediately followed by sealing of the LF. A wide range of repair techniques and grafting was described. Most frequently, repair of the fistula was conducted with fascia and bone dust, pate or wax (eight studies) (9,10,16,18,36,44–46), only fascia (three

TABLE 1. *Most relevant study and patients-related details of each study included in the systematic review*, Continued

Fistula Management			Hearing Performance				
Matrix Removal	Material Used for Sealing	i.v. Steroid	Frequencies (kHz)	Preoperative BC (dB)	Preoperative Anacusis	Postoperative BC (dB)	New-Onset Postoperative Anacusis
26/27 (96.3%)	Multiple	No	N.S.	N.S.	4/27 (14.8%)	N.S.	0/23 (0%)
N.S.	N.S.	No	N.S.	N.S.	3/25 (12.0%)	N.S.	0/22 (0%)
52/54 (96.3%)	Multiple	Yes	0.5, 1, 2, 4	N.S.	5/54 (9.3%)	N.S.	5/49 (10.2%)
12/20 (60%)	Fascia + bone chip	No	0.5, 1, 2, 4	19 (median)	4/20 (20.0%)	19.7	0/16 (0%)
25/25 (100%)	Multiple	No	N.S.	N.S.	5/25 (20.0%)	N.S.	2/20 (10%)
14/14 (100%)	Fascia + bone dust, pate or wax	Yes (14/14)	0.25–4	N.S.	0/14 (0%)	N.S.	0/14 (0%)
45/46 (97.8%)	Multiple	No	0.5, 1, 2, 3	34.5	2/46 (4.3%)	38.4	2/44 (4.5%)
31/31 (100%)	Multiple	No	0.5, 1, 2	N.S.	0/31 (0%)	N.S.	0/31 (0%)
22/22 (100%)	Muscle + bone dust + fascia	Yes (22/22)	0.5, 1, 2, 4	21.5	3/22 (13.6%)	18.5	0/19 (0%)
31/33 (93.9%)	Fascia + cartilage	Yes (33/33)	0.5, 1, 2, 4	N.S.	1/33 (3.0%)	N.S.	2/32 (6.2%)
N.S.	Multiple	No	0.5, 1, 3	22.6	5/24 (20.8%)	21.15	0/19 (0%)
22/22 (100%)	Fascia + bone pate + bone chip	No	0.5, 1, 2, 4	29.2 (mean)	7/22 (31.8%)	33.8 (mean)	1/15 (6.7%)
28/28 (100%)	N.S.	No	0.5, 1, 2, 3, 4	23.2 (mean)	3/28 (10.7%)	24.5 (mean)	N.S.
31/31 (100%)	Bone dust + cartilage	Yes (26/31)	0.5, 1, 2, 4	35 (mean)	0/31 (0%)	36 (mean)	2/31 (6.4%)
38/38 (100%)	Multiple	No	0.5, 1, 2, 3	N.S.	10/38 (26.3%)	N.S.	0/28 (0%)
Fascia + bone dust, pate or wax	No	0.5, 1, 2	N.S.	1/16 (6.3%)	N.S.	0/15 (0%)	
46/47 (97.9%)	Fascia + bone chip	No	1, 2, 4	30.6 (mean)	7/47 (14.9%)	33.5 (mean)	0/40 (0%)
97/97 (100%)	Fascia + bone dust, pate or wax	Yes (52/97)	0.5, 1, 2, 4	21.5 (mean)	1/97 (1.0%)	19.5 (mean)	0/96 (0%)
14/14 (100%)	Fascia + cartilage	No	0.5, 1, 2, 4	26.3 (mean)	N.S.	31.3 (mean)	0%
17/17 (100%)	Fascia + bone dust, pate or wax	Yes (17/17)	0.5, 1, 2, 4	35.4 (mean)	0/17 (0%)	27.5 (mean)	0/17 (0%)
23/23 (100%)	Fascia	No	0.5, 1, 2, 3	N.S.	2/23 (8.7%)	N.S.	N.S.
42/42 (100%)	Multiple	No	0.5, 1, 2, 4	21.6 (mean)	1/42 (2.4%)	31 (mean)	4/41 (9.8%)
35/35 (100%)	Fascia	No	0.5, 1, 2, 4, 8	29.35	1/35 (2.9%)	22.4	0/34 (0%)
3/8 (37.5%)	N.S.	No	0.25, 0.5, 1, 2, 4	39.4 (mean)	N.S.	42.5 (mean)	0%
45/45 (100%)	N.S.	No	1, 2, 4	18.6 (mean)	11/45 (24.4%)	20.5 (mean)	2/34 (5.9%)
14/14 (100%)	N.S.	No	0.5, 1, 2, 3	N.S.	N.S.	N.S.	0%
43/43 (100%)	Fascia + cartilage	No	0.5, 1, 2, 3	36.6 (mean)	5/43 (11.6%)	43.3 (mean)	0/38 (0%)
24/24 (100%)	Fascia + bone dust, pate or wax	No	0.5, 1, 2, 4	13 (median)	0/23 (0%)	14.5 (median)	0/23 (0%)
7/8 (87.5%)	Fascia + bone pate	Yes (8/8)	0.5, 1, 2, 3, 4	N.S.	N.S.	N.S.	0%
36/36 (100%)	Fascia + fibrin tissue glue	No	0.5, 1, 2, 3	N.S.	0/36 (0%)	N.S.	N.S.
30/30 (100%)	Fascia + bone dust, pate or wax	No	0.5, 1, 2, 4	N.S.	9/30 (30.0%)	N.S.	0/21 (0%)
32/32 (100%)	Fascia	Yes (32/32)	0.5, 1, 2, 4	20.8 (mean)	0/32 (0%)	21.8 (mean)	0/32 (0%)
38/38 (100%)	Multiple	Yes (20/38)	0.5, 1, 2, 3	29 (mean)	3/38 (7.9%)	N.S.	2/35 (5.7%)
20/20 (100%)	Fascia + bone pate	Yes (20/20)	0.25, 0.5, 1, 2, 4, 8	20 (mean)	2/20 (10.0%)	17.5 (mean)	0/18 (0%)

studies) (8,37,39,47), fascia and cartilage fragments (three studies) (29,35,43), and fascia and bone chips (two studies) (24,34). Multiple materials and techniques were used in nine studies (7,17,23,25,27,29,30,33,38).

Auditory Outcomes

Most studies reported auditory outcomes providing the mean BC either as the result of the thresholds at frequencies 0.5, 1, 2, and 3 kHz (7,8,26,33,37,42,43) as recommended, or as the results of the thresholds at frequencies 0.5, 1, 2, and 4 kHz (10,11,23,24,28,29,31,35,36,38,44,46,47) or 1, 2, and 4 kHz (34,41), which are considered comparable to the standard set by the Committee on Hearing and Equilibrium guidelines (48,49).

Cohort average preoperative BC was provided in 19 studies (7,9–11,24,26,28,30–32,34,36,38–41,43,44,47), ranging from 13 (44) to 39.4 dB (40). Preoperative anacusis was found in 11% of patients (95% CI, 8–15%; I^2 = 53%) (Supplementary Fig. 16, http://links.lww.com/MAO/B515). Postoperative BC was available in 18 articles (9–11,24,26,28, 30–32,34,36,38–41,43,44,47), ranging from 14.5 (44) to 43.3 dB (43). After exclusion of patients with preoperative anacusis and those without follow-up data, the pooled proportion of patients with hearing preservation or improvement after surgery was 81% (95% CI, 76–85%; I^2 = 47%; Supplementary Fig. 17, http://links.lww.com/MAO/B515).

New-onset postoperative anacusis was a rare occurrence (pooled proportion, 5%; 95% CI, 4–8%; I^2 = 0%; Supplementary Fig. 18, http://links.lww.com/MAO/B515); when observed (7,11,23,25,29,31,38,41), it did not exceed 10% of cases (Table 1).

Meta-analysis of the effect of fistula extension on hearing preservation revealed that the most significant predictor was membranous labyrinth sparing (OR, 4.56; 95% CI, 2.33–8.93; I^2 = 0%; Fig. 3A). Comparing fistulae without membranous extension, no significant difference in hearing outcomes was found between "blue lines" (intact endosteum) and bony fistulae (OR, 1.79; 95% CI, 0.71–4.51; I^2 = 0%; Fig. 3B). No significant difference emerged comparing Dornhoffer type I and IIa fistulae (OR, 1.39; 95% CI, 0.24–8.08; I^2 = 0%; Fig. 3C). In contrast, Dornhoffer type IIa fistulae showed significant higher chance of hearing preservation compared with type IIb fistulae (OR, 4.67; 95% CI, 1.26–17.37; I^2 = 0%; Fig. 3D), suggesting the detrimental effect of perilymphatic disturbance rather than endosteum erosion alone.

Fistulae located on the LSCC (OR, 3.52; 95% CI, 1.32–9.38; I^2 = 0%; Fig. 4A) and smaller fistulae, categorized either as less than 2 mm (OR, 3.03; 95% CI, 1.24–7.40; I^2 = 0%; Fig. 4B) or less than 3 mm (OR, 6.15; 95% CI, 1.47–25.68; I^2 = 0%; Fig. 4C), were associated with significantly better hearing outcomes.

Eleven studies reported on the use of intraoperative steroids (7,9–11,16,23,28,29,36,45,47), but only three described auditory outcomes with complete matrix removal comparing groups of patients receiving or not i.v. steroids (7,10,11). The steroid infusion protocols of Albu et al. (10) and Gocea et al. (11) were consistent with that proposed by Dornhoffer and Milewski (intraoperative infusion of 500 mg of methylprednisolone 20 min before matrix removal and after surgery for 2 d) (6). Bartochowska et al. (7) opted for a lower intraoperative dose (16 mg of dexamethasone), followed by 8 mg daily for at least 3 days (mean, 5 d). Higher odds of BC preservation were found when steroid infusion was performed (OR, 7.87; 95% CI, 2.34–26.42; I^2 = 22%; Fig. 4D).

Postoperative occurrence of new-onset anacusis was significantly higher in case of involvement of the membranous labyrinth (OR, 11.94; 95% CI, 3.07–46.45; I^2 = 0%; Fig. 5A) or subsites other than LSCC (OR, 15.60; 95% CI, 1.53–159.58; I^2 = 0%; Fig. 5B). A higher risk was observed for larger fistulae (>2 mm) in the experience of Sari et al. (29) (cutoff, 2 mm), whereas no difference was reported according to intraoperative infusion of steroids by Albu et al. (10). For each pooled OR estimate, no publication bias was detected at funnel plot inspection and Egger's test (Supplementary Figs. 19–21, http://links.lww.com/MAO/B515).

DISCUSSION

LF was a complication in 7% (95% CI, 5–9%) of patients treated for chronic otitis media (COM) with cholesteatoma. In the past two decades, complete removal of the cholesteatoma matrix overlying the LF has been widely accepted. Except for two studies, either because older (24) or smaller (40), all studies reported to have completely removed the matrix in all patients (7–11,16,18,25,27,28,31–33,35–39,41–44,46,47) or in the vast majority (17,23,26,29,34,45). Complete matrix removal finds support in the excellent proportion of BC preservation after surgery (81%; 95% CI, 76–85%) and the low rate of new-onset postoperative anacusis (5%; 95% CI, 4–8%).

Regarding clinical presentation, this was highly heterogeneous between studies. Hearing loss (95%; 95% CI, 90–98%) and otorrhea (75%; 95% CI, 67–82%) were the most frequent complaints, followed by dizziness (54%; 95% CI, 48–60%), tinnitus (29%; 95% CI, 18–44%), and otalgia (29%; 95% CI, 18–43%). A nonnegligible rate of anacusis (11%; 95% CI, 8–15%) and concurrent facial nerve palsy (9%; 95% CI, 7–13%) was observed. Results of the fistula test were heterogeneous, with a pooled poor sensitivity. Fistulae involving the LSCC (90%; 95% CI, 87–93%) and larger than 2 mm (53%; 95% CI, 43–64%) were common findings, whereas advanced cases with membranous involvement were less frequently observed (20%; 95% CI, 12–30%).

The radiological accuracy was overall good (82%; 95% CI, 69–91%), but a high heterogeneity between studies was observed, mostly because of poorer performance in older and smaller series. Specifically, high-resolution computed tomographic scan has been shown to be a very precise tool for detection of LF, and some features may even help predicting membranous involvement with satisfactory sensitivity and specificity (LF size >3.55 mm) (32).

Many fistula-related features were significantly associated with BC preservation. Although difficult to establish intraoperatively, LF depth was associated with increased risk of hearing impairment. The most significant predictor was membranous labyrinth sparing (OR, 4.56; 95% CI, 2.33–8.93) (Fig. 3D). When comparing fistulae without membranous

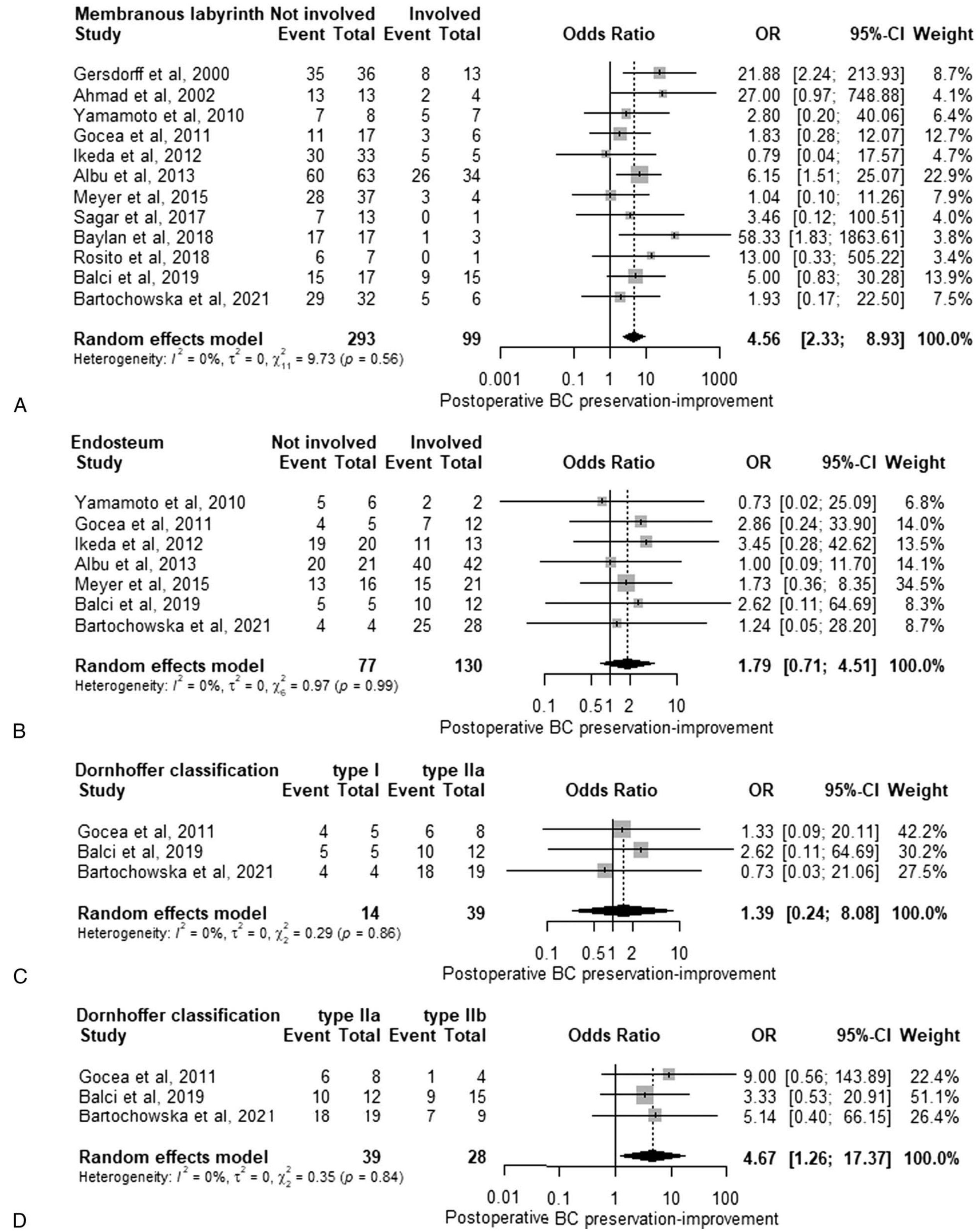

FIG. 3. Forest plots reporting OR estimates on postoperative bone conduction hearing preservation/improvement according to depth of fistula extension. (*A*) Fistulae with and without involvement of the membranous labyrinth; (*B*) blue line (bone erosion with intact endosteum) versus "true" bony fistulae without membranous involvement; (*C*) Dornhoffer type I (intact endosteum) versus Dornhoffer type IIa (eroded endosteum, undisturbed perilymphatic space); (*D*) Dornhoffer type IIa (undisturbed perilymphatic space) versus type IIb (disturbed perilymphatic space). No publication bias was found at funnel plot inspection (supplementary material, http://links.lww.com/MAO/B515). OR indicates odds ratio.

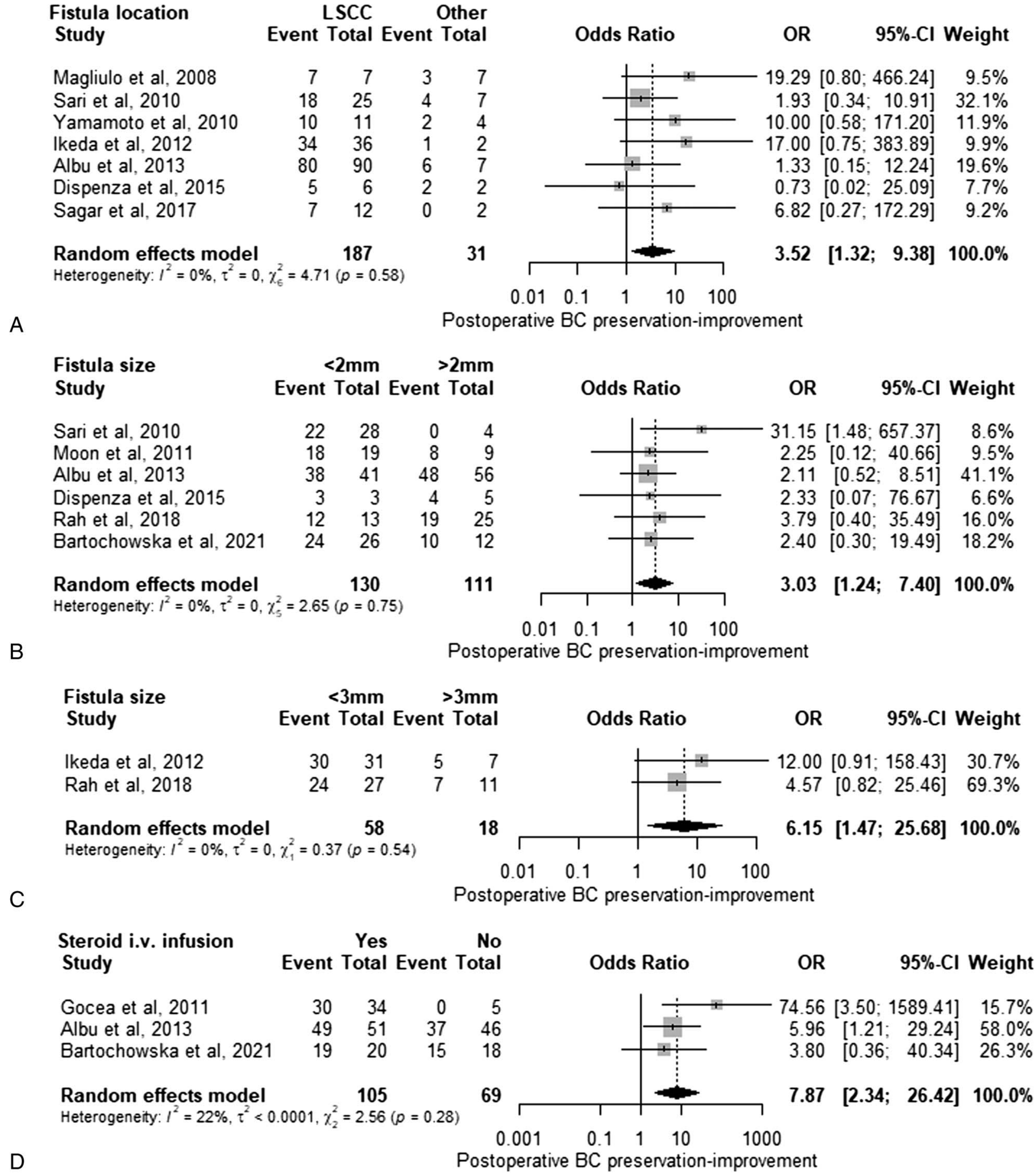

FIG. 4. Forest plots reporting OR estimates on postoperative bone conduction hearing preservation/improvement according to (*A*) exclusive LSCC involvement, fistula size with a cutoff of (*B*) 2 mm or (C) 3 mm, and (*D*) i.v. infusion of steroids, intraoperative and in the first days after surgery. No publication bias was found at funnel plot inspection (supplementary material, http://links.lww.com/MAO/B515). i.v. indicates intravenous; LSCC, lateral semicircular canal; OR indicates odds ratio.

extension, an undisturbed perilymphatic space (Dornhoffer type IIa versus IIb; OR, 4.67; 95% CI, 1.26–17.37) was a strong predictor of BC preservation, whereas no significant differences were found according to erosion of the bony labyrinth endosteum (Fig. 3A–C). These findings confirm the progressively increased risk of hearing loss secondary to perilymphatic space disturbance and membranous labyrinth involvement, but not after endosteum resorption alone

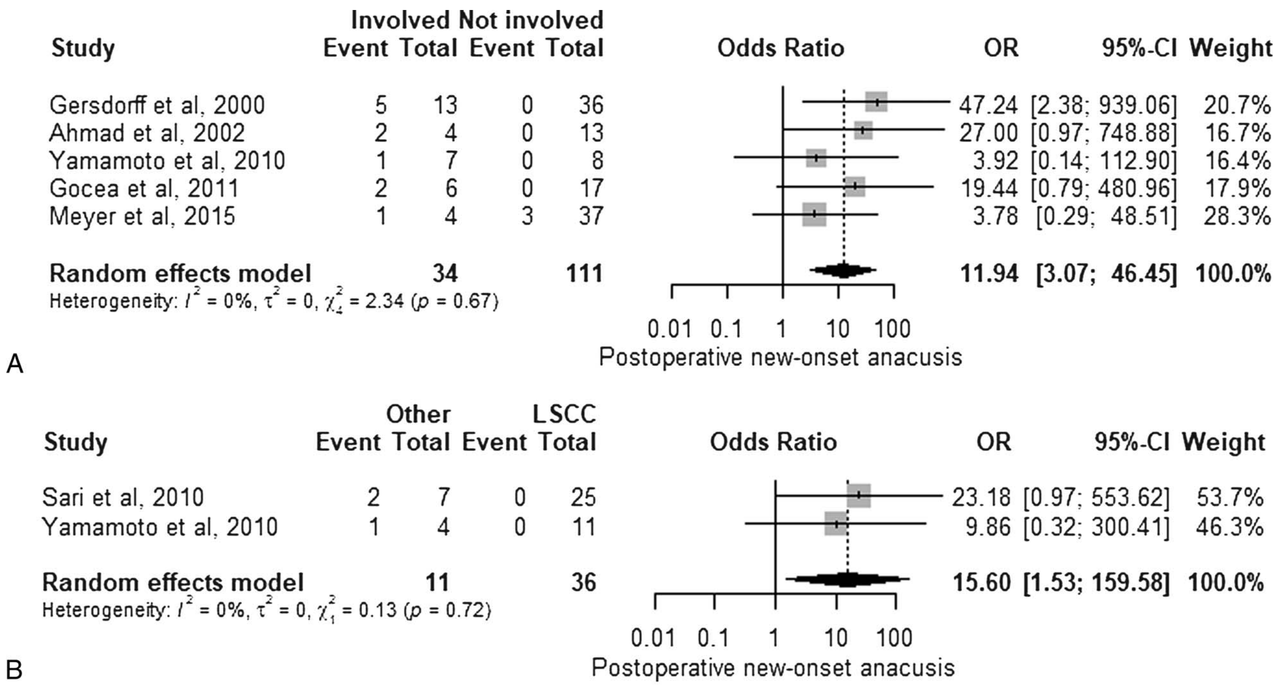

FIG. 5. Forest plots reporting OR estimates on postoperative new-onset anacusis according to (*A*) extension to membranous labyrinth and (*B*) exclusive LSCC involvement. No publication bias was found at funnel plot inspection (supplementary material, http://links.lww.com/MAO/B515).

(Dornhoffer type I versus IIa). Other fistula-related factors that were associated with higher chances of postoperative hearing preservation were exclusive LSCC involvement (OR, 3.52; 95% CI, 1.32–9.38), and smaller size, either when categorized according to the cutoff of 2 (OR, 3.03; 95% CI, 1.24–7.40) or 3 mm (OR, 6.15; 95% CI, 1.47–25.68; Fig. 4A–C). The negative effect of membranous (OR, 11.94; 95% CI, 3.07–46.45) and non-LSCC involvement (OR, 15.60; 95% CI, 1.53–159.58) was also confirmed by the significantly higher probability of new-onset postoperative anacusis (Fig. 5, A and B).

The surgical management of LF has seen much controversy over the years. The type of mastoidectomy and the most appropriate approach to the matrix overlying the fistula have long been debated to find the ideal balance between surgical radicality and hearing preservation.

For what concerns mastoidectomy, CWD and canal wall up (CWU) mastoidectomy may offer different advantages, with the former guaranteeing better control in case of residual disease (17),and the latter offering superior protection to the exposed labyrinth (5,50–52). In the series included, CWD mastoidectomy was the most common approach; however, nowadays, most authors agree that the decision on preservation of posterior canal wall should not depend on the presence of LF, but should be based on multiple variables, including hearing status, comorbidities, surgical history, cholesteatoma extension, and other complications (7,24,32,38,41,44).

Regarding the management of the matrix overlying the LF, different strategies have been proposed, mostly distinguished into conservative approaches, aimed at matrix preservation, and radical approaches, aimed at complete matrix removal. In case of superficial erosion of the LSCC dome with intact endosteum (“blue line”) or in case of advanced membranous destruction, the surgical decision seems to be straightforward. Delicate matrix peeling without violation of the endosteum for the former and radical surgery with no chance of hearing restoration for the latter have typically been pursued. On the contrary, management of bony fistulae (i.e., erosion of endosteum but without membranous involvement) is far more challenging. On one hand, a conservative approach, leaving the cholesteatoma matrix overlying the fistula, may prevent sensorineural hearing loss secondary to labyrinth exposure (3,4,52–55). Dornhoffer and Milewski (6) highlighted the relevance of perilymphatic integrity on auditory outcome by further categorizing type II as type IIa, an opened but undisturbed perilymphatic space, and type IIb, an opened perilymphatic space in which the perilymph was disturbed by active suctioning before recognition of the fistula or ingrowth of cholesteatoma. On the other hand, many authors, with either multiple (1,50) or single surgical procedures (52,55–57), have advocated complete removal of the matrix not only to obtain a dry ear through disease eradication but also to prevent further enlargement of the bony fistula and its extension to the membranous labyrinth secondary to the action of matrix collagenase, as well as related complications (e.g., suppurative labyrinthitis).

In the studies included, matrix removal was generally performed at the end of the surgical procedure through gentle peeling from the labyrinth and sealed immediately thereafter with a wide variety of materials, primarily fascia with or without bone pate, chips, or cartilage fragments. In one study (7), better auditory outcomes were found when the “sandwich technique" (interposition of fascia–bone pate–fascia) was used. Basu and Hamilton (8) described an alternative approach for matrix removal using a modified laser technique that denatures cholesteatoma epithelium without disrupting over the fistula with good auditory outcomes.

Regardless of the technique adopted, the authors of the studies included mostly considered removal of the cholesteatoma epithelium and repair of the fistula in a single procedure to be safe and effective. However, a conservative approach may still be considered whenever matrix removal may result in a high risk of iatrogenic deafness in a hearing ear. In the current meta-analysis, two LF features were associated with the highest risk of iatrogenic deafness, namely, non-LSCC and membranous labyrinth involvement. In these cases, a conservative approach toward the matrix after CWD mastoidectomy may be considered, allowing preservation of labyrinth integrity and easy accessibility for follow-up. However, surgeons must consider that these patients may still experience dizziness after surgery because of the exposed labyrinth in the exteriorized mastoid cavity, and hearing deterioration is likely in the long term because of matrix collagenase activity.

Whenever matrix removal is performed, corticosteroids should be administered, and significantly better auditory outcomes (OR, 7.87; 95% CI, 2.34–26.42) were found with i.v. steroid infusion 15 to 20 minutes before matrix removal and in the first days after surgery (Fig. 4D) (7,10,11). The possible explanation for the protective role exerted by steroids may be the multifactorial origin of sensorineural hearing loss associated with COM, which is related not only to mechanical trauma but also to chemical stress. Penetration into the labyrinth of exogenous noxious substances such as bacterial toxins or endogenous inflammatory mediators that may be present in middle ear effusions may, in fact, cause irreversible damage to cochlear hair cells (58–64). In this light, steroid infusion before matrix removal and in the first 2 days after surgery may be useful to prevent sensorineural hearing loss secondary to intralabyrinthine penetration of inflammatory mediators. In addition, continuous intraoperative irrigation with a saline mixture of corticosteroids (prednisolone) and antibiotics (cefuroxime) during matrix removal ("underwater technique") has been shown to be helpful in reducing perilymphatic leakage and further preventing inflammatory changes within the labyrinth spaces, as reported by Thangavelu et al. (9).

Finally, regarding long-term auditory outcomes after complete matrix removal, Katsura et al. (35) reported auditory performance after 5 years of follow-up and found that BC gradually deteriorates in the 1- to 2-kHz range over time. To explain this result, the authors suggest a potentially detrimental effect of chronic inflammation on cochlear hair cells not only through the LF but also through the round window membrane in the long-term despite surgery.

CONCLUSIONS

LF is a relatively common complication (7%) of COM with cholesteatoma. In the past two decades, complete removal of the cholesteatoma matrix and sealing of the defect have been favored. A wide variety of techniques and materials have been described, but most authors generally agree on the safety and efficacy of this approach, which is supported by satisfactory auditory outcomes. BC preservation is achieved in most patients (81%), but surgeons should be aware that it depends primarily on nonmodifiable, fistula-related features, namely, sparing the perilymphatic space (OR, 4.67) and membranous labyrinth (OR, 4.56), exclusive LSCC involvement (OR, 3.52), and smaller size (<2 mm: OR, 3.03; <3 mm: OR, 6.15). Membranous involvement (OR, 11.94) and non-LSCC fistulae (OR, 15.60) carry the highest risk of iatrogenic anacusis. Nonetheless, specific surgical strategies significantly influence auditory outcomes. Early intraoperative recognition, gentle matrix removal followed by immediate sealing at the end of surgery, and intraoperative and postoperative i.v. steroids infusion are recommended.

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