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IMPROVING THE SUCCESS IN SURGERY OF CHRONIC MIDDLE EAR DISEASES

Ph.D. Thesis

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"The improvement of understanding is for two ends: first, our own increase of knowledge; secondly, to enable us to deliver that knowledge to others."

John Lock

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1. LIST OF ABBREVIATIONS

ABG: air-bone gap

AC: air conduction

AOM: acute otitis media

BC: bone conduction

CI: confidence interval

COM: chronic otitis media

CWD: canal wall down

CWR: canal wall reconstruction

CWU: canal wall up

DP: proton density

DWI: diffusion-weighted imaging

EAONO/JOS: European Academy of Otology and Neurotology/ Japanese Otological Society

HRCT: high-resolution computed tomography

MRI: magnetic resonance imaging

Non-EPI: non-echo planar

OR: odds ratio

QUIPS: Quality in Prognostic Studies

ROB: risk of bias

ROBINS-I: Risk of Bias in Non-randomised Studies of Interventions

TMP: tympanic membrane perforation

WHO: World Health Organisation

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2. STUDENT PROFILE

2.1 Vision and mission statement, specific goals

My vision is for clinicians to use the most effective therapeutic options in the field of middle ear surgery. Ultimately, my goal is to enhance the quality of life for patients through superior surgical care and advanced therapeutic solutions.

Furthermore, my mission is to rigorously investigate and evaluate therapeutic options in middle ear surgery to identify the most effective treatments. I am committed to conducting high-quality research that generates robust evidence to inform clinical decision-making.

I work towards creating high level of evidence that supports best practices and elevates the standard of care in middle ear surgery.

2.2 Scientometrics

Number of all publications: 6 With impact factor: 5 Without impact factor: 1
Cumulative IF: 11.5
Av IF/publication: 2.3
Ranking (Sci Mago): D1: 1, Q1: 3, Q4:1
Number of publications related to the subject of the thesis:2
Cumulative IF: 4.1
Av IF/publication: 2.05
Ranking (Sci Mago): D1: 1, Q1:1
Number of citations on Google Scholar: 32
Number of citations on MTMT (independent):26
H-index: 3

The detailed bibliography of the student can be found on page 65- 66.

2.3 Future plans

I would like to continue the scientific and medical work in the field of middle ear surgery and provide more high-quality evidence to help clinical decision-making. Pursuing research and clinical work aligns with my dedication to advancing healthcare and improving patient outcomes. Through research, I am able to explore and uncover new insights, enhancing our understanding of complex medical conditions and identifying innovative treatment options. I hope my future work will contribute to evidence-based practices that can shape future healthcare standards. On the clinical side, working directly with patients allows me to apply this knowledge in real-time, witnessing firsthand the impact of research-driven approaches on individual lives. The combination of research and clinical practice offers a balanced perspective that keeps me grounded in theory and practical application, ultimately enabling me to make a meaningful contribution to the medical field.

3. SUMMARY OF THE PH.D.

In middle ear surgery, there is a risk of recidivism; therefore, it is important to choose the most effective surgical method, either in cholesteatoma surgery or tympanic membrane reconstruction.

The factors of the tympanic membrane reconstruction have been studied systematically, but multiple factors could still influence the success rate. Extending our knowledge for more precise patient education and surgical management is important. Therefore, we examined the potential factors of myringoplasty and type-I tympanoplasties by conducting a meta-analysis and systematic review.

Moreover, we built a meta-analysis and systematic review study to analyse the outcome of the mastoid obliteration technique compared to the canal wall up (CWU) surgery to reveal the true potential of reducing recidivism of this more and more favoured technique.

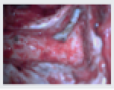
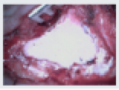
Our analysis identified four predictive factors of tympanic membrane grafting: age of the patients, size of the perforation, condition of the contralateral ear and the surgeon's experience. Regarding mastoid obliteration, our results showed that the odds of pooled residual and recurrent disease proportion were reduced in the obliteration group compared to CWU without any difference between the quality of life and hearing outcomes in qualitative analyses. Although both systematic studies we created included mostly retrospective studies without individual patient data. As a result, we could not make multivariate statistics in terms of predictive factors or high-evidence recommendations about cholesteatoma surgery.

By conducting our meta-analysis studies, we are one step closer to increasing the success rate and creating a more effective healthcare system for patients. However, there is still a need to investigate more extensively these questions. Mastoid obliteration could reduce the risk of recidivism, although high-quality prospective trials are missing. The success of tympanic membrane grafting is influenced by many factors; for a more precise understanding, further comprehensive studies are needed to analyse the interaction between factors.

4. GRAPHICAL ABSTRACT

IMPROVING THE SUCCESS IN SURGERY OF CHRONIC MIDDLE EAR DISEASES

Our focus is on how to integrate our current knowledge about middle ear surgery and increase the success of the surgical outcome after cholesteatoma surgery and tympanic membrane grafting.

Title	**Study I:** Mastoid Obliteration Decreases the Recurrent and Residual Disease: Systematic Review and Meta-analysis	**Study II:** Factors influencing successful reconstruction of tympanic membrane perforations: a systematic review and meta-analysis
Publication	Illés et al., 2022, The Laryngoscope	Illés et al., 2023, European Archives of Oto-Rhino-Laryngology
Comparism	CWU vs. (CWU or CWD or CWR+ mastoid obliteration)  ⇆ 	Success rate without individual potential factor VS Success rate with individual potential factor
Results	**Recidivism** OR: 0.45 [0.26;0.80] p:0.014	**Identified factors:** Patients' age OR:0.62 [0.50;0.78]; Perforation's size OR:0.52 [0.29;0.94]; Diseased opposite ear OR:0.32 [0.12;0.85]; Surgeon's experience OR:0.42 [0.26;0.67]
	In the mastoid obliteration group, the proportion of recidivism significantly decreased	

Implication: Applying mastoid obliteration could reduce recidive cholesteatoma and provide a disease-free life for more patients. Knowing the predictive factors of middle ear surgeries helps inform patients and helps make decisions.

5. INTRODUCTION

5.1 Overview of the topic

5.1.1 What is the topic?

Our focus is on integrating our current knowledge about middle ear surgery and increasing the success of surgical outcomes after cholesteatoma surgery and tympanic membrane grafting.

5.1.2 What is the problem to solve?

There is a debate in the field of middle ear surgery about which surgical method should be used. Since there are no guidelines, the surgical method is chosen based on the surgeon's experience and the extent of the middle ear disease. Our aim was to integrate the knowledge by creating a meta-analysis and retrospective analysis of our database to find out how to develop everyday practice.

5.1.3 What is the importance of the topic?

Cholesteatoma is one of the most dangerous middle ear diseases; it could lead to severe complications without treatment. Due to hearing loss and recurrent discharge, the tympanic membrane perforation could also negatively affect the patient's quality of life. Both problems can only be solved by surgery. The major aim of the operation is to eradicate the disease; however, there is a risk of recidivism; thus, applying the right surgical method is essential.

5.1.4 What would be the impact of our research results?

Increasing the success rate in the field of middle ear surgery by applying the scientifically proven best care could reduce the number of reoperations, and knowing the predictors of the success could lead to more precise patient education and tailored surgical techniques.

5.2 Middle ear diseases

5.2.1 Burden of chronic middle ear diseases

There are a variety of middle ear diseases, such as acute suppurative or non-suppurative otitis media (AOM), myringitis, and chronic otitis media (COM) with or without cholesteatoma. According to a prevalence survey by WHO in 2004, 65–330 million people are affected with COM and draining ears, and 60% have significant hearing impairment (1). One of the most dangerous forms of COM is presented with cholesteatoma disease. Without treatment, it can lead to severe complications and even death. The prevalence of cholesteatoma among adults is 9-12,6/ 100.000, and in children 3-15 /100.000 (2-6).

5.2.2 Cholesteatoma disease

There are many categorizations and classifications of the cholesteatoma. In this thesis, the European Academy of Otology and Neurotology/ Japanese Otological Society

(EAONO/JOS) Joint Consensus Statements on the Definitions, Classification and Staging of Middle Ear Cholesteatoma is used for interpretation(7).

The cholesteatoma is a keratinizing squamous epithelium growing in the middle ear spaces; while it grows, it could destroy the surrounding anatomical structures; in some cases, it can cause several intra and extracranial complications. The EAONO/JOS statement classifies it into two major categories: congenital and acquired(7).

Congenital cholesteatoma typically appears as a whitish, pearl-like mass located behind an intact eardrum, with no prior history of otorrhea or ear surgeries(7).

The acquired cholesteatoma can be further subclassified based on whether it resulted from a retraction pocket or not, or the location (pars tensa, pars flaccida)(7). The most common type of cholesteatoma is the acquired, retraction pocket-based form.

The pathogenesis of cholesteatoma has not been fully understood yet. No proven theory exists; however, there are several concepts. The invagination, immigration, squamous metaplasia, and basal cell hyperplasia are the most widely discussed theories(8).

According to the invagination theory, due to the negative middle ear pressure caused by eustachian tube dysfunction, recurrent inflammation or small middle ear space, a retraction pocket develops from the tympanic membrane, keratinizing squamous epithelium accumulates in it and creates ingrown toward the middle ear cavity(9-11). Immigration theory hypothesises that the squamous epithelium turns into the middle ear cavity on the edges of a tympanic membrane perforation(12, 13). The squamous metaplasia theory assumes the middle ear mucosa can metaplastically transform to squamous epithel and create cholesteatoma(14). This transformation was observed in animal models(15, 16), but no human experimental evidence exists. According to the basal cell hyperplasia, the basal keratinocytes migrate to the basement membrane, creating pseudopodia into the subepithelial space, which can develop into cholesteatoma. In 2015, a new and complex theory was introduced by R. K. Jacker and colleagues called mucosal traction theory(17). According to this hypothesis, the mucosal layer migrates on the ossicles, and due to the mucosal traction, the tympanic membrane follows it. The mucociliary clearance has a major role in increasing the tympanic membrane ingrown. The second phase of this theory is the inflammatory reaction due to proinflammatory mucosal elements being trapped and initiating keratinocyte proliferation. The third phase is very similar to the retraction theory, and keratin accumulates behind a narrowed opening that creates an expansive force(17). Three years later, evidence was published against this theory, proving the ciliated cells are mostly in the hypotympanum and around the Eustachian tube opening(18).

However, no theory has been accepted or proved; some authors believe a combination of these might be the real answer to the cholesteatoma pathogenies.

The diagnosis of the cholesteatoma could be made by examination of the tympanic membrane, particularly the pars flaccida, with a microscope or endoscope. In questionable cases, especially in already operated ears, or when the microscopic findings make it difficult to diagnose, imaging techniques could help.

Magnetic resonance imaging (MRI) techniques have been developed in the last decades, and diffusion-weighted imaging (DWI) and proton density (DP) methods have become more specific to cholesteatoma, making it possible to diagnose or follow up without second-stage surgery. However, MRI has its own limit; the minimum size of the cholesteatoma that can be recognized with the most sensitive modality, non-echo planar (Non-EPI) DWI, is 3 mm(19, 20).

High-resolution computer tomography (HRCT) imaging is an indispensable technique; however, it is less specific for cholesteatoma compared to targeted MRI imaging. HRCT is the most important tool for surgical planning, clearly showing the bony structures, detecting anatomical variations (sigmoid sinus and jugular bulb alterations, location of the middle scala dura), potential complications, and assessing the ossicular chain integrity; therefore, it became mandatory examination before cholesteatoma surgery (21, 22).

5.2.3 Tympanic membrane perforations

The causes of tympanic membrane perforations (TMP) are various; it can be caused by trauma (barotrauma, injury), infection, or it can be iatrogenic (previous ear operation, tube insertion). TMP is one of the most common ear diseases; the prevalence among the US population based on census data is 2.1 % (23). In a German study, chronic tympanic membrane perforation was found in 8 people from 1000 population (24).

Acute TMP has a good healing potential; in general practice, the surgery is offered at least after 3 months of follow-up. However, chronic TMP could lead to deterioration of quality of life due to conductive hearing loss, otorrhea, and the constant need to keep water away from the external ear canal. The treatment of TMP in case of chronic disease is surgical.

Many predictive factors that influence the success of the tympanic membrane closure have been suggested in the scientific literature. Three meta-analyses have been published regarding these predictive factors. However, two of them investigated only the pediatric population, while the one published in 2016 investigated both adult and pediatric populations. Since then, several new studies have been performed, investigating even more potential factors with more intention to follow the modern rules of outcome reporting. Identifying the real factors that have an impact on success is essential for many reasons: it results in more precise patient education by informing patients of the expected results, it can affect preoperative patient care, and it helps in selecting the proper surgical approach.

5.2.4 Treatment options for middle ear diseases

For the cholesteatoma and the persistent tympanic membrane perforations, the only treatment is surgical up to now. There are many different available surgical techniques for both middle ear problems. The choice of the technique is based on the extent of the disease, the surgeon's experience and preferences due to the lack of guidelines and studies with a high level of evidence.

There are several methods known to repair a perforated tympanic membrane such as transcanal, endaural, or retroauricular techniques, it can be done with the use of a microscope or endoscope, and the graft material (fascia, perichondrium, cartilage, fat, etc.), and its position relative to the tympanic membrane (underlay, inlay, or overlay) are variable as well (25-27). The success of the tympanic membrane grafting varies between 60 to 90% in the literature. It depends on many factors, such as surgical types or patient-related factors(28, 29).

In traditional cholesteatoma surgery, two major surgical approaches are commonly used. The canal wall up (CWU) approach is a functional technique that preserves the posterior wall of the outer ear canal during surgery(30). This method allows the surgeon to restore a functional middle ear within the original dimensions of the tympanic cavity, without altering the shape or entrance of the outer ear canal. However, the intact posterior wall limits the surgeon's ability to control the cholesteatoma during the procedure, and any residual disease may be hidden in the mastoid cavity, potentially leading to recurrence.

The canal wall down (CWD) approach, on the other hand, often results in an open cavity. During this procedure, the posterior wall of the ear canal is removed, creating a common cavity between the outer ear canal and the mastoid. This approach provides better intraoperative control of the tympanic cavity and simplifies postoperative follow-up by allowing direct visualization of the mastoid area. However, it has several drawbacks, such as frequent cleaning, water avoidance, cosmetic concerns, recurrent infections, and potential difficulties fitting hearing aid (31-33).

The original main purpose of mastoid obliteration was to reduce the exteriorised cavity's size after canal wall down and radical mastoidectomies, therefore decreasing the chance of developing troublesome cavities with recurrent discharge and minimizing cosmetic issues related to the surgery (34-36). Later, it also began to be applied during CWU tympanoplasty to reduce the possibility of mastoidal recidivism while maintaining the posterior wall of the ear canal. It has been claimed that if the mastoid cavity is obliterated at the end of the surgery, the risk of developing a recurrent cholesteatoma is reduced. Besides this, obliteration helps reconstruct the posterior wall of the ear canal in CWD surgery; hence, it has been named the canal wall reconstruction (CWR) technique (37) . However, the surgery is elongated when the mastoid cavity is obliterated, patients must be radiologically followed postoperatively, and reoperations can sometimes be challenging (38, 39).

6. OBJECTIVES

6.1 I. Study- Mastoid Obliteration Decrease the Recurrent and Residual Disease: Systematic Review and Meta-analysis

The aim of cholesteatoma surgery is the complete eradication of the disease. However, the residual rates can be 5-35 % depending on the surgical technique, patient age and cholesteatoma extension (40-42). The mastoid obliteration technique was invented to reduce the size of the drilled mastoid bowl and prevent disadvantages such as recurrent discharge and infection of the ear after canal wall down mastoidectomy (34). It has been hypothesised that this could also reduce the recurrent and residual disease rate (43, 44). Our systematic review and meta-analysis aimed to evaluate the effectiveness of mastoid obliteration, to summarize the knowledge from the published comparative studies to assess the effectiveness of mastoid obliteration compared to the CWU technique.

6.2 II. Study- Factors influencing successful reconstruction of tympanic membrane perforations: a systematic review and meta-analysis

One of the most common mesotympanic type ear diseases is the perforation of the eardrum (1). The treatment of the residual perforation is surgical, and its success rate depends on many personal and external factors besides the surgical technique (25, 26). To provide adequate and precise patient information, it is necessary to know what these factors are and how they affect the success rate of the surgical procedure. Uncovering the most important factors also helps to choose the appropriate surgical technique.

The reason behind focusing on the patient-related factors is that the surgical approach is the choice of the surgeon, while patient-related factors are given. Furthermore, the predictive factors are, by definition, the characteristics of the patient that affect a particular treatment. Evaluating and comparing a surgical technique requires different scientific questions and approaches.

Our study aimed to provide comprehensive and more accurate information about prediction of tympanic membrane reconstruction without evaluating the approaches, including all the new studies, and focus on patient-related factors based on a systematic review and meta-analysis.

7. METHODS

The Cochrane Handbook recommendations and PRISMA 2020 updated guideline for reporting systematic review were followed during the first and second study process (45, 46). The PICO framework was applied to create the study protocols registered on Prospero (registration number I. Study: CRD42021282485, II. Study: registration number: CRD42021289240). The II. Study included a pilot period of recurring studies, which resulted in a minor addition to the exclusion criteria; the experimental studies were excluded.

7.1 Eligibility Criteria

Both studies had strict and rigorous inclusion criteria, which are detailed below. Both meta-analyses included only English language studies with at least 12 months follow-up time and excluded animal studies, literature reviews, meta-analyses, and guidelines.

7.1.1 I. Study- Mastoid Obliteration Decrease the Recurrent and Residual Disease: Systematic Review and Meta-analysis

All the studies that reported on the outcomes of mastoid obliteration in CWU tympanoplasties or CWD with the reconstruction of the posterior wall were compared with CWU without obliteration were included in the I. Study. There was no restriction to age or sex and material of the mastoid obliteration, such as autologous bone dust, any synthetic material, cartilage, muscle, muscle flap, or a combination of any of these if the surgical description was well-designed and clear. Exclusion criteria were congenital cholesteatoma, the follow-up period of less than 12 months, unclear descriptions of surgical methods, and animal studies. Our first meta-analyses concentrated on the effect of mastoid obliteration directly after the CWD, CWU, or CWR technique compared to the CWU approach (38).

Primary outcomes were the proportion of recidivism and recurrent and residual cholesteatoma rates; secondary outcomes were quality of life, hearing results, infection rates, operation time, and the ear discharge rate. The European Academy of Otology and

Neurotology/Japanese Otological Society (EAONO/JOS) Joint Consensus Statements were used for cholesteatoma decisions(7).

7.1.2 II. Study: Factors influencing successful reconstruction of tympanic membrane perforations: a systematic review and meta-analysis

Observational studies that reported the predictive factors of type-I tympanoplasty or myringoplasty without age or sex restrictions were included. The cases with cholesteatoma, non-type-I tympanoplasty, a combined procedure with cortical mastoidectomy or ossiculoplasty, patients with specific inflammatory diseases (e.g., tuberculosis and SLE) or with previous irradiation on the temporal bone were excluded. Primary outcome was the success rate of the above-mentioned procedures; the secondary outcome was the hearing measured according to the statement of Committee on Hearing and Equilibrium guidelines (4 frequencies 0.5 kHz, 1 kHz, 2kHZ and 3 kHz, or alternatively, the 3 kHz was replaced with the average of 2 kHz and 4 kHz) (47, 48).

7.2 Information sources and search strategy

Four databases were screened in the I. Study (MEDLINE, Web of Science, EMBASE, and CENTRAL) on October 14, 2021, and three in the II. Study (CENTRAL, EMBASE, and MEDLINE) on November 24, 2021. No filter or restriction was used during the search. The included studies' references were reviewed in both meta-analyses.

The I Study’s search key was: *cholesteatoma OR cholesteatomas OR mastoidectomy OR “canal wall up” OR CWU OR CWUM OR “intact canal wall” OR (ICW OR ICWM) AND (obliteration OR “canal wall reconstruction” OR CWR OR BOT OR “bone pâté” OR autologous OR synthetic OR cartilage OR bioglass OR “osteoplastic flap” OR muscle OR silicon OR hydroxyapatite OR fascia.*

The II. Study’s search key was *myringoplasty OR tympanoplasty*.

7.3 Selection process and data collection

Two independent reviewers (Kata Illés, Fanni Adél Meznerics) completed the selection process in the first and three independent reviewers (Kata Illés, Gergő Dorottya, Fanni Adél Meznerics) in the II. Study after the duplicates were removed. In the case of the second II. Study, a pilot test was performed to refine and clarify the eligibility criteria and train the reviewers. Both times a management program (EndNote X9, Clarivate Analytics, Philadelphia, PA, USA) was used. Disagreement after the title and abstract selection were resolved by the third reviewer (Tamás Horváth) in the I. Study and by discussion in the II. Study. The full-text selection was made in the same manner. There was no disagreement during the full-text selection in the I. Study. The II. Study's disagreement after the full-text selection was resolved by fourth reviewer (Tamás Horváth).

Inter-rater reliability was tested after the title, abstract selection, and full-text selection in both meta-analyses with Cohen's kappa calculations.

Data were collected by two independent authors (I Study: Kata Illés and Gergő Dorottya, II Study: Kata Illés and Fanni Adél Meznerics).

Predefined Microsoft Excel datasheet (Microsoft Corporation, Redmond, Washington, United States) was used in all their studies.

The following data were collected in the I. Study: the first author, year of publication, country of origin, study design, basic demographic characteristics (female percentage, age, number of patients), follow-up period, bivariate data of the residual and recurrent disease, and if it was possible, the data of the secondary outcomes (quality of life, hearing results, complication rates, and rate of discharge of the ear) were also extracted. All included patients' surgical data from one ear was registered once; a patient could appear in the analysis twice if there was a bilateral surgery.

We collected the following data from the eligible articles in the II. Study: the first author, year of publication, country of origin, study design, basic demographic characteristics (female percentage, age, number of patients), follow-up period, type of surgical procedure, and success rate of the patient groups with or without predictive factors, and if it was possible the hearing outcomes (ABG: air-bone gap, AC: air conduction) as well.

7.4 Risk of Bias Assessment for Meta-analyses

According to the Cochrane recommendations, the “Risk of Bias In Non-randomised Studies of Interventions” (ROBINS-I) tool (I. study) and the “Quality In Prognostic Studies” (QUIPS) tool (II. study) were applied. In both times, two independent reviewers evaluated the risk of bias (ROB) (I. Study: Kata Illés and Fanni Adél Meznerics, II. Study: Kata Illés, Zsuzsanna Keresztély). The disagreement was solved by discussion.

Contour enhanced Funnel plots were created to visualise publication bias, and the publication bias was statistically tested if more than 10 studies were involved by Harrer et al.'s recommendation (49).

7.5 Synthesis methods and statistics

The first and second studies used similar methods. The odds ratio (OR) with 95% confidence interval (CI) was used for the effect measure: the total number of patients in each group and those with the event of interest were extracted from each study to calculate the odds ratio. Raw data from the selected studies were pooled using a random effect model with the Mantel–Haenszel method and the Hartung–Knapp adjustment (50-53). To estimate τ2 we used the Paule–Mandel method (50, 54), and the Q profile method for calculating the confidence interval of τ2. A funnel plot of the logarithm of effect size and comparison with the standard error for each trial was used to evaluate publication bias. Statistical heterogeneity across trials was assessed by means of Cochrane Q test, and the I2 values(55). I2 values of 25%, 50%, and 75% were identified as low, moderate and high estimates, respectively. Outlier and influence analyses were carried out following the recommendations of Harrer et al. (2021) and Viechtbauer and Cheung (2010) (49, 56). Publication bias was assessed with Egger’s test using the Harbord method (57).

Forest plots were used to summarize the results graphically (58). Where applicable, we reported the prediction intervals (i.e., the expected range of effects of future studies) of results following the recommendations of IntHout et al (59). In the I. Study, subgroup comparisons were carried out following the description in Harrer et al. (49).

In the first and second studies, analyses were carried out using the R 4.1.3 (60, 61) using the packages “meta” (62) and “dmetar” (63).

8. RESULTS

8.1 Search and selection, characteristics of the included studies

8.1.1 I. Study: Mastoid Obliteration Decreases the Recurrent and Residual Disease: Systematic Review and Meta-analysis

The systematic search resulted in 2756 articles after the duplicates were removed. The selection process is shown in the PRISMA flowchart 2020 (see Figure 1). Cohen's kappa of the title and abstract selection was 0.91, and after the full-text selection, it was 1. No additional studies were found eligible during the reference-checking process (38). Eight studies in the quantitative (64-71) analysis and seven studies in the qualitative analysis (64, 66, 69, 70, 72-74) were included.

The baseline characteristics of the involved studies are shown in Table 1. All the included studies were retrospective cohort studies. Ten of the eleven studies were from Europe, and one study was from the USA. The age distribution among the patients was wide; five studies included their analysis of children's data, and six of them used only the adult population. The follow-up period of the included studies was 12–144 months. The number of surgeries were counted, and all surgeries were counted once. Nine original studies stated or suggested including only primary operations, whereas two studies also included patients with prior operations. The separation of the recurrency and residuum was based on clinical reports in every study. The residual cholesteatoma is a result of incomplete removal, usually presenting as an epithelial pearl independent of the tympanic membrane, whereas the recurrence is the reformation of a retraction pocket in the tympanic membrane (7, 38).

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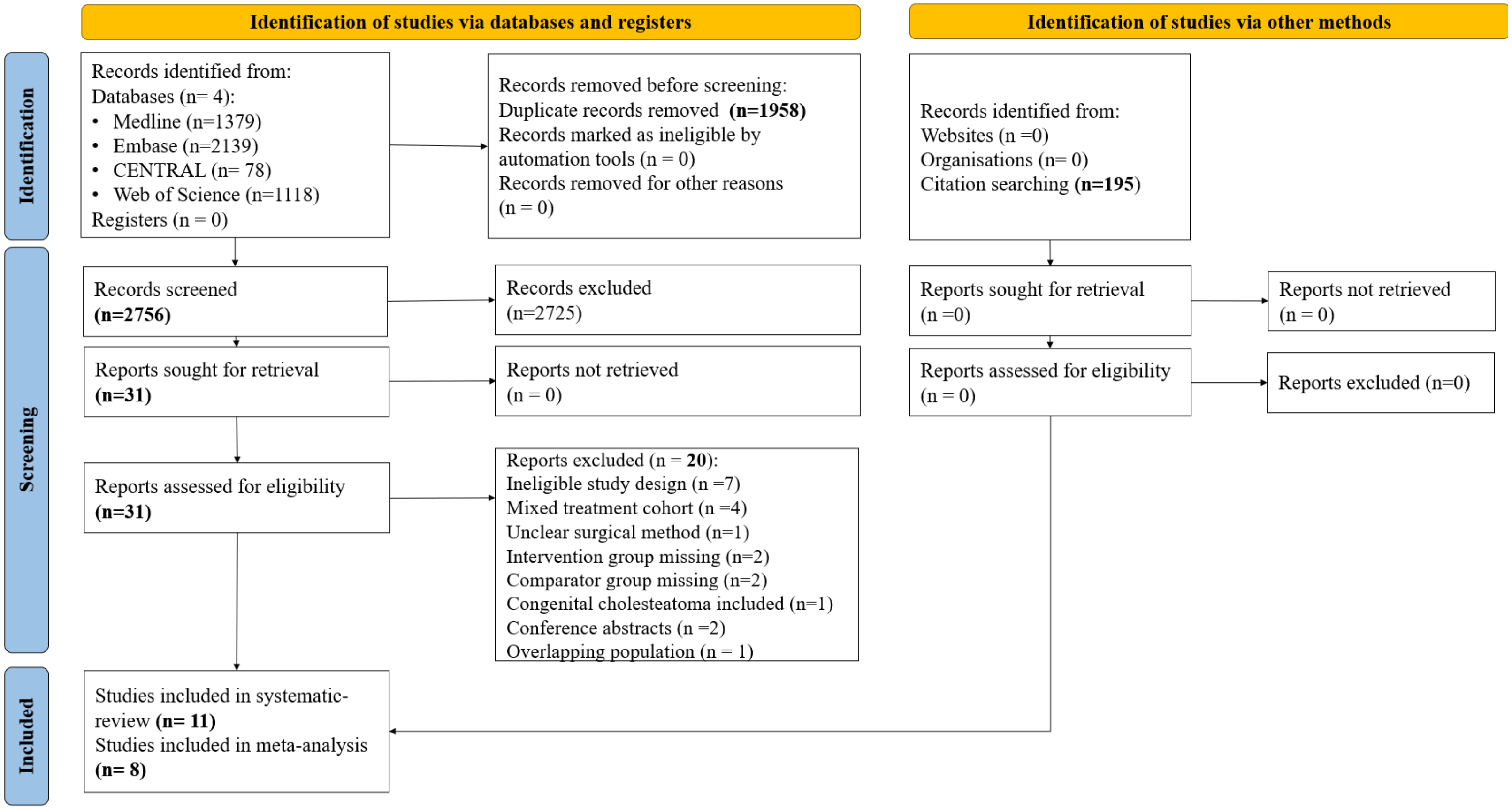

Figure 1.PRISMA 2020 flowchart of the screening and selection process of the I. Study

Table 1Characteristics of included studies of Study

First author, year of publication	Study design	Country	Patient's age at the time of the operation (year)	Total number of operated ears	Intervention	Obliteration material	Follow up Min (months)	Follow up Max (months)	Outcome	
									Meta-analysis part	Review Part
Toom, 2021	Retrospective cohort study	Nether-lands	>18	290	**Canal wall up with mastoid obliteration**	Autologous bone pate and bioactive glass	Interquartile range 16-51 5 years follow-up		Recurrent disease Residual disease	Hearing outcome Operation time Infection rate
Møller, 2019	Retrospective cohort study	Denmark	Median: 33	777	**Canal wall up with mastoid obliteration**	Hydroxyapatite granule	5 years follow up		Recurrent and residual disease	-
Rayneau, 2019	Retrospective, controlled	France	Rage: 24-63	165	Canal wall reconstruction with mastoid obliteration	MBCP and fibrin glue	18	67	Recurrent disease Residual disease	-
Wilkie, 2019	Retrospective cohort study	UK	26-82	104	Canal wall down with mastoid obliteration	Autologous bone pate	12	52	Recurrent and residual disease	Hearing outcome Ear discharge
Yung, 2001	Retrospective, controlled	UK	Median: 35 Range: 5-89	72	Canal wall down with mastoid obliteration	Hydroxyapatite granule	12	144	Residual disease	-
Nyrop, 1997	Retrospective, controlled	Denmark	Median: 28 Range: 4-77	60	**Canal wall up with mastoid obliteration**	Autologous bone pate and pedicle muscle	12	94	Recurrent disease Residual disease	Hearing outcome
Smyth, 1988	Retrospective, controlled	Ireland	21% of the control group and 35% of the intervention group were ≤16	200	Canal wall reconstruction with mastoid obliteration	Palva flap	108	120	Recurrent disease Residual disease	-
Cody, 1984	Retrospective, controlled	USA	NR	251	Canal wall down with mastoid obliteration	Pedicle muscle flap	48	72	Recurrent disease Residual disease	
Lailach, 2015	Retrospective cohort study	Germany	SD mean: 56.1 ± 14.4 Range: 9.6–82.7	97	Canal wall down with mastoid obliteration	Autologous bone pate and sliced concha cartilage plates	12.8	160.5	-	Quality of life (CES questionnaire)
Quaranta, 2014	Retrospective cohort study	Italy	Control group SD mean: 48.9 ± 14.8 Intervention group SD mean: 48.5 ± 17.2	100	Canal wall down with mastoid obliteration	Autologous bone pate, blood, and fibrin glue	24	NR	-	Quality of life (COMOT-15 questionnaire) Hearing Outcome
Toner,1990*	Retrospective, controlled	Ireland	Same as Smyth,1988	200	Canal wall reconstruction with mastoid obliteration	Palva flap	96	144	-	Hearing outcome Cavity status

*Same population with Smyth study but the reported outcome different

Abbreviations: MBCP: Biphasic calcium phosphate, CES: Chronic Ear Survey, COMOT-15: chronic otitis media outcome test 15, SD mean: Standardized mean In these studies, were children included: Møller, 2019, Nyrop, 1997, Yung, 2001, Smyth, 1988 (Toner,1990)

8.1.2 II. Study: Factors influencing successful reconstruction of tympanic membrane perforations: a systematic review and meta-analysis

The selection flowchart was made according to the PRISMA 2020 reporting guideline see Figure 2. (45) . During the systematic search, 15,573 records were found; this number decreased to 9454 after the duplicate removal. 322 original studies were identified by the reviewers at the time of the title and abstract selection. At the end of the selection, 39 studies were found eligible for inclusion (75-113). Twenty articles from the original pool could not be found. Two local university libraries were contacted for help, but their search was unsuccessful. The first author (Kata Illés) made attempted to contact the first authors of the missing articles without success. In total, 28 articles were included in the quantitative and 36 in the qualitative synthesis. The interrater reliability tests were substantial. Cohen’s kappa was 0.72 after the title and abstract selection and 0.71 after full-text selection. No additional studies were found to be eligible during the reference-checking process (48).

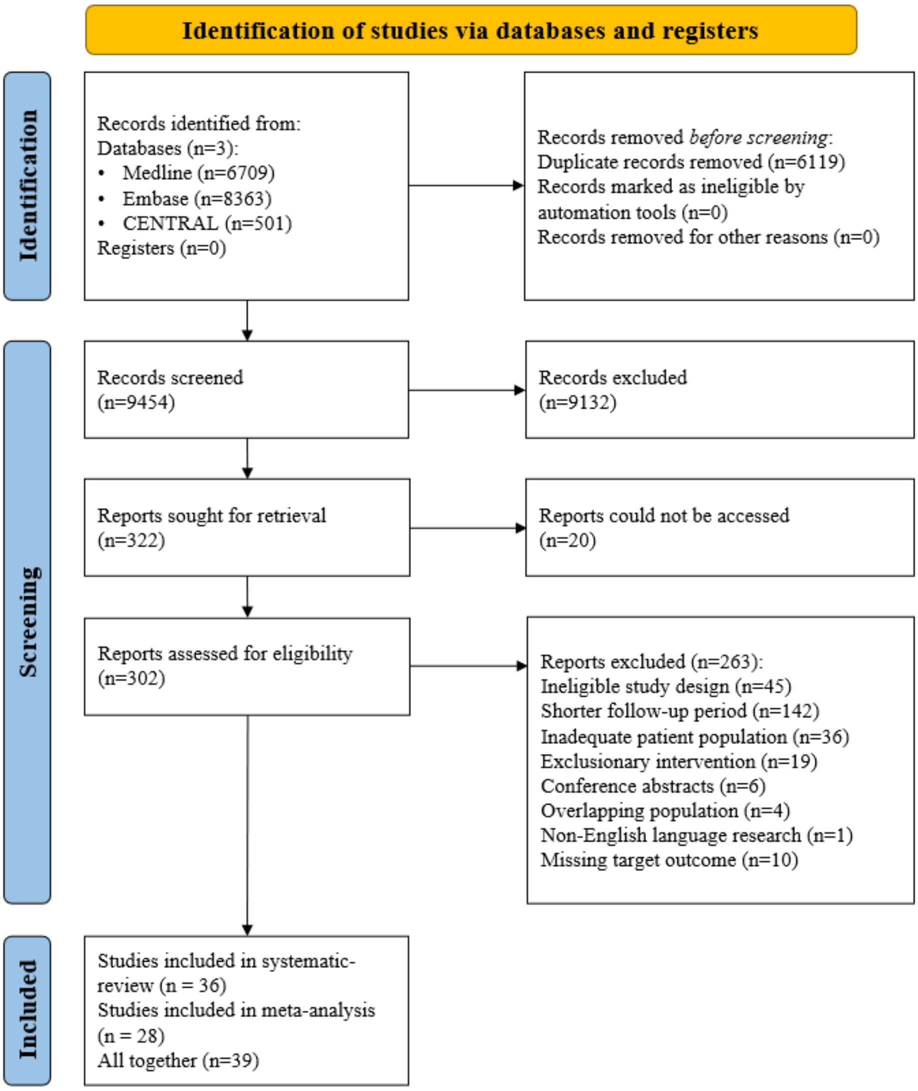

Figure 2. PRISMA 2020 flowchart representing the selection process of Study II

The characteristics of the eligible studies are detailed in Table 2.

The oldest was issued in 1970, and the latest in 2021 from the analysed studies. Three of the studies were prospective, and 36 were retrospective. The age distribution of the patients was wide, and the mean age ranged from 8.1 to 48.9 years. The most common operative technique was the underlay type-I tympanoplasty using temporal fascia graft. However, other types of surgeries were also used in several articles, see Table 2. There was no mention of using an endoscope, except the articles included fat graft tympanoplasty or paper patch tympanoplasty.

Table 2. Characteristics of included studies of Study II

Publication data First Author, Publication year	Study design	Operative technique and material	Country	Demography Age (years) Mean	Range	Sex (female % of total)	No. of patients	No. of operated ear	Follow-up period (months)
Abdelhameed,2017	Prospective	Underlay, perichondrium	Egypt	19.3	9-65	40	50	50	Min. of 12
Adkins, 1984	Retrospective	Underlay, TF	USA	25	4-67	NI	71	71	Min. of 18
Albera, 2006	Inception cohort	Modified overlay or underlay	Italy	37	3-73	58	212	212	Mean: 68
Al-Khtoum.,2009	Retrospective	Underlay, TF	Jordan	12	9-14	NI	35	35	Min. of 12
Babu, 2019	RCR	Medial or over-under, TF or perichondrium	USA	24	3-80	NI	95	95	Mean: 25.7
Bajaj, 1998	Prospective	Underlay or overlay, TF	India	NI	5-14	NI	45	45	Min. of 12
Buchwach,1980	Retrospective	Underlay, TF	USA	9	3-17	NI	74	80	Mean: 25.2
Callioglu, 2016	Retrospective	Over-underlay, TF or chondro-perichondrial island	Turkey	32.7	NI	53.7	121	121	Mean: 35.76
Caylan, 1998	Retrospective	Underlay, TF	Turkey	NI	5-16	47	51	51	Min. of 18
Dangol, 2016	Prospective	Underlay, TF	Nepal	26.14	13-62	54.8	219	219	12
Denoyelle, 1999	Retrospective	Underlay, TF	USA	10.5	4-17	43.6	188	188	Mean: 31
Emir, 2007	RCR	Underlay, TF	Turkey	27.4	7-NI	48.6	607	607	Min. of 12
Emmett, 1999	Retrospective	Underlay, perichondrium or TF	USA	NI	<19	NI	260	260	72-120
Gaslin, 2007	RCR	Cartilage interleave	USA	7.9	3-16	NI	42	42	Mean: 30.3
Gersdorff, 1995	Retrospective	Underlay, TF	Belgium	36	5-73	48	320	320	36
Gianoli, 1995	Retrospective	NI (Wullstein's type-I)	USA	8.1	2-16	55	36	36	Mean: 15.3
Gun, 2014	Retrospective	FGM	Turkey	26.4	4-97	47	172	183	12-60
Holmquist, 1970	Retrospective	NI (Wullstein's type-I.)	Sweden	NI	16-72	NI	120	124	Min. of 24
Iso-Mustajärvi,2018	Retrospective	Underlay, TF, perichondrium or FGM	Finland	33	4-78	NI	315	315	Mean: 38
Kaya, 2018	Retrospective	Over-underlay, cartilage	Turkey	12.68	9-16	50	76	76	Mean: 76.8

Knutsson, 2017	Retrospective	FGM	Norway	30.4	4-85	43	100	100	12
Lee, 2016	Retrospective	Paper patch myringoplasty	Republic of Korea	41.6	NI	52.6	114	114	Min. of 12
Li, 2020	Retrospective	Underlay, TF	China	45.92	19-68	56.6	53	53	12–24
Lou, 2021	Retrospective	Underlay, cartilage	China	48.87	NI	40	131	131	24
Migirov, 2013	Retrospective	Underlay, TF or tragal perichondrium	Israel	35.9	18-79	63	65	65	Min. of 12
Ophir, D., 1987	Retrospective	Underlay, overlay, TF	Israel	NI	5-12	43.9	155	172	Mean: 38.4
Övet, 2016	Retrospective	Overlay–Underlay, chondro-perichondrial island	Turkey	children: 9 adults: 30	children: 8-16 adult: 19-64	53	133	133	24
Podoshin,1996	Retrospective	NI (Wullstein's type-I, TF)	Israel	12	9-14	NI	51	51	24-108
Salvador, 2021	RCR	Underlay, TF	Portugal	39.7	18-69	57	155	155	Mean: 15.6
Sengupta, 1974	Retrospective	NI	India	NI	NI	NI	104	104	12-24
Shankar, 2015	Prospective	Over-underlay, TF	India	NI	15-45+	44	70	70	Mean: 14.4
Strahan,1971	Retrospective	Medial or lateral technique, TF, perichondrium, or vein	USA	NI	>10-70	38	483	483	Mean: 18.8
Takahashi-Tatsumi,2014	Retrospective	NI	Japan	children: 8.7 adult: 47.1	children: 2-16 adult: NI	46	130	130	Mean: 40.7
Tseng,2018	Retrospective	Underlay, TF, or perichondrium	Taiwan	51.7	18-86	51	181	181	Mean: 15.4
Ullah, 2008	Retrospective	Underlay or overlay,TF	Pakistan	10	8-14	44	100	100	36
Vartiainen, 1993	Retrospective	Underlay or lateral graft, TF	Finland	NI	>10-60+	NI	404	404	Mean: 66
Vartiainen, 1997	Retrospective	Underlay or lateral graft, TF	Finland	11.1	5-17	55	60	60	Min. of 60
Westerberg, 2011	RCR	Underlay, TF	Sweden	29	3-82	45.7	232	243	12-60
Yung, 2007	Retrospective observational	Underlay, TF, perichondrium, or cartilage	UK	NI	4-13	NI	54	54	12-36

No: number, **NI:** no information, **Min.**: minimum, **USA:** United States of America, **UK:** United Kingdom, **RCR**: Retrospective chart review **TF:** temporalis fascia, **FGM:** Fat graft myringoplasty

8.2 Quantitative and qualitative analyses of I. Study: Mastoid Obliteration Decrease the Recurrent and Residual Disease:Systematic Review and Meta-analysis

8.2.1 Quantitative synthesis

8.2.1.1 Disease Recidivism

Seven articles' data (64-70), along with 1847 operations, were pooled together in Figure 3. The target of statistics were the residual and recurrent disease proportions, which were reported together in two articles (65, 70) and separately in five articles (64, 66-69). According to our analysis, the proportion of recurrent and residual disease was significantly lower than in the CWU group (OR: 0.45, CI:0.26;0.8, p-value: 0.014). The between-study heterogeneity was moderate (I2: 67%, p < 0.01).

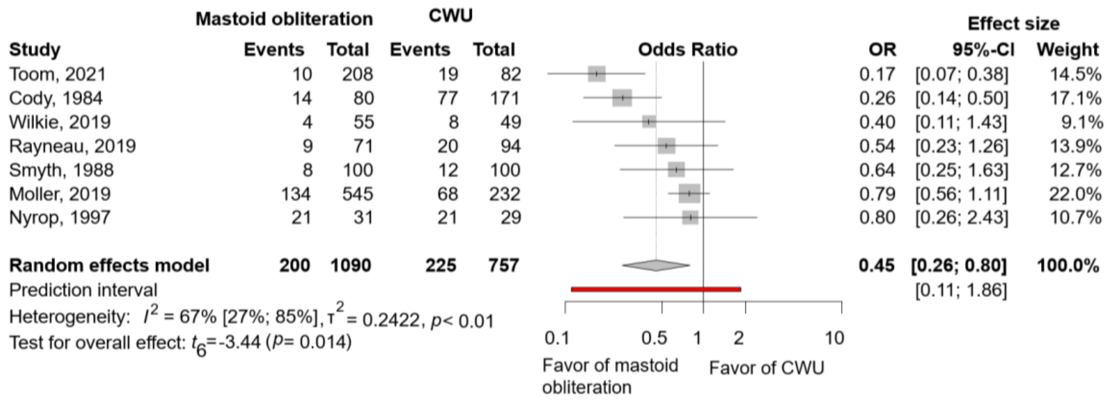

Figure 3. Forest plot representing the pooled odds ratio of recurrent and residual disease between treatment groups

8.2.1.2 Separate Analyses of Recurrent and Residual Disease Proportions

The residual disease proportion was separately disclosed in six studies (64, 66-69, 71), five of them have appeared in the previous analysis (recidivism), and one article reported data only about the residual disease (71), whereas the recurrent disease proportion was reported in the same five studies. Analyses of these outcomes are shown in Figure 4 and Figure 5.

The result of the pooled analyses of recurrent disease proportion alone showed a reduction in odds ratio compared to CWU, although it was not statistically significant (OR: 0.41 CI:0.11;1.57, p-value: 0.140) as can be seen in Figure 4. Heterogeneity among the studies was moderate (I2: 59%, p-value: 0.04) (38).

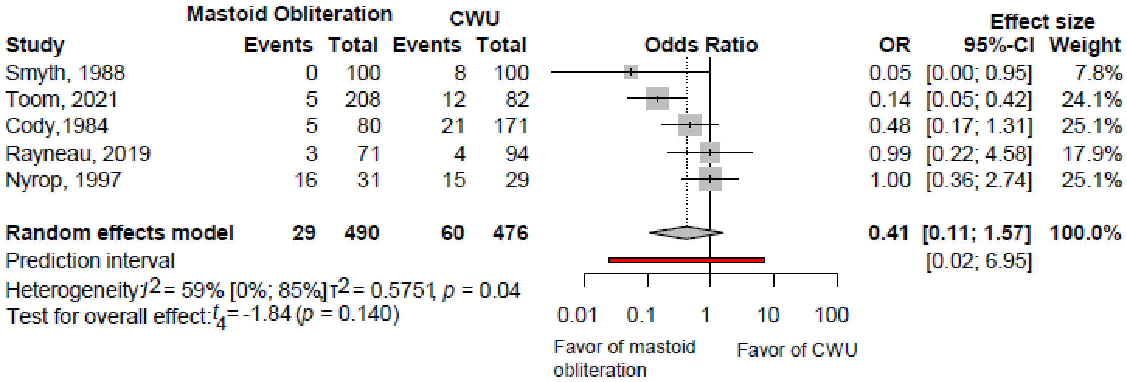

Figure 4. Forest plot depiction representing the pooled odds ratio of recurrent disease between treatment groups

We found no clear statistical confirmation that mastoid obliteration reduces the proportion of residual disease (OR: 0.59 CI:0.23,1.5, p-value: 0.207). The p-value and the wide confidence interval of the overall OR indicated that the outcome is not significant, which can be seen in Figure 5. Heterogeneity among the studies was moderate (I2: 56%, p-value: 0.05).

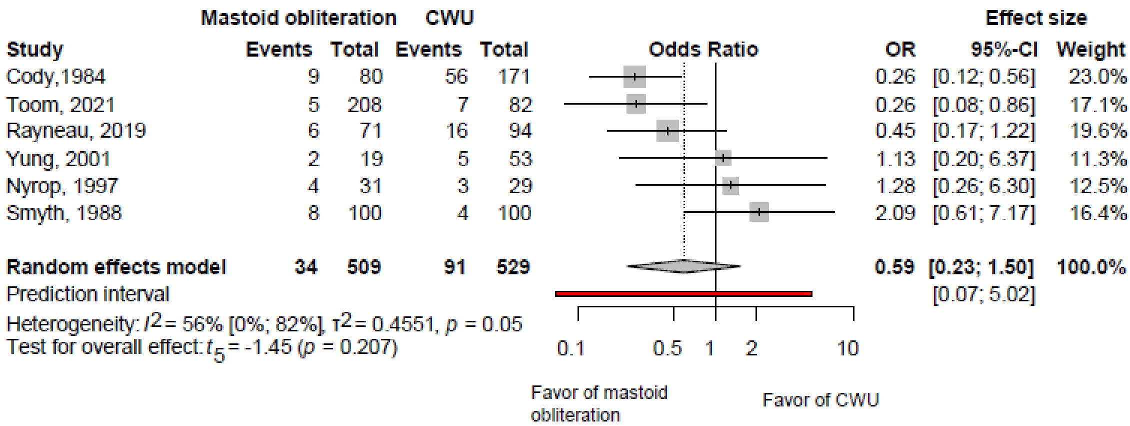

Figure 5. Forest plot depiction representing the pooled odds ratio of residual disease between treatment groups

8.2.1.3 Subgroup Analysis on Obliteration Material

A subgroup analysis was created among studies where bone or bone replacement material was used for mastoid obliteration. There were four articles eligible to do this calculation; results are given in Figure 6 (65, 67, 69, 70). The target of the measurement was the proportion of residual and recurrent disease.

The OR of the bone or bone replacement material subgroup was 0.43 (CI:0.15; 1.30) with high between-study heterogeneity (I2: 75%, p < 0.01). The pooled OR of studies that used muscle or muscle and bone for obliteration was 0.46 (CI: 0.10; 2.13) with moderate heterogeneity (I2: 52%, p-value: 0.13). No significant difference was found between the groups according to the X2 test (X2: 0.01, fd:1, p-value: 0.91).

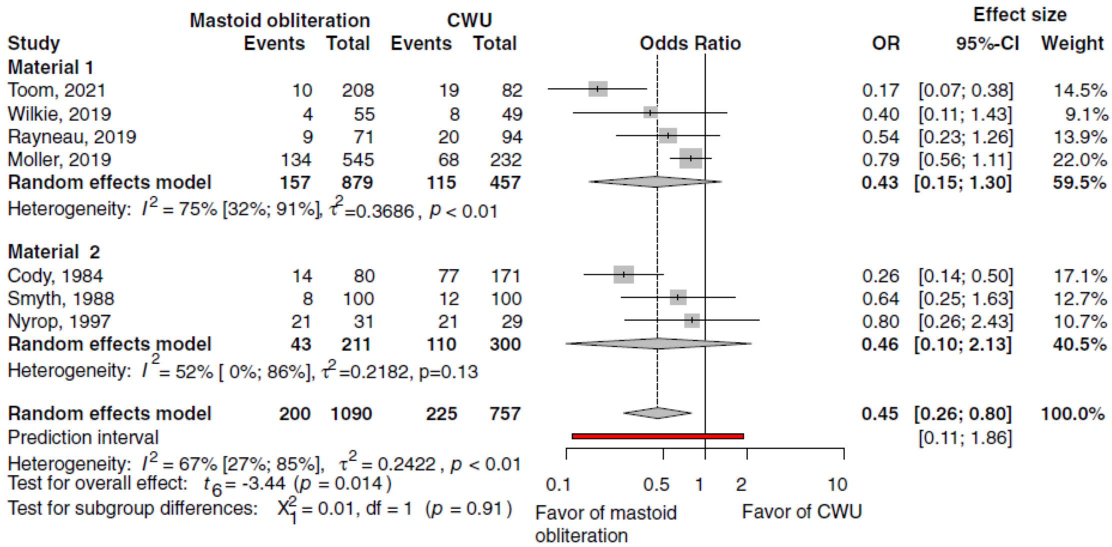

Figure 6. Forest plot for subgroup analyses on the material used for obliteration. Material 1: bone or bone replacement material; Material 2: exclusively muscle or muscle with bone

8.2.1.4 Subgroup Analysis of Technique

Studies that compared CWU without obliteration to CWU with obliteration were measured as a subgroup. Only three articles eligible for inclusion in the analysis were found (65, 66, 69). The target of the measurement was also the residual and recurrent proportion. The OR of this subgroup was 0.48 with wide CI (0.05; 4.38) and high heterogeneity (I2: 83%, p < 0.01). The other four studies compared CWU without obliteration to CWD or CWR with obliteration; the OR among this group was 0.41 with narrow CI (0.20; 0.81) and low heterogeneity (I2: 3%, p-value: 0.38). There was no significant intergroup difference (X2: 0.08, df: 1, p-value: 0.77) according to data in Figure 7.

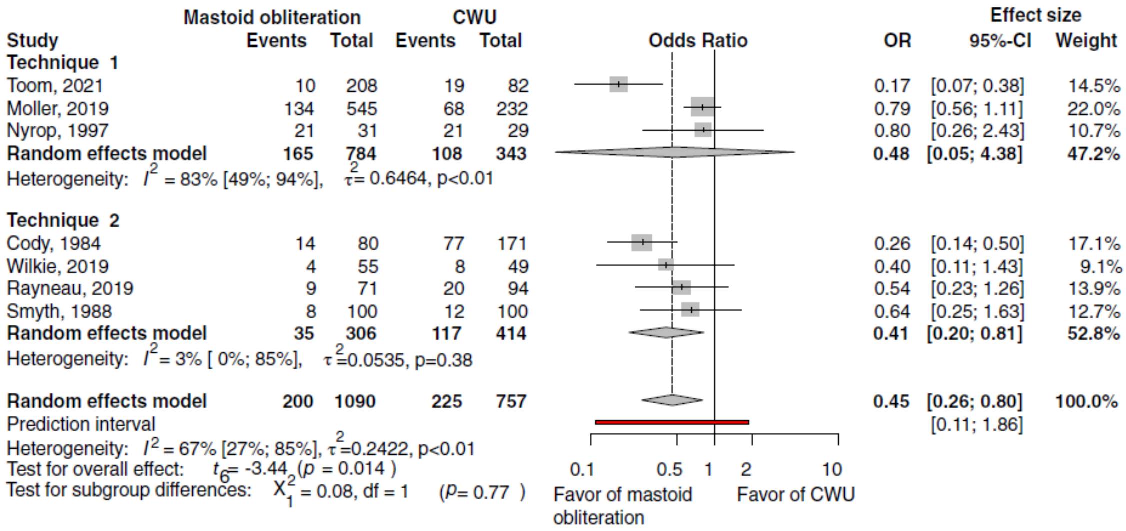

Figure 7. Forest plot for subgroup analyses on surgical technique. Technique 1: Canal wall up (CWU) + obliteration; Technique 2: Canal wall down (CWD) + obliteration or Canal wall reconstruction (CWR) + obliteration

8.2.2 Qualitative synthesis

The secondary outcomes, such as hearing outcomes, infection rates, discharge of the ear, operating time, and quality of life, could not fulfil the requirements of the mathematical synthesis, so we provide a qualitative one. The hearing outcomes were detailed in five articles. Different audiometric measurements were used in the studies. Three of them addressed no significant differences in hearing results among the groups (66, 70, 74). Two studies reported that the CWU group without obliteration had better hearing postoperatively (69, 73). However, that difference was clinically irrelevant or disappeared over time. None of these studies reported hearing gain over 10 dB in AC. None of the included studies found differences in infection rates or ear discharge rates (64, 69, 70, 73).

Minor complications occurred infrequently, and no major complications were reported. The operation time was mentioned in one article (69). That study reported a significant difference in favour of the CWU technique, showing clearly that mastoid obliteration prolongs the operation time. The quality of life as an outcome is reported in two articles (72, 74). One of them compared the CWU without mastoid obliteration to the CWD with mastoid obliteration (72). The other one compared three different surgical techniques, two of which were in our target of interest: CWU without mastoid obliteration and CWU with obliteration (74). These studies used different questionnaires and methods, but the results were identical. They found that the most important factor that determines quality of life was hearing loss, and the two groups were associated with similar results.

8.3 Quantitative and qualitative synthesis of II. Study: Factors influencing successful reconstruction of tympanic membrane perforations: a systematic review and meta-analysis

8.3.1 Quantitative synthesis

To make more homogenous groups, the fat graft and paper patch myringoplasties were not included in the quantitative synthesis.

The following factors were analysed: age, separating adult and paediatric population (under vs. over 16 years), age among children (under vs. over 8 years), presence of prior adenectomy or adenotonsillectomy vs. no prior surgery, size of the perforation (perforation affecting more than 50% of the tympanic membrane vs. less than 50%), site of the perforation 1 (central or marginal), site of the perforation 2 (anterior or posterior), condition of the operated ear (discharging/wet ears vs. dry), condition of the opposite ear (diseased or normal), the experience of the surgeon (senior or resident), and smoking status. The outcome measurement was the success rate, and the odds of success were calculated. (48) The pooled results can be seen in Table 3. Pooled outcomes of ten predictive factor analyses, and the detailed forest plots are below (see Figure 8-17).

Table 3. Pooled outcomes of ten predictive factor analyses

Outcomes: Factors	Outcomes: Comparators	N⁰ of the included studies	Total N⁰ of included patients	Group of patients with the predictive factor: No. of the success	Group of patients with the predictive factor: Total	Comparator group: N⁰ of success	Comparator group: Total	Overall OR	CI	P-value	Heterogeneity: I²	Heterogeneity: CI
Age: under 16 years	**Age: over 16 years**	7	1798	335	401	1229	1397	**0.62**	**0.50;0.78**	**0.0002**	0%	0%;71%
Age: under 8 years	Age: over 8 years	4	309	85	111	155	198	0.89	0.75;1.06	0.119	0%	<0%;<85%
No prior surgery	Prior adenectomy or adenotonsillectomy	4	411	247	286	108	125	1.14	0.42;3.11	0.698	0%	0%;85%
Size of the perforation over 50%	**Size of the perforation under 50%**	13	2207	657	783	1270	1424	**0.52**	**0.29;0.94**	**0.033**	51%	8%;74%
Site: Anterior	Site: Posterior	7	405	234	270	126	135	0.52	0.11;2.52	0.338	52%	0%;81%
Site: Marginal	Site: Central	3	643	87	98	467	545	0.99	0.14;7.09	0.984	9%	0%;90%
Operated ear status: wet/discharging	Operated ear status dry	9	1952	267	307	1400	1645	0.95	0.57;1.57	0.39	5%	0%;67%
Opposite ear: diseased	**Opposite ear: normal**	9	1005	267	384	514	621	**0.32**	**0.12;0.85**	**0.028**	73%	46%;86%
Patients: smoker	Patients: Non-smoker	3	439	51	68	310	371	0.50	0.11;2.39	0.198	8%	0%;90%
Surgeon experience: resident	**Surgeon experience: senior**	6	1559	733	869	639	690	**0.42**	**0.26;0.67**	**0.005**	0%	0%,75%

CI: confidence interval, **N⁰**: number

The significant outcomes are bold.

Four factors were found statistically significant: patients under vs. over 16 years of age (OR: 0.62, CI 0.50; 0.78, p-value: 0.0002), see Figure 8, the size of the perforation (OR: 0.52, CI 0.29; 0.94, p-value: 0.033), see Figure 9, the condition of the opposite ear (OR: 0.32, CI 0.12; 0.85, p-value: 0.028), see Figure 10, and the experience of the surgeon (OR: 0.42, CI 0.26; 0.67, p-value: 0.005), see Figure 11.

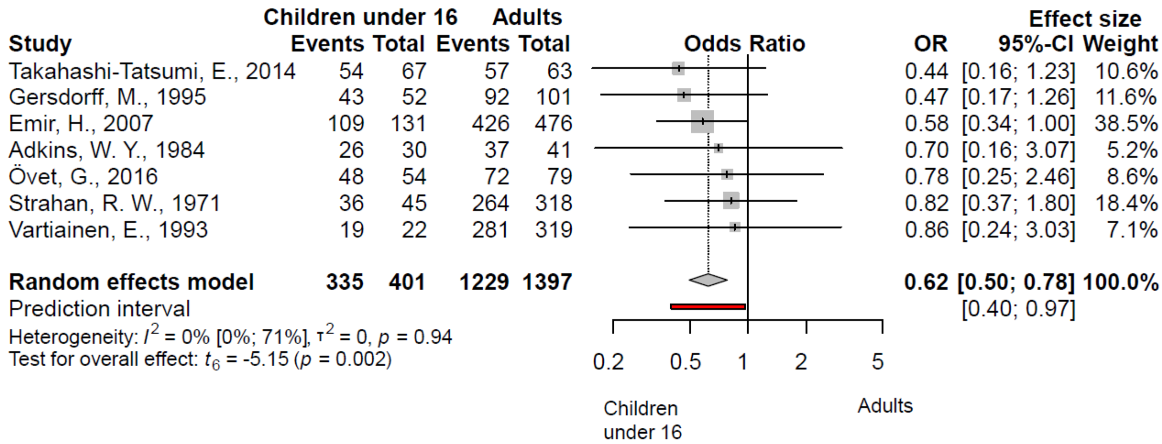

Figure 8. Forest plot presenting the pooled odds of success after tympanic membrane reconstruction: comparison between the paediatric population under 16 years of age and adults

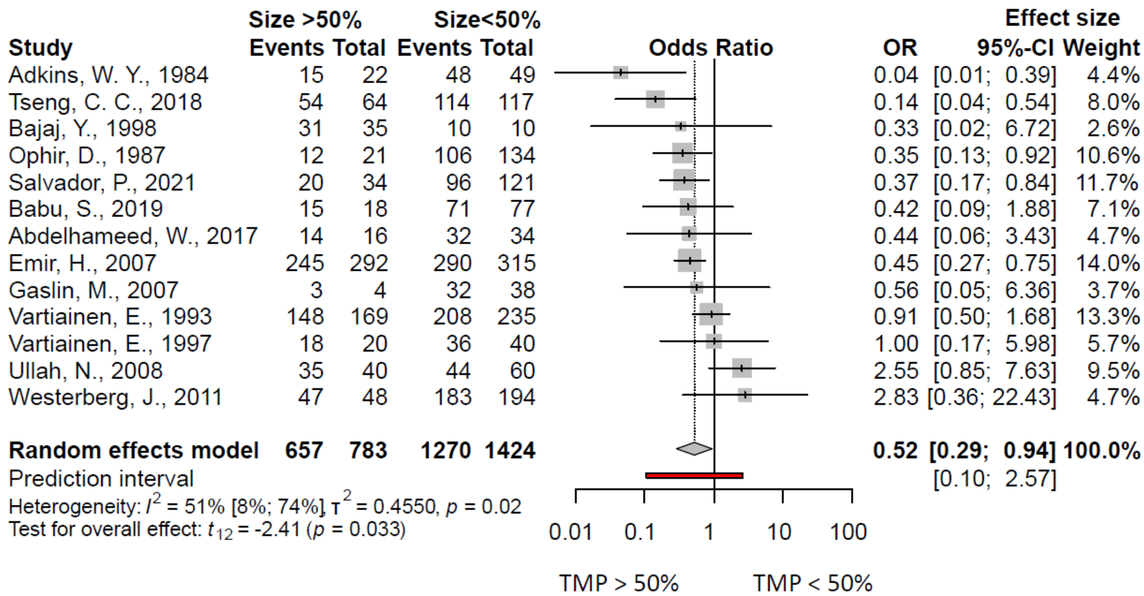

Figure 9. Forest plot presenting the pooled odds of success after tympanic membrane reconstruction: comparison between perforation sizes over 50% to under50%

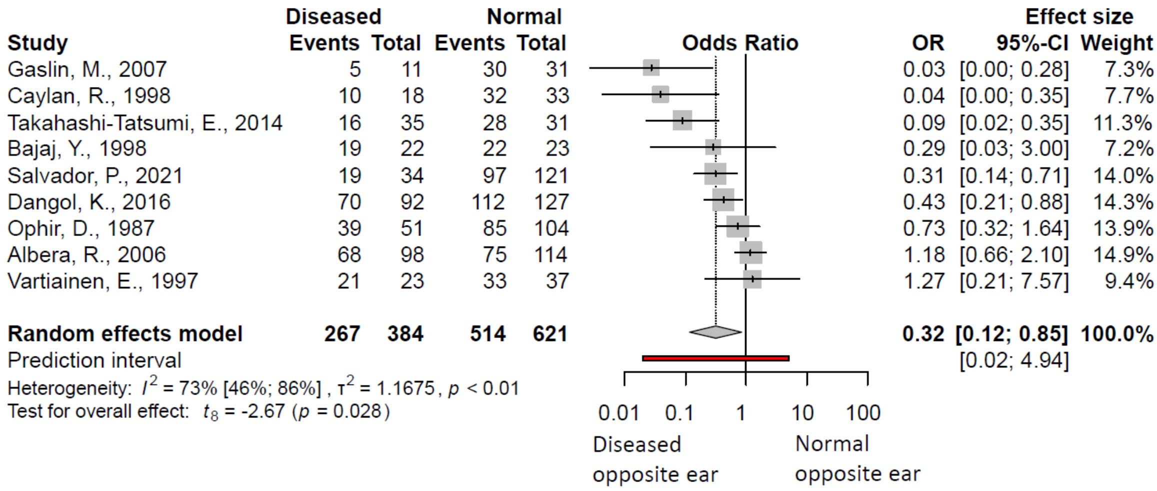

Figure 10. Forest plot presenting the pooled odds of success after tympanic membrane reconstruction: comparison between patients with normal opposite ear status and patients with diseased opposite ear status

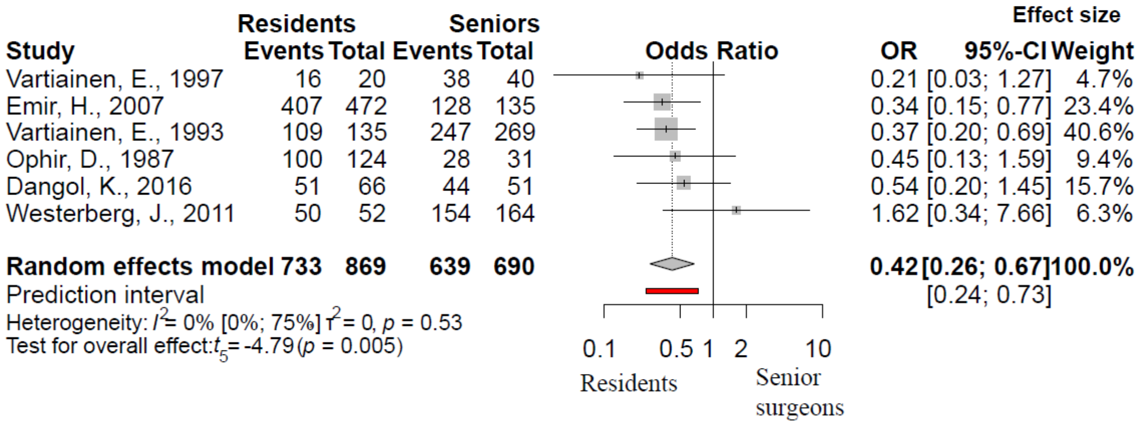

Figure 11. Forest plot presenting the pooled odds of success after tympanic membrane reconstruction: comparison between experience of the surgeons

In addition, when the age group of children was targeted (children under 8 years compared to over 8 years), no significant result was found (OR: 0.89, CI: 0.75; 1.06 p-value: 0.119); see Figure 12.

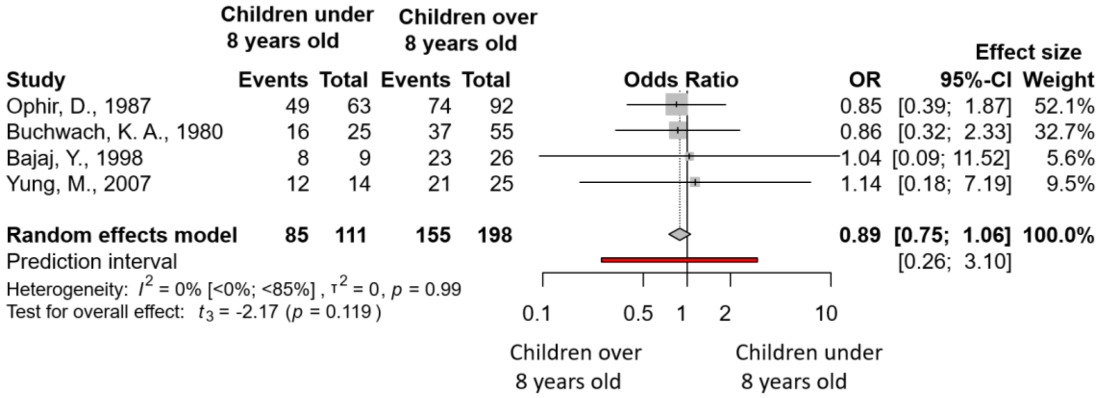

Figure 12. Forest plot presenting the pooled odds of success after tympanic membrane reconstruction: comparison between the pediatric population

Effect regarding the condition of the ear (discharging/wet compared to dry) at the time of the surgery (OR: 0.95, CI 0.57; 1.57, p-value: 0.39), nor regarding prior adenectomy or adenotonsillectomy vs. no prior surgery outcome could not be shown (OR: 1.14, CI 0.42; 3.11, p-value: 0.6989), see Figure 13 and Figure 14.

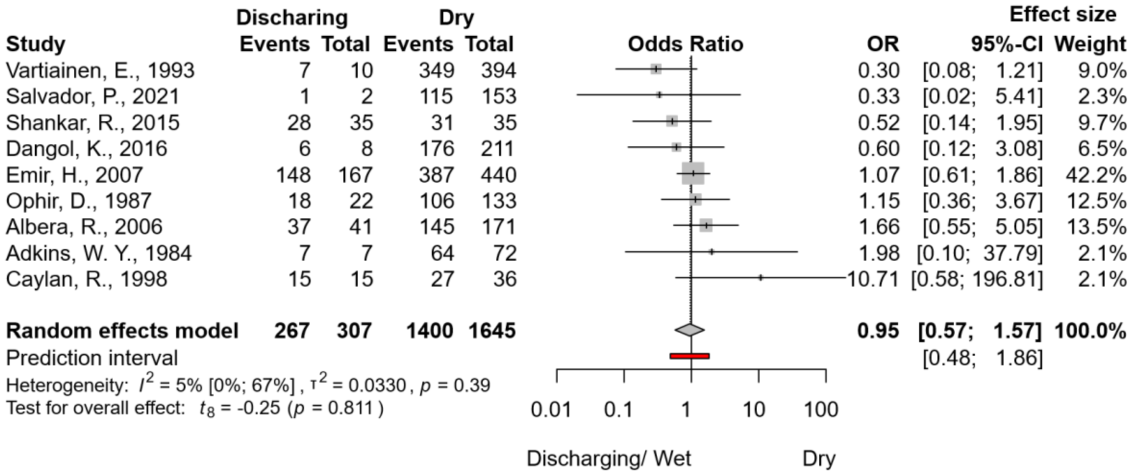

Figure 13. Forest plot presenting the pooled odds of success after tympanic membrane reconstruction: comparison between the discharging/wet ear and dry ear at the time of the operation

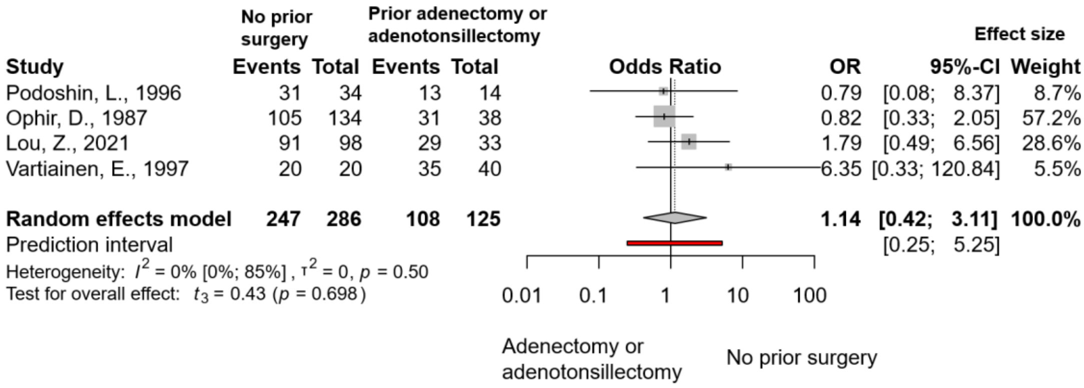

Figure 14. Forest plot presenting the pooled odds of success after tympanic membrane reconstruction: comparison between patients who underwent adenectomy or adenotonsillectomy and patients who had no prior surgery

The site of the perforation showed no statistically significant differences when comparing anterior versus posterior perforations (OR: 0.52, CI 0.11;2.52, p-value: 0.338) or central versus marginal perforations (OR: 0.99, CI 0.14;7.09, p-value: 0.984), see Figure 15 and Figure 16.

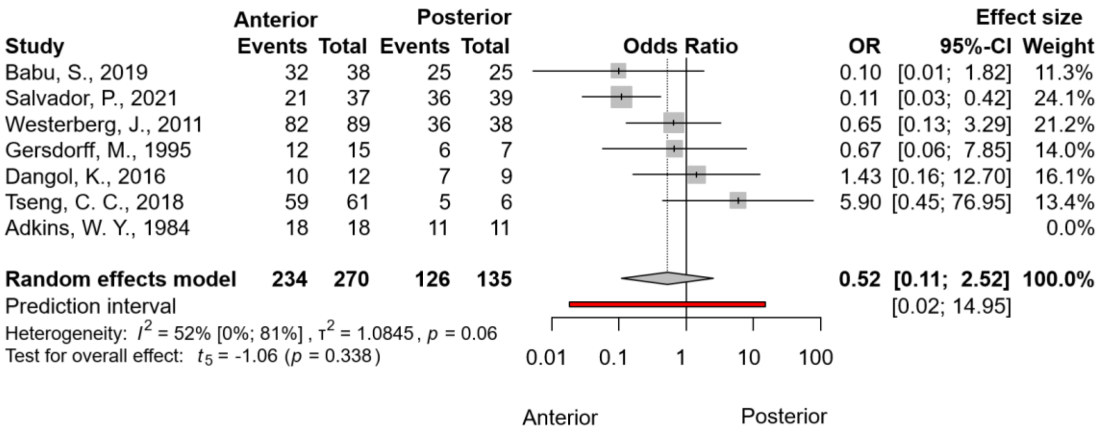

Figure 15. Forest plot presenting the pooled odds of success after tympanic membrane reconstruction: comparison between anterior and posterior site perforation

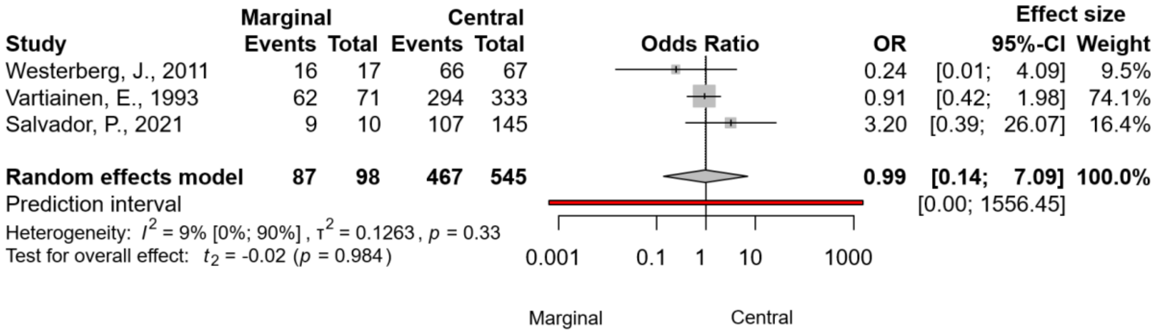

Figure 16. Forest plot presenting the pooled odds of success after tympanic membrane reconstruction: comparison between marginal perforations and central perforations

The comparisons between the smoker and non-smoker groups found no statistically significant effect (OR: 0.50, CI 0.11; 2.39, p-value: 0.198) due to the wide confidence interval and high p-value, see Figure 17.

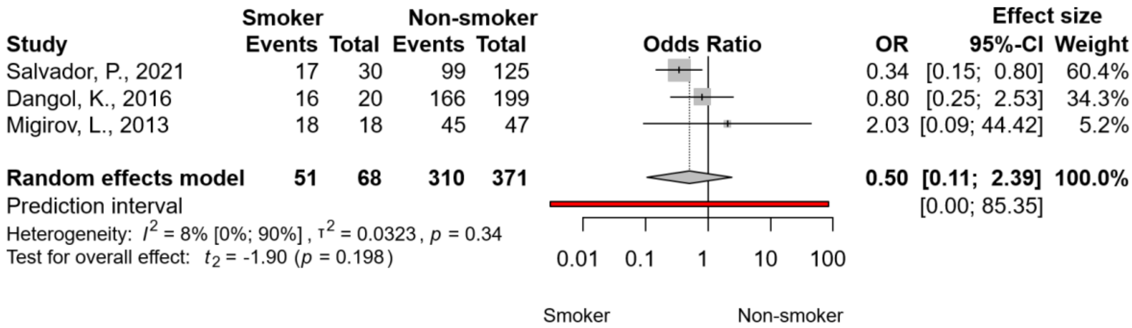

Figure 17. Forest plot presenting the pooled odds of success after tympanic membrane reconstruction: comparison between smoker and non-smoker patients

8.3.1 Qualitative synthesis

We were unable to perform a mathematical analysis for four factors: the etiology of the perforation (93, 110, 112), Eustachian tube function (92, 97, 102), concomitant allergic rhinitis (82), and duration of the ear discharge (77, 80).

The studies that evaluated the etiology of the perforation used distinct classifications and did not find any clear relationship between the etiology and the outcomes (93, 110, 112).

There are no widely accepted or reliable measuring methods to evaluate Eustachian tube function. However, the dysfunction can be estimated using different methods. In three studies, three different methods were used. Their data showed a correlation between the decreased success of type-I tympanoplasty and Eustachian tube dysfunction (92, 97, 102).

One study tried to explore the connection between allergic rhinitis and surgical success, but it could not confirm a significant difference (82).

Two studies measured the duration of the ear discharge before the surgery. Their data suggested that a long duration of discharge influences graft uptake negatively (77, 80).

8.3.2 Fat Graft and Paper Patch Myringoplasty

Two studies examined the predictive factors for fat graft myringoplasty (FGM) (91, 95) , while one study focused on paper patch myringoplasty (96). Unlike the traditional underlay techniques, these methods do not involve elevating the tympanomeatal flap during the procedure (114). As a result, we created a separate section for these specific interventions. The two studies on FGM reported no statistically significant differences in outcomes based on site of perforation, size, or patient age at a 1-year follow-up (91, 95). However, the studies were limited to small and medium-sized perforations. In contrast, the study on paper patch myringoplasty identified three key predictors of success: patient age, the cause of the perforation, and a history of otorrhea (96).

8.3.3 Hearing outcomes

In most cases, hearing improved after surgery. According to data from 14 articles, the average ABG improvement was 10.46 dB (range 5.6–18.83 dB) (115).

The increase of the hearing level at AC measurement was 11.26 dB (range 8.4–17 dB) (78, 83-85, 93, 101, 103, 112) in eight articles, see Table 4. There was a correlation between anatomic success and hearing improvement: when the anatomic success rate (percentage of the closed tympanic member after 12 months) was high, hearing improvement followed the result, but the percentage of significantly improved hearing was less than the anatomic success rate (48)

Table 4. Table 4. Pooled Air Bone Gap (ABG) and Air Conduction (AC) difference before and a minimum of 12 months after the surgery

First author, Publication year	**ABG difference (dB)**	**AC difference (dB)**
Abdelhameed, 2017	9.9	NR
Albera, 2006	8	10
Babu, 2019	11.8	NR
Caylan, 1998	13.5	15
Dangol, 2016	9.8	11.44
Denoyelle, 1999	10.85	10.85
Iso-Motahari, 2018	5.6	NR
Kaya, 2018	16.22	17
Li, 2020	6.8	NR
Lou, 2021	18.83	NR
Övet, 2016	7.37	9.97
Salvador, 2021	7.42	7.44
Tseng, 2018	11.5	NR
Westerberg, 2011	8.6	8.4
MEAN	10.46	11.26

ABG: Air Bone Gap, AC: Air Conduction, dB: decibel

8.4 Risk of Bias Analysis (ROB)

ROBINS-I (Risk of Bias Analysis for Non-Randomized Studies) tool was used for risk of bias analysis in the first study titled Mastoid Obliteration Decrease the Recurrent and Residual Disease: Systematic Review and Meta-analysis. For the outcomes included in the meta-analyses, the ROB assessment was 61.5% at serious and 38.5% at medium level; see more details in Figure 18, Figure 19, and the original publication supplementary material. The ROB evaluation for the qualitative syntheses was 8% at serious and 91% at medium risk level; see it in more detail below and original publication supplementary material.

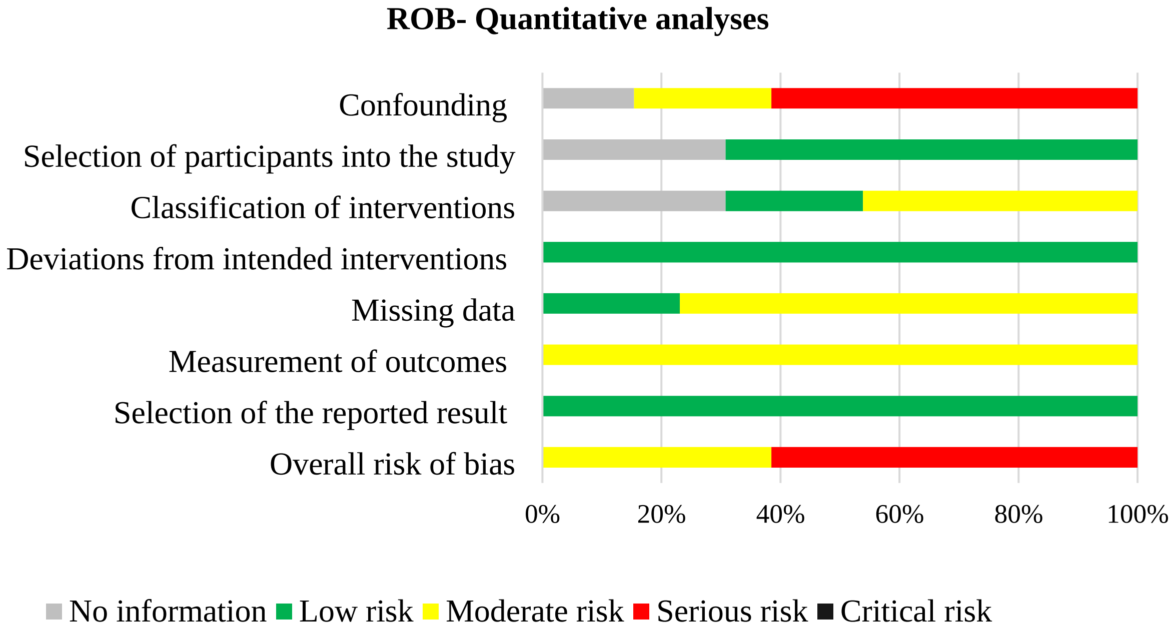

Figure 18. Overall risk of bias of the quantitative analyses shown in percentage

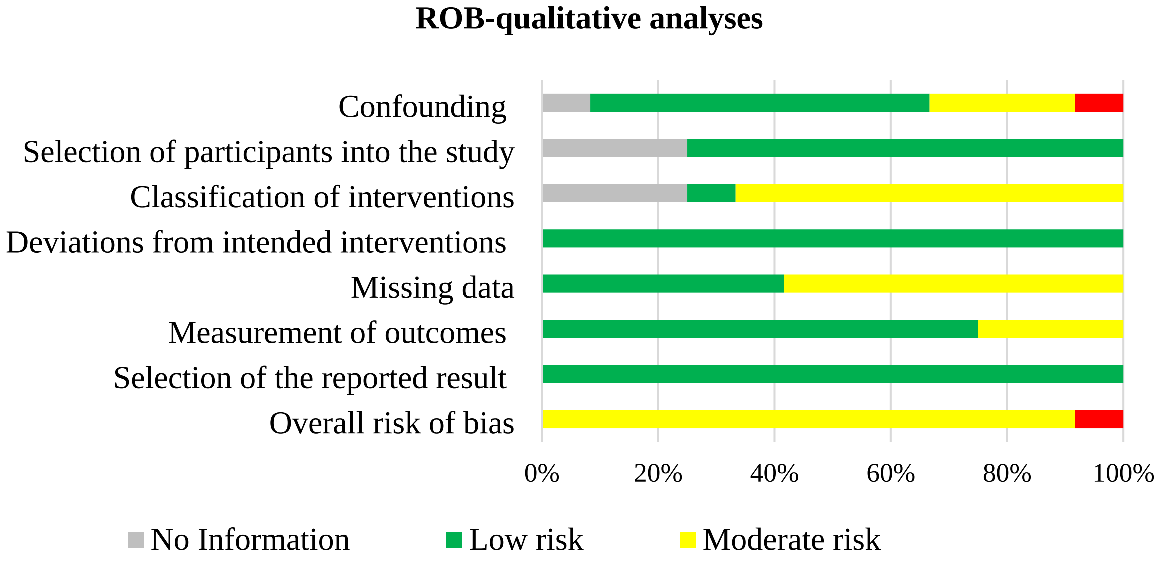

Figure 19. Overall risk of bias of the qualitative analyses shown in percentage

According to the Cochrane Handbook recommendation, the QUIPS (Quality in Prognostic Studies) risk of bias tool was used for II. Study titled Factors influencing successful reconstruction of tympanic membrane perforations: a systematic review and meta-analysis. The results of the risk of bias assessments are presented below (see Figure 20, Figure 21), and a more detailed manner is available from the original publication's supplementary material. The overall risk of bias in the included studies for success rate outcome was 50% low, 36.8% medium and 13.2% high. Articles with high ROB were not included in the quantitative analyses. Regarding the hearing outcome, the overall risk of bias was 81% low, 9.5% medium and 9.5% high.

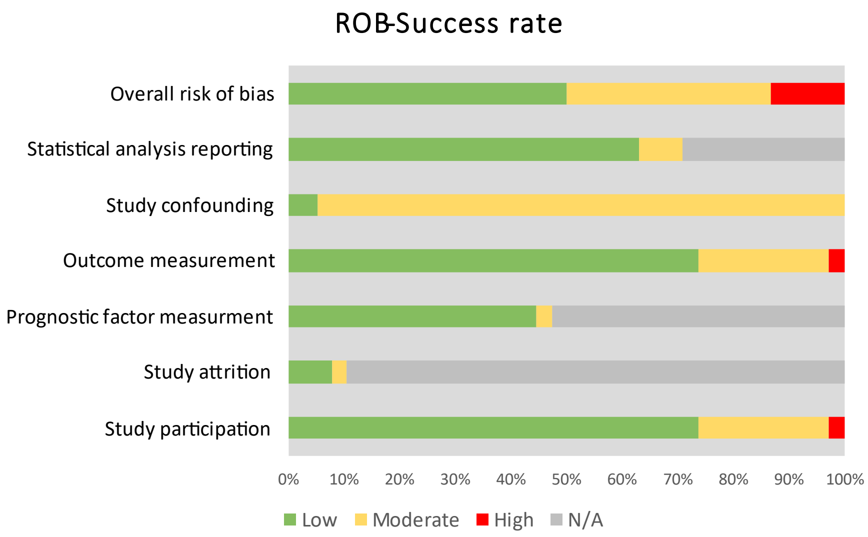

Figure 20. Overall risk of bias (ROB) assessment of success rate shown in percentage

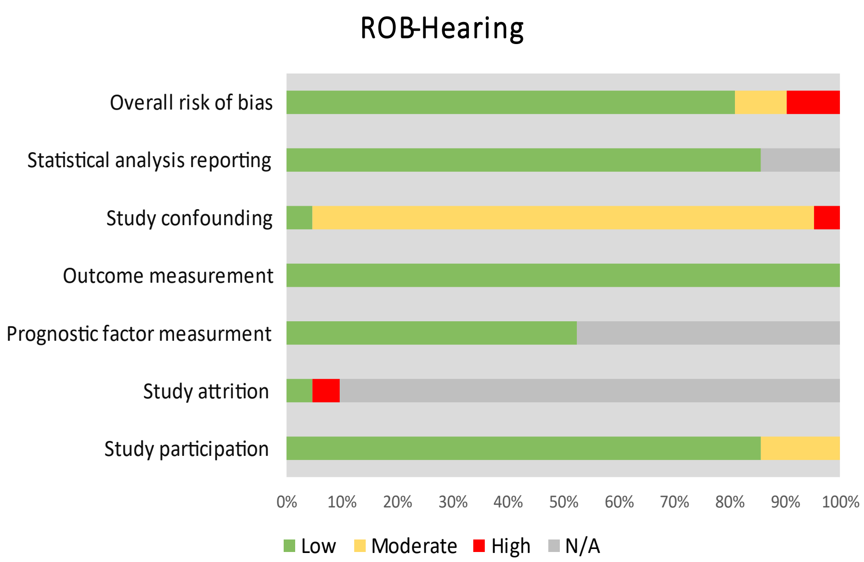

Figure 21.Overall risk of bias assessment (ROB) of hearing shown in percentage

Funnel plots were completed as a publication bias. Tests for the first and second studies did not assume major publication bias, as seen from the original publications' supplementary material. Egger's test was calculated for one outcome (size of the perforation) of the second study, in which more than ten articles were included in the analysis. It gave a p-value of 0.798 (t: − 0.34, df:11), indicating no publication bias.

9. DISCUSSION

9.1 Summary of findings, international comparisons

After thoroughly and systematically processing the available literature about mastoid obliteration and predictive factors of tympanic membrane perforations, we were able to create meta-analyses and found novel outcomes.

9.1.1 I. Study- Mastoid Obliteration Decrease the Recurrent and Residual Disease: Systematic Review and Meta-analysis

Based on data from seven independent articles, our results showed reduced odds of developing recurrent or residual cholesteatoma in mastoid obliteration group (CWU or CWD or CWR with obliteration) compared with the CWU technique. In the same year when our study was published, other meta-analyses were issued with results lowering the recurrence rate in CWD with mastoid obliteration compared to CWU alone with similar rates of otorrhea (116). While they compared CWD with obliteration to CWD surgery alone, and no difference was found in the recurrence rate, but the rate of discharge was significantly decreased (116).

Our separate analyses of residual disease proportions and recurrent disease proportions showed no significant difference, while the odds were similar with fewer patients included. Differentiating between recurrent and residual cholesteatoma may be significant because of their distinct pathomechanisms, it is not relevant from the patients' viewpoints. Additionally, this separation was not possible in all the studies included.

We would like to highlight that these results are based on a minimum follow-up of one year, utilizing diverse methods of disease management. Optimal surveillance would extend beyond this timeframe, employing survival analysis similar to tumours, as recurrence is associated with the duration of observation (117, 118). Furthermore, while recurrent diseases can be easily identified through physical examination, otomicroscopy, effectively monitoring residual disease in the mastoid bowl necessitates clear second-stage surgery or advanced imaging techniques, such as non-EPI DWI MRI, which has limitations in sensitivity depending on the size of the cholesteatoma and was not available during the period of many of the studies reviewed (119). Additionally, the selection of patients for specific surgical approaches was not standardized across these studies. One study indicated, and two others suggested, that the choice of obliteration over canal wall up (CWU) surgery was influenced by the extent and severity of the cholesteatoma, with obliteration preferred in more extensive cases (65, 67, 69)

We found insufficient raw data in the analysed studies to conduct a higher-level statistical comparison regarding the location of residual and recurrent diseases, particularly within the mastoid bowl. Only two studies compared outcomes based on location between the obliteration and CWU groups (67, 69). One study reported benefits related to the mastoid cavity, while the other indicated better results in the tympanic cavity. In the latter case, CWD combined with CWR and obliteration was compared to CWU, with authors suggesting that improved visualization of the tympanic cavity post-CWD could explain the better outcomes observed.

The heterogeneity among the available articles was deemed moderate, likely arising from varied surgical techniques, reconstruction methods, different materials used for obliteration, varying follow-up durations, and age differences among participants. Although we attempted to create more compact and homogeneous subgroups, this paradoxically increased heterogeneity, probably due to the limited number of studies and their retrospective nature.

We were unable to analyse the impact of patient age on outcomes. While cholesteatoma is often regarded as more dangerous and unstable in children, we could not statistically determine if age influences results in mastoid obliteration (69, 120, 121). One article noted that only children benefitted from obliteration after CWU (65), while other studies also suggested advantages for adults (69). These conflicting findings indicate a need for further research to understand age-related outcomes better.

Most cholesteatoma recurrences occur within the first few years post-surgery, and the traditionally accepted minimum follow-up in middle ear surgery studies is one year (122) We could select studies with a minimum follow-up of 12 months; all had a mean or median follow-up of at least 30 months. Variations in follow-up periods could lead to differences in results; however, since the subgroups had approximately similar follow-up durations without significant deviation from the overall outcome's odds ratio, we concluded that while this is a limitation, analyses should still be conducted.

It is known that muscle used for obliteration tends to shrink and atrophy over time, which may impact outcomes (39, 123, 124). Unlike muscle, a histopathological study also demonstrated that bone dust remains in the mastoid cavity without size change (125). Therefore, we conducted a subgroup analysis for studies utilizing autologous bone dust or bone replacement materials, including hydroxyapatite granulate or bioglass, as these materials behave similarly to bone paté (126).

The results of this analysis did not indicate differences based on material used, but further conclusions cannot be drawn without randomized controlled trials and larger sample sizes.

The most straightforward comparison regarding the effectiveness of mastoid obliteration is between CWU alone and CWU with obliteration. We were able to perform a subgroup analysis on this basis, but we could only include three articles. The heterogeneity was high for the previously mentioned reasons. The subgroup analyses did not reveal any intergroup differences; however, the small sample size and quality of the studies necessitate further evaluation of this question with more robust data.

The duration of the surgery can depend on various factors. In mastoid obliteration cases, additional time is required to thoroughly remove all air cells from the mastoid cavity, gather bone dust for the bony obliteration technique, and reconstruct the posterior wall in CWD cases. One study that compared surgery duration found that obliteration significantly extends the operation time (69). Although it is challenging to generalize the extent of this increase based solely on one study, we believe that a correlation exists.

9.1.2 II. Study: Factors influencing successful reconstruction of tympanic membrane perforations: a systematic review and meta-analysis

After processing all the data from the included articles about predictive factors influencing type-I tympanoplasty, we found ten potential factors appearing in at least three studies with comparable methods. Four factors were found statistically significant out of ten with robust effects (Table 3). These were the age of the patient, the perforation size, the opposite ear's condition, and the surgeon's experience. These findings were associated with low or moderate heterogeneity, indicating that these factors play a significant role in the success of tympanic membrane reconstruction. However, the interaction among these factors remains unclear, and additional influences may exist. The lack of statistical significance in other factors (such as location of the perforation, and smoking status) could be attributed to small sample sizes or mitigating effects from other variables.

Previous meta-analyses have also explored factors like age, size of the perforation, condition of the contralateral and operated ear, and prior adenoidectomy or adenotonsillectomy (127, 128). However, none investigated the impact of surgeon experience or patients' smoking status. This study applied rigorous inclusion criteria, limiting the analysis to studies with a minimum follow-up of 12 months. Moreover, 15 of the studies included here were published after the last meta-analysis conducted in July 2014. One pediatric meta-analysis found age as a significant factor (127), while another determined that neither the size of the perforation nor the condition of the contralateral ear were significant (128). A study similar to ours, which included both adults and children, concluded that larger perforations and pediatric populations negatively influenced outcomes (129).

9.1.2.1 Comparison among age groups

A total of 21 studies evaluated age as a predictive factor for tympanoplasty success. Definitions of age groups varied across studies, with some considering individuals over 16 years as adults and others using 18 years as the threshold. For consistency, our analysis set the age limit at 16 years, in line with most studies. Comparing adults and children yielded clear and homogeneous results from seven studies indicating that children have approximately 50% lower odds of success (Figure 7). Further analysis of the pediatric population from four studies compared children younger and older than eight years. While the results were not statistically significant, a detectable trend was observed (Figure 11). Previous meta-analyses produced mixed findings: one reported no significant difference based on age (127), while the other found that younger children had lower success rates compared to older ones (128). It should be noted that the pediatric population in this study was relatively small, with wide confidence intervals. Other factors may have also contributed to variability in the results.

9.1.2.2 Size of the Perforation

A significant and strong correlation was identified regarding the size of the perforation after analysing data from 13 studies. Perforations exceeding 50% of the tympanic membrane are thought to decrease the likelihood of success (Figure 8). The result exhibits moderate heterogeneity at 51%, which may stem from challenges in clear categorization.

9.1.2.3 Condition of the opposite ear

Nine studies provided data on the condition of the opposite ear, which could include perforation, effusion, or cholesteatoma. These ear problems are often linked to presumed Eustachian tube dysfunction. Although pooling diverse conditions resulted in high heterogeneity, the results were statistically significant, showing the most pronounced effect among all findings (Figure 9).

9.1.2.4 Experience of the surgeon

While not directly a patient-related factor, surgeon experience is relevant from the patient's perspective. Six studies reported on the impact of surgeon experience (Figure 10). Results with low heterogeneity indicate significantly lower success odds for patients treated by resident doctors compared to senior surgeons. This strong correlation highlights the importance of considering the surgeon's expertise.

9.1.2.5 Condition of the Operated Ear

Nine studies addressed the condition of the operated ear. The comparison focused on dry versus discharging (wet) ears at the time of surgery. The analysis's odds ratio and confidence indicated that no substantial effect was observed (Figure 12).

9.1.2.6 Prior Adenectomy or Adenotonsillectomy

Four studies included data on prior adenoidectomy or adenotonsillectomy. The comparison was based on the hypothesis that frequent inflammation near the Eustachian tube could affect tympanoplasty outcomes. However, this was not supported by the results (Figure 13).

9.1.2.7 Site of the Perforation

Two analyses were conducted regarding the perforation site: marginal versus central perforations (Figure 14) and anterior versus posterior perforations (Figure 15). Neither analysis yielded statistically significant results due to a limited sample size. While no effect was detected between marginal and central perforations, anterior perforations decreased the overall odds ratio compared to posterior perforations. Although this result was not significant, anterior perforations are generally more challenging to assess and operate on, suggesting a clinically relevant difference. Even though in the included articles, mainly underlay tympanoplasty with temporal facia was performed, later studies are needed with more homogenous treatment groups to analyse the location effect on the surgical outcome due to its sensitivity to the surgical method.

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9.1.2.8 Smoking Status

Three studies examined the impact of smoking on success rates (Figure 16). Although the results were not statistically significant due to the small sample size, a discernible effect was noted. One study reported an overall odds ratio greater than one with a wide confidence interval, while the other two suggested that smoking negatively affects success odds. Previous reviews have also indicated that smokers tend to have lower success rates compared to non-smokers.

9.2 Strengths

Both studies use rigorous and contemporary methodology with precise inclusion criteria. Protocols of the studies have been published in PROSPERO, increasing the transparency of our work. All included studies have at least 12 months of follow-up time, improving the raw data's validity and reliability. Subgroup analyses were created on relevant data about mastoid obliteration materials and surgical techniques. In our research about predictive factors of tympanic membrane reconstruction, we could include an analysis of a high number of potential factors with a long follow-up of patients from studies with low and medium bias.

9.3 Limitations

Regarding the limitations of our work, there is variability in the surgical techniques employed. Additionally, the absence of sufficient data prevented us from conducting a multivariate analysis of the predictive factors, leaving the relationships between the factors unexplored. Studies about mastoid obliteration are retrospective, with several confounding factors, such as low quality of data and a serious risk of bias. Some of the analysed studies also reported or suggested that the obliteration groups included a higher proportion of patients with extensive disease compared to the CWU group.

10. CONCLUSIONS

Our findings indicate that four factors significantly influence the success rate of tympanic membrane reconstruction: patient age, perforation size, the condition of the opposite ear, and the surgeon's experience. Factors such as a discharging operated ear, perforation site, history of adenoidectomy or adenotonsillectomy, and patient smoking status were not found to have a significant impact. Mastoid cavity obliteration could effectively decrease recidivism without leading to severe complications or a decline in quality of life. However, due to the low quality of available data, we are unable to make definitive recommendations.

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11. IMPLEMENTATION FOR PRACTICE

About mastoid obliteration, we could not give a recommendation due to the low quality of the data; this method is an option for choice. Our findings on predictive factors are important for middle ear surgeons in patient education and decision-making regarding interventions. High-risk patients, such as children with large perforations and diseased opposite ears, require experienced surgeons capable of selecting and applying the most suitable technique for perforation repair.

12. IMPLEMENTATION FOR RESEARCH

Further studies on predictive factors with large sample sizes and multilevel methods for reliable prescriptions are needed. Also, prospective randomized trials comparing CWU to CWU with mastoid obliteration with longer follow-up time and reporting survival analyses are essential for proving the real effectiveness of mastoid obliteration. Additionally, documenting observations from reoperations in obliterated mastoid cavities could provide valuable insights for future research.

13. IMPLEMENTATION FOR POLICYMAKERS

It is important for policymakers to prioritize the implementation of the most effective surgical methods to minimize the risk of recurrence by increasing the surgical success rates; given not only the significant costs associated with revision surgeries but also the impact on patient quality of life perspectives. Establishing guidelines based on current knowledge of middle ear surgery can promote a more standardized understanding of procedures, facilitating more consistent and feasible research efforts.

14. FUTURE PERSPECTIVES

Looking ahead, middle ear surgeons must be open-minded about novel and reliable techniques and be able to implement them in daily practice to provide the best possible care for their patients. Additionally, providing targeted patient information derived from synthesized evidence can assist healthcare professionals in selecting the most appropriate surgical approach, ultimately enhancing both the quality of care and resource allocation.

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Fül-orr-gégegyógyászat

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