

Supporting Cholesteatoma Management by Investigating Disease Extension

Ph.D. Thesis

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“Your reward will be the widening of the horizon as you climb. And if you achieve that reward, you will ask no other.”

Prof. Cecilia Payne-Gaposchkin

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1. LIST OF ABBREVIATIONS

ABG: air-bone gap

AC: air conduction

ADC: attenuation diffusion coefficient

BC: bone conduction

CI: confidence interval

COM: chronic otitis media

CWD: canal wall down tympanomastoidectomy

CWR: canal wall reconstruction

CWU: canal wall up tympanomastoidectomy

CWU+MO: canal wall up tympanomastoidectomy with mastoid obliteration

EAONO-JOS: European Academy of Otolology and Neurotology - Japanese Otological Society

GRADE: Grades of Recommendation, Assessment, Development, and Evaluation

HRCT: high-resolution computed tomography

MD: mean difference

MRI: magnetic resonance imaging

Non-EPI DWI MRI: non-echoplanar diffusion weighted magnetic resonance imaging

Non-EPI: non-echo planar imaging

PICO: Population, Intervention, Comparator, Outcome

PTA: pure-tone average

QUIPS: Quality In Prognostic Studies

RoB 2: Risk-of-bias tool for randomized trials

ROB: risk of bias

ROBINS-I: Risk Of Bias In Non-randomised Studies of Interventions

RR: risk ratio

SD: standard deviation

WHO: World Health Organisation

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to secure the highest level of care for patients living with chronic otitis media and cholesteatoma. Through helping clinicians choose the most appropriate surgical procedure based on disease extension and optimizing follow-up, recidivism rates and complications can be minimized, and the need for reoperations may be lessened.

Thus, my mission is to evaluate and summarize data collected in trial and real-world settings, as well as to analyse patient data in our own clinical practice. I am committed to keeping up with the newest guidelines, employing contemporary imaging methods, and finding the most effective staging systems to help plan surgeries and standardize our results to make them comparable on a multi-institutional and international level.

2.2. Scientometrics

Number of all publications: 4
With impact factor: 4 Without impact factor: 0
Cumulative IF: 8,7
Av IF/publication: 2,175
Ranking (Sci Mago): Q1: 3 Q3: 1
Number of publications related to the subject of the thesis: 2
Cumulative IF: 4,4
Av IF/publication: 2,2
Ranking (Sci Mago): Q1: 2
Number of citations on Google Scholar: 3
Number of citations on MTMT (independent): 4
H-index: 2

The detailed bibliography of the student can be found on page 56.

2.3. Future plans

Through the generous support and guidance of my supervisor and seniors over the last three years, which has been, thus far, the most challenging and rewarding of my life, I have gained a glimpse into the extraordinary world of otological surgery. In the future, I aim to

hone my clinical skills in otorhinolaryngology and contribute to the scientific world through continuing research activities and deepening my understanding of statistics.

3. SUMMARY OF THE THESIS

Cholesteatoma is a fundamentally benign growth of squamous epithelium inside the middle ear; however, it leads to a significantly decreased quality of life (ear discharge, hearing loss) and severe, even potentially life-threatening complications (facial nerve palsy, meningitis, intracranial abscess). Due to high recidivism rates, meticulous surgical planning and technique are required with long and diligent follow-up afterwards using specialized cholesteatoma-dedicated imaging protocols. However, high-level evidence regarding how the extent and growth rate of this disease determine management is still missing.

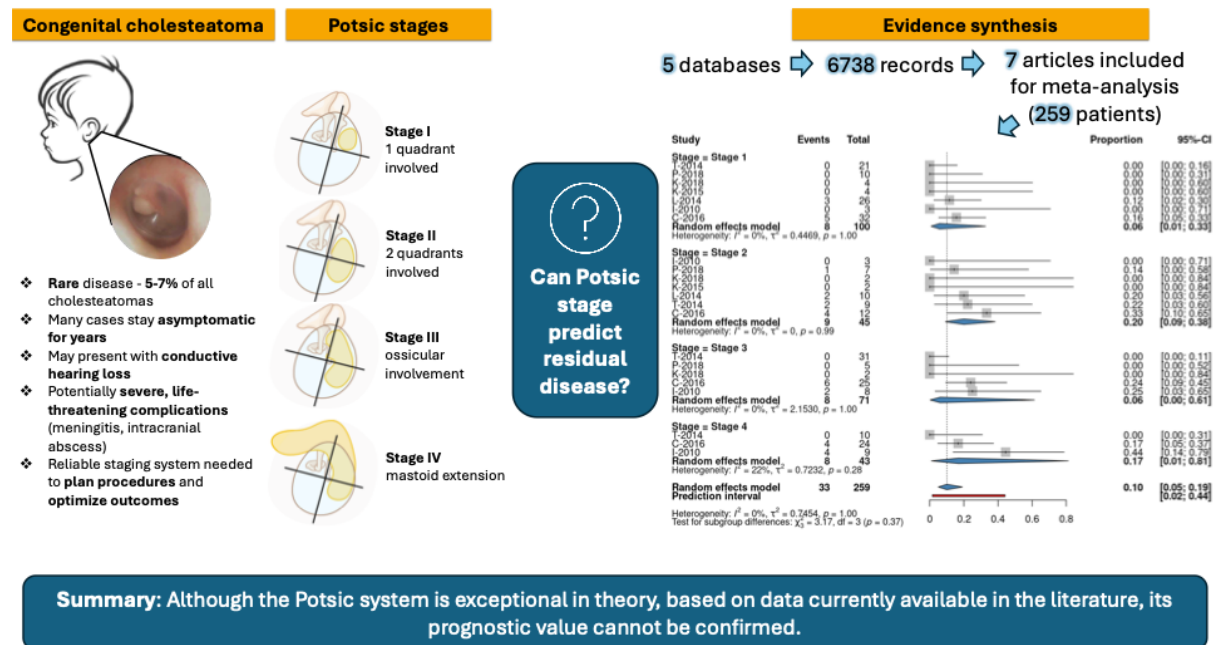
In this thesis, we investigated the usefulness of the Potsic staging system intended for congenital cholesteatoma as a tool to predict residual disease proportions and analysed individual growth rate measurements in order to create an evidence-based simulation model to estimate optimal timing of follow-up imaging.

During our first study, we observed that despite outstanding clinical applicability, due to varied reporting, the Potsic staging system's prognostic value cannot be confirmed. The cholesteatoma simulation model in our second study shows that the optimal timing of follow-up imaging to screen for residual cholesteatoma is 28-35 months postoperatively.

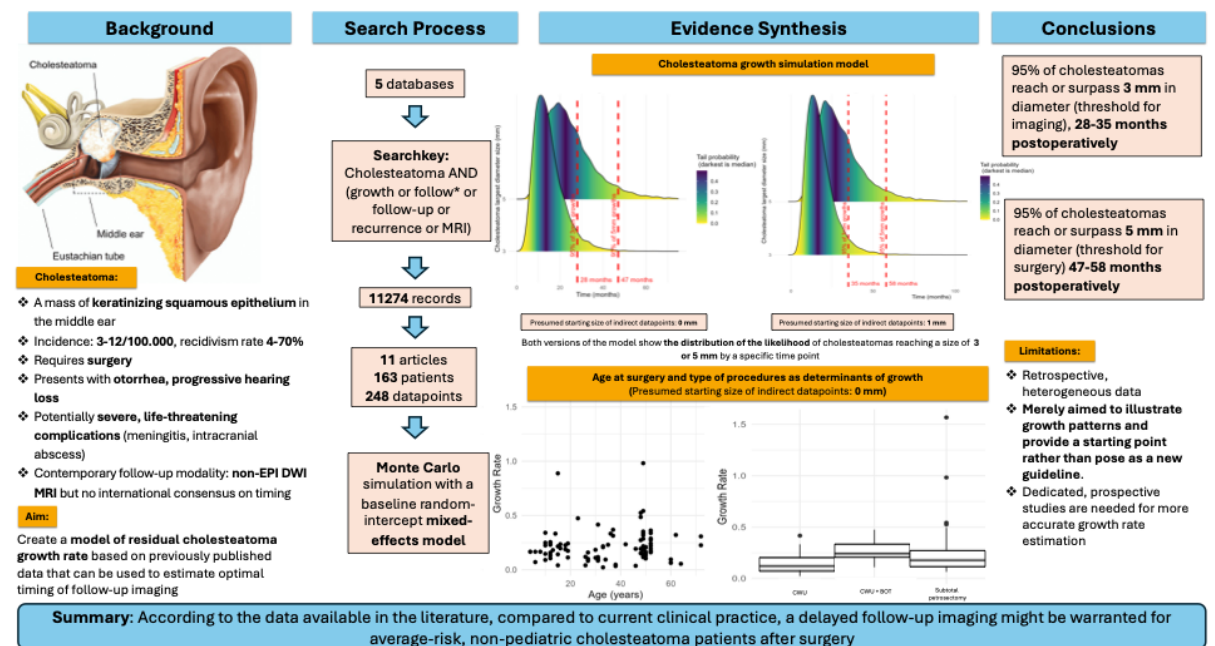
Thus, we conclude from the first project that staging systems are widely used and are an essential tool for planning procedures and estimating outcomes. Nevertheless, standardized reporting is just as important in order to compare international results on a multi-institutional scale and create a higher level of evidence. The second study shows that, contrary to current clinical practice, a somewhat later timing may be more advantageous in cholesteatoma-specific follow-up imaging to lower the rate of false-negative examination results.

4. GRAPHICAL ABSTRACT

Study I. - Predicting residual cholesteatoma with the Potsic staging system still lacks evidence:
a systematic review and meta-analysis



Study II. - Modeling residual cholesteatoma growth rate: a meta-analysis of individual participant data



5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

Given the array of possible surgical procedures in middle ear surgery, each affecting patients' pre- and postoperative quality of life to varying degrees, cholesteatoma expansion is crucial to consider during diagnostics to minimize recidivism and optimize outcomes.

5.1.2. What is the problem to solve?

Many extension-based cholesteatoma staging systems, such as the Potsic staging system for congenital cholesteatomas, have been proposed and linked to outcomes, but evidence is scarce regarding whether these are supported by the available data.

The recently developed non-echoplanar diffusion weighted magnetic resonance imaging (non-EPI DWI MRI) is becoming a key element of long-term follow-up after cholesteatoma surgery. This imaging modality is highly specific and sensitive to cholesteatoma; however, no widely accepted international protocol exists for timing these examinations, and accessibility is also limited in many regions.

5.1.3. What is the importance of the topic?

Cholesteatoma recidivism and the concomitant possibility of reoperations place considerable pressure on both patients and surgeons. Optimized staging systems could help plan successful procedures and compare results across multiple institutions. Difficult access to cholesteatoma-specific, time-intensive imaging methods also calls for a robust, internationally accepted follow-up protocol.

5.1.4. What would be the impact of our research results?

To gauge the possibility of recurring disease and choose the optimal time to screen for it may offer significant help to physicians in minimizing residual rates and further lowering the need for additional surgeries, thus ensuring a higher quality of life for patients.

5.2. A brief introduction to cholesteatoma

5.2.1. Cholesteatoma history, theories, histology

5.2.1.1. Definition, classification, and epidemiology

As defined in the European Academy of Otolology and Neurotology - Japanese Otological Society (EAONO/JOS) Joint Consensus Statements(1), cholesteatoma is a mass of keratinizing squamous epithelium located in the middle ear and/or the mastoid cavity that leads to a gradual buildup of squamous debris and a surrounding inflammatory reaction, while potentially causing extensive damage in the hearing ossicles and the temporal bone. Thus, the term “cholesteatoma”, as first mentioned by Johannes Müller in 1838(2) when it was still believed that cholesteatomas were adipose tissue tumors, is quite misleading, because no cholesterol is involved in the buildup of the mass, and though expansive in nature, cholesteatomas are benign, non-neoplastic lesions.

Cholesteatomas are classified as congenital or acquired, and the latter category is subdivided into retraction pocket or non-retraction pocket cholesteatomas (although in advanced cases, defining the exact origin may not be possible, these cases are grouped as unclassifiable) (1). It is important to make a distinction when considering postoperative findings: recidivism is the umbrella term for all renewed cholesteatoma formation and is subdivided into residual and recurrent cases. Residual cholesteatoma originates from squamous tissue left behind during surgery and might not be apparent during otomicroscopic follow-up. Recurrent cholesteatoma describes the formation of a new retraction pocket, which may reappear after successful eradication(3).

As of 2026, the global prevalence of cholesteatoma is estimated to be 4.02 per 100.000 people(4). Congenital cholesteatoma is rather scarce, comprising 1-5%(5) of all cholesteatomas. In a recent meta-analysis, cholesteatoma recidivism was shown to be 16.20%(4), although international results are highly varied, with recidivism rates spanning between 4-70%(6, 7, 8, 9, 10).

5.2.1.2. Pathogenesis theories

Several theories exist for acquired cholesteatoma formation, all of them controversial to varying degrees in their explanation for how exactly squamous epithelium, from the outermost layer of the tympanic membrane, penetrates the tympanic cavity.

The least contested and oldest of them is the **retraction pocket theory**(11), which names Eustachian tube dysfunction and a resulting negative pressure as a cause for retraction pocket

formation. Although seemingly proven in an early gerbil model(12) and providing a clear justification for acquired pars flaccida cholesteatoma, Eustachian tube function by itself fails to explain several real-world scenarios, such as cholesteatoma recurrence in ears with functional ventilation tubes(13). Nevertheless, newer theories, such as selective epitympanic dysventilation syndrome (14), seem to provide an explanation for cases by describing an isolated, hypoventilated space just medial to one of the common sites of retraction pockets, the pars flaccida.

Another, less popular theory is the *theory of squamous immigration*(15). This theory burdens tympanic membrane perforations with the responsibility of acting as a pathway for squamous cells to enter the tympanic cavity. This might be the process behind some pars tensa cholesteatomas, but even if only a fraction of perforations led to cholesteatoma, the incidence should be significantly higher.

According to the *squamous metaplasia theory*, as demonstrated in previous in vivo experiments (16), chronic inflammation of the middle ear leads to squamous metaplasia of the middle ear mucosa. This theory failed to gain significant traction because it does not explain the formation of retraction pockets.

A further theory places the blame on *squamous basal hyperplasia*. In this scenario, keratinocytes migrate medially and extend through the subepithelial space through pseudopodia, thus forming a retraction pocket. Since it was established previously that the main migration pathways in the tympanic membrane are lateral instead of medial (17), this theory also leaves many clinicians sceptical.

The most novel theory, based on a retrospective analysis of second-look procedures, is called the *mucosal traction theory* (18). Its author hypothesizes that just like in many other inflammatory processes in the human body, a self-reparatory mechanism, complete with migration of immunologically active tissue (in this case, the tympanic membrane) towards chronically inflamed areas, is aided by ciliary epithelial cells. Although this theory seemed to have a sturdy basis, thanks to a study of young patients with primary ciliary dyskinesia and chronic otitis media (none developed cholesteatomas) (19), during a later analysis, the concentration of ciliary epithelial cells in the area in question proved low (20), thus leaving clinicians without a theory to rule them all once again.

Similarly, little is known about the exact etiology and pathogenesis of congenital cholesteatoma. Many theories exist, but the two with the most ample evidence behind them are the theory of epidermoid formation presented by Teed and Michaels(21, 22) and the acquired inclusion theory introduced by Tos(23). According to the first, clusters of viable epithelial cells

(later named epithelial formations) that migrated either from the amniotic fluid or the first and second branchial arches persist past the 33rd week of gestation and grow in tympanic cavities. The presence of such epidermoid formations has been proved in fetal tympanic cavities, but multiple working groups failed to show keratinization(24, 25, 26). The second theory hypothesizes that, as the tympanic membrane retracts during transient tubal dysfunction, it adheres to the malleus neck or incus, and later moves back to its physiological position, the membrane may leave behind squamous cells on these ossicles that form the keratinous pearl. However, this theory only explains congenital cholesteatomas in the anterosuperior quadrant.

5.2.1.3. Histology, cellular, and molecular mechanisms

Cholesteatomas are divided into 3 parts histologically(27). The center of cholesteatomas is an acellular, mixed mass of keratinous and sebaceous debris. The next layer is the matrix, which has a skin-like structure, for the most part, stratified squamous epithelium. The outermost zone, the perimatrix, rich in inflammatory cells and granulation tissue (28), is the main site of expression of tissue factors responsible for the damage caused by cholesteatomas, such as inflammatory cytokines, bone-resorbing and osteoclast-stimulating cytokines (interleukin-1, interleukin-6, and interferon β) (29). Through these factors, perimatrix fibroblasts and matrix keratinocytes interact in a paracrine and autocrine loop, furthering the inflammatory reaction(30). Previously, a larger proportion of fibrous tissue was found in adult perimatrices than in children's, thus seemingly strengthening the dogma of pediatric cholesteatoma being more active (31). However, in a recent analysis, the expression of cytokines, remodeling, angiogenic, and transcription factors in this layer showed no significant difference between the two age groups (32). Based on these results, it was theorized that the previously observed difference may be due to anatomical reasons, such as Eustachian tube anatomy, mastoid cell aeration, and the higher incidence of otitis media in children(33).

5.2.2. Cholesteatoma diagnosis and imaging

5.2.2.1. Symptoms, otoscopic and audiological findings

Patients with cholesteatomas present most commonly with nonspecific symptoms such as otorrhea, aural fullness, hearing loss, and, less frequently, vertigo, facial palsy, or tinnitus(34). In many cases, especially congenital cholesteatomas, remain asymptomatic for years and are only diagnosed incidentally(35). In this time, they may grow extensively, leading to potentially life-threatening intracranial or extracranial complications, such as meningitis, subperiosteal abscess, labyrinthine fistula, or venous thrombosis(36, 37). Frequent

otomicroscopic findings in patients with acquired cholesteatoma may include granulating aural polyps(38), squamous debris emerging from a retraction pocket in the tympanic membrane (28). Congenital cholesteatoma, as defined by the 1986 Levenson criteria, presents as a white, pearl-like lesion behind an intact pars tensa and flaccida in patients without a history of otorrhea, perforations of the tympanic membrane, or previous otosurgical interventions(39). During pure-tone audiometry, conductive hearing loss is often reported due to ossicular erosion, but sensorineural and mixed hearing loss may also present in advanced cases due to cochlear damage (40).

5.2.2.2. Imaging modalities (HRCT, non-EPI DWI MRI)

Cholesteatomas are usually diagnosed based on otoscopic findings, but as bony erosion frequently occurs in tympanic cavities affected by cholesteatoma, high-resolution computer tomography (HRCT) is an important tool for planning the ideal surgical approach and the extent of surgery needed (41). Examinations are quick, require no contrast (unless intracranial complications such as abscesses are suspected), and help surgeons prepare for procedures by showing anatomical variations and nerve or vessel dehiscences, which may be causes for complications (42). Radiation might be an important factor to consider, especially in pediatric cases, but novel modalities such as cone-beam CT (CBCT) deliver 40% less radiation (43) while providing close to equal resolution (44).

Although HRCT is invaluable for preoperative planning, it is unhelpful for the purposes of follow-up. Traditionally, all cholesteatoma patients' ears were reexamined approximately 1 year after surgery during a mandatory procedure called "second-look"; however, a new imaging modality is rendering these interventions obsolete(45). When differentiating between granulation tissue, fibrosis, scarring, and residual cholesteatoma tissue, non-echoplanar diffusion-weighted magnetic resonance imaging (non-EPI DWI MRI) with apparent diffusion coefficient (ADC) mapping (41) proved highly sensitive and specific for cholesteatoma (46, 47) as small as 3 millimetres (48). Non-EPI DWI MRI undoubtedly has some drawbacks, such as long acquisition times, which may prove challenging for younger patients (42), but on the other hand, it involves less financial burden than second-look procedures (49) and no radiation. Timing these examinations is highly sensitive. To prevent false negative results due to residuals still being too small, early scans should be avoided(50, 51), but postponing examinations may lead to extensive growth going unnoticed in residual cases.

Despite the evidence detailed above, an international guideline for follow-up imaging has yet to emerge.

5.2.3. Staging systems for cholesteatoma

Using staging systems can be helpful in many aspects. Standardizing outcomes could make them internationally comparable between institutions, which may lead to more robust evidence to help manage patients' expectations and assist surgeons in planning procedures while anticipating severity and risk of recidivism.

Several staging systems have been proposed in the past. In the contemporary literature, one of the most widely known systems was based on a joint consensus by the European and Japanese otological societies (EAONO/JOS) in 2017(1), which was intended for all cholesteatomas except for petrous bone cholesteatomas (for these, the location-based Sanna classification was devised a few years earlier(52)), and divided them into 4 stages: stage I if the cholesteatoma was still confined to its origin site, such as the attic or the tympanic cavity, stage II if cholesteatomas extended to two or more locations, stage III included extracranial complications, e.g. labyrinthitis or facial nerve palsy and stage IV incorporates intracranial complications like brain abscesses or sinus thrombosis.

The ChOLE classification(53) was introduced at the same conference as the EAONO/JOS staging for all cholesteatomas, and is intended to classify them in a more intricate manner based on extension, ossicular chain status at the end of surgery, Eustachian tube function, and the presence of complications. To aid the calculation of the score and staging, a web application was developed.

The Potsic system(54), first published in 2002, is specific for congenital cholesteatoma. The staging is also based on extension: stage I is defined as cholesteatoma visible behind one quadrant of the tympanic membrane, stage II is cholesteatoma extending behind multiple quadrants, stage III means hearing ossicles are also involved, and stage IV consists of cases with mastoid involvement. The Potsic staging was updated in 2025 by Marchand et al.(55). The new version, named Mod-Pot, has a similar, extension-based system (tympanic cavity, attic/ossicular involvement, and mastoid involvement), but extension to the anterior epitympanum/protympanum or stapes superstructure demolition can be added as bonus points to further stratification.

However, cholesteatoma is a highly heterogeneous disease even without considering the multitude of possible treatment modalities. As evidence regarding prediction based on these systems is scarce, there is still ample room for refinement.

5.2.4. Goals of cholesteatoma surgery, traditional procedures

The sole treatment modality for cholesteatoma is surgery. Fundamental goals are the complete eradication of squamous tissue, the prevention of complications and recurrence, the creation of a dry, safe ear, and, if possible, the restoration or preservation of hearing (28). When considering the surgical options detailed below, it is important to remember that all patients are unique, from the stage of disease and symptoms they present with to their postoperative expectations. Despite novel minimally invasive techniques, clinicians need to strive to balance functional preservation with maximum disease eradication(56).

5.2.4.1. Canal-wall-down tympanomastoidectomy (CWD)

The more traditional approach in cholesteatoma surgery is canal-wall-down tympanomastoidectomy, which refers to a modified radical mastoidectomy, in which the posterior wall of the bony external ear canal is removed, resulting in a so-called open cavity. In a more extended, nowadays near-obsolete version of this procedure (radical mastoidectomy), the middle ear was also opened into the cavity, and the Eustachian tube was obliterated(28). Although CWD provided excellent visual control for clinicians before the endoscopic era(57), it also has some drawbacks from the patients' point of view. Hearing rehabilitation and aesthetics tend to bring modest results, and numerous patients need regular appointments for cleaning their cavities, which do not tolerate water exposure(58). From a surgical point of view, revisions are often made necessary by meatal stenosis(8), inadequately removed bony overhangs, and ridges(59).

5.2.4.2. Subtotal petrosectomy (STP)

This term was first used by Ugo Fisch to describe the total extirpation of the temporal bone's pneumatic cavities, performing abdominal fat obliteration of the resulting cavity, and finally a blind sac closure of the external auditory canal(60). STP is an extensive procedure, resulting in maximal conductive hearing loss; however, for select patients who already have profound hearing loss and poor quality of life due to several previous procedures, the possibility of a dry, water-tolerant ear still may be worth this sacrifice(61).

5.2.4.3. Canal-wall-up tympanomastoidectomy (CWU)

In contrast to CWD, during CWU, the posterior wall of the bony outer ear canal is kept intact. Endoscopes provide optimal visualisation, thus rendering the previously higher recidivism rates post-CWU comparable to those post-CWD(56, 62, 63). Although planned second-look procedures or non-EPI DWI MRI examinations are needed for follow-up since direct otomicroscopic visualisation of the mastoid cavity is not possible, there is no need for regular cleaning appointments, closed cavities tolerate water, and hearing aids are easily fitted(64, 65).

5.2.4.4. Mastoid obliteration (MO) and Canal Wall Reconstruction (CWR)

To combine the advantages of CWD and CWU procedures, the concept of CWU mastoid obliteration was introduced(66). During this procedure, after performing CWU, the mastoid cavity is filled with autologous or synthetic material (in the original description, soft tissue flaps, but in contemporary practice, bone pâté, hydroxyapatite, or bioactive substances are used most often) to prevent the invasion of a potential new retraction pocket into the mastoid or attic. This procedure is not only advantageous because it results in lower recidivism, but also keeps the canal wall intact(67). In comparison, during a more technically demanding procedure, CWR, a CWD procedure is carried out first, then the posterior canal wall is reconstructed with bone chips or cartilage, and as a final step, the mastoid cavity is also obliterated(68, 69). Mastoid obliteration has gained considerable significance in recent years because it provides significantly lower recurrence rates than either of the procedures discussed above(70, 71, 72, 73).

5.2.5. Future perspectives

As biomolecular data on cholesteatomas rapidly expand and new technologies emerge, new perspectives emerge in cholesteatoma treatment.

A Japanese working group in 2019 published early but promising results on treating patients with cholesteatoma using the topical application of a cream containing the cytostatic agent 5-fluorouracil(74). Other targeted molecular therapeutic agents already used in other disorders were also proposed, but further in vivo evaluations are needed. In the future, these pharmacologic therapies could be used to limit not only growth but also recurrence by preventing the inflammatory circulus viciosus of cholesteatoma expansion (75).

The compact dimensions of the temporal bone and the relative closeness of vital structures within it always meant a considerable challenge for surgeons. However, emerging augmented reality (AR) technology, wherein imaging data such as cholesteatoma extension

and facial nerve position are superimposed on the surgeon's endoscopic or microscopic field of view(76). This renders minimally invasive procedures such as keyhole mastoidectomies feasible(77).

New hardware in the form of extracorporeal video endoscopes (exoscopes) was also introduced. These devices combine a heads-up display previously utilized by endoscopes with the two-handed methodology of microscopes (78, 79).

Surgical procedures and imaging modalities may develop rapidly, but cholesteatoma still challenges even seasoned surgeons daily due to high recidivism rates and its destructive nature. Thus, minimizing morbidity and optimizing surgical treatment is still the cornerstone of research in contemporary cholesteatoma surgery.

6. OBJECTIVES

6.1. Study I - Predicting residual cholesteatoma with the Potsic staging system still lacks evidence: a systematic review and meta-analysis

In the first study, we aimed to investigate the incidence of residual cholesteatoma in the 4 stages defined in the Potsic system for congenital cholesteatomas. Using individual follow-up data, our goal was to assess the prognostic capabilities of this staging system, and as a secondary outcome, analyse the connection between Potsic stage and hearing improvement.

6.2. Study II - Modeling residual cholesteatoma growth rate: a meta-analysis of individual participant data

In our second meta-analysis of individual participant data, our objective was to analyse residual cholesteatoma growth rate through a simulation model in order to provide an optimal, evidence-based time window for imaging or operative follow-up.

7. METHODS

7.1. Methodology and Protocol

Both meta-analyses were conducted based on the recommendations of the PRISMA 2020 guideline(80), the PRISMA-IPD guideline(81), and the Cochrane Collaboration(82). The two study protocols have been registered on PROSPERO(83) (Study I.: CRD42022383932, Study II: CRD42023465320) and followed in every aspect, aside from one exception in the second study, where congenital cholesteatomas were ultimately omitted from the analysis.

7.2 Study I.

7.2.1. Inclusion Criteria

Patients of any age and sex who received a diagnosis of congenital cholesteatoma according to the Levenson criteria(39) and were assigned a Potsic stage(54) either intraoperatively or prior to surgery, undergoing primary procedures with more than 1 year of follow-up postoperatively. The last criterion was omitted in the systematic review section of the analysis to enable the inclusion of more sources, considering the low incidence of congenital cholesteatomas. Articles were only included if they were retrospective cohort or observational studies written in English, whereas we chose to omit conference abstracts and case reports.

7.2.2. Outcomes

The primary outcome of our analysis was the incidence of residual cholesteatoma in each Potsic stage, which, according to the definitions adopted by the EAONO-JOS in 2017(1), is squamous tissue left behind in the tympanic or mastoid cavity after a surgical procedure, which later becomes the starting point for serving as a focal point for repeated cholesteatoma formation.

As additional outcomes, we collected data on the location of residual growth, grouped based on tympanic membrane quadrants, mean age at diagnosis, and audiological outcomes reported as pre- and postoperative pure tone averages (PTA) with air-bone gap (ABG).

7.2.3. Search and selection

A systematic search with no filters applied was conducted on December 14, 2022, in 4 databases (PubMed, Embase, Web of Science, and Cochrane Library) using a 2-domain search

key: (*"Potsic" and stag* or system or classification or congenital or pediatric*) AND *cholesteatoma*

Duplicates were removed first automatically, then manually using a citation manager program (EndNote 20(84)). Afterwards, the title-abstract, then full text selection was performed by two independent authors in a collaborative citation manager application called Rayyan(85). After both selection stages' results were compared, differences were resolved with a third author, and Cohen's Kappa(86) was calculated to measure interrater reliability. The references listed in all studies identified during the full-text selection were also searched for potentially includable articles using CitationChaser(87).

7.2.4. Data extraction

The two authors performing the selection process moved on to extract data independently and enter it into a predesigned Excel(88) datasheet. The following items were included, if available: first author family name, publication year, demographic characteristics (age, sex, number of cases), Potsic stage, number of cases in each stage, surgical procedure, mean duration of follow-up period, audiological results, cholesteatoma location, criteria for exclusion, and inclusion.

7.2.5. Risk of Bias and Quality of Evidence Assessment

To assess risk of bias, the QUIPS tool(89) was chosen, and the process was completed by two authors independently, assisted by a third one to resolve disagreements. Results were visualised with the RobVis application(90). As proposed by the GRADE recommendations(91), a single author assessed the quality of evidence.

7.2.6. Synthesis Methods

Across all 4 Potsic stages, the effect size was measured using the total number of patients with and without residual cholesteatoma. Then, a random intercept meta-logistic regression model was utilized for pooling proportions with stage acting as a moderator variable(92). The Hartung-Knapp adjustment(93) was used to control for the uncertainty in between-study heterogeneity. The maximum likelihood method was applied to calculate random effect heterogeneity (τ^2). We anticipated differences in the between-study heterogeneity within the subgroups defined by the stages, thus different τ^2 values were assigned to them. The between-subgroup difference was assessed using the Cochrane Q

test(92). Heterogeneity (I^2) was assessed between the different studies according to Harrer et al.'s recommendations(92).

7.3. Study II.

7.3.1. Inclusion Criteria

Studies were eligible for inclusion if they contained individual patient data on residual cholesteatoma growth and the time of measurement, either from direct intraoperative visualisation or from imaging. Articles not written in English, case reports, and animal studies were all excluded. According to our original study protocol, congenital cholesteatomas also would have qualified for inclusion, but through the systematic search process, only one article was identified with such data. Thus, we ultimately excluded this cholesteatoma type, given that the difference in etiopathogenesis between congenital and acquired cholesteatomas may lead to distinct growth dynamics. To restrict distortions in growth rate, we also decided not to include residual cholesteatomas that were discovered less than 2 months postoperatively.

7.3.2. Outcomes

For our primary outcome, we defined cholesteatoma growth rate in 2 forms: direct and indirect growth data, as shown in *Figure 1*. In those cases where residual cholesteatomas were measured at 2 different points and the time passed between studies was reported (for example, following a pregnant patient without operation using non-EPI DWI MRI). These data points will be mentioned as “direct measurements”. On the other hand, “indirect measurements” were collected from articles in which only one postoperative size measurement was available, with the interval between the primary procedure and imaging/second-look surgery reported. With these measurements, the exact size of intraoperative residuals, i.e. the starting point for growth, was probably below the visually detectable range; their extent cannot be identified accurately. We hypothesized that the intraoperative size is somewhere between 0 and 1 mm and ran our analysis accordingly. It was also questionable whether indirect and direct measurements could be pooled to maximize sample size and thus decrease variability within the model. Therefore, we also planned to assess the statistical difference between the two groups as well as differences between cohorts created based on sex, age, and previous surgery.

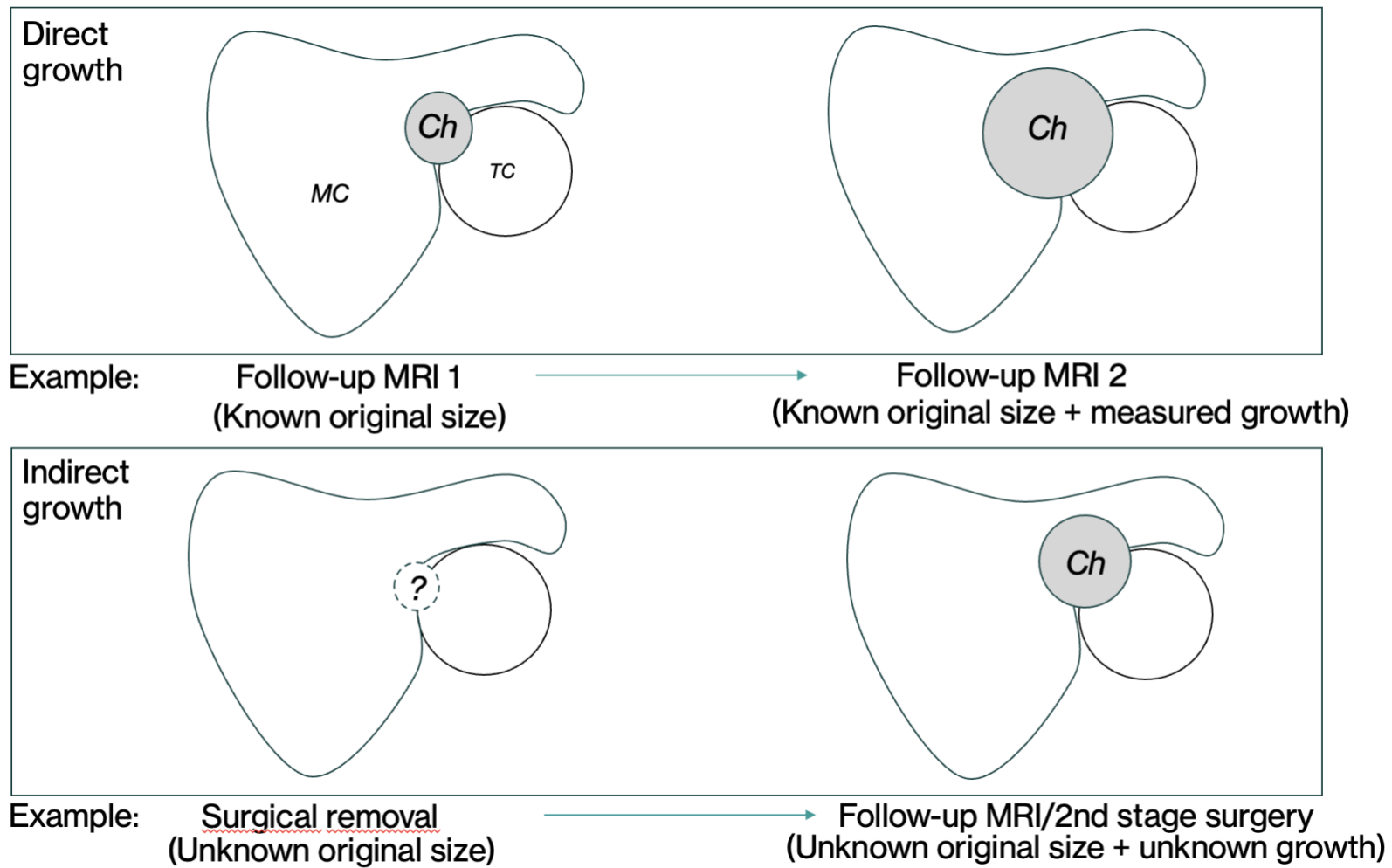


Figure 1 Direct and indirect cholesteatoma measurements MC – mastoid cavity, Ch – cholesteatoma, TC – tympanic cavity, ? – cholesteatoma of unknown size

7.3.3. Search and selection

Four databases (PubMed, Web of Science, Embase, and Cochrane Library) were searched without filters first on September 20, 2023, and then again on July 12, 2024, with the 2-domain search key below:

Cholesteatoma AND (growth or follow or follow-up or recurrence or MRI)*

The additional search was deemed necessary because we learned of recently published articles containing more data for our analysis. Duplicates were removed automatically and manually in EndNote 20 (84), after which two independent reviewers conducted first title-abstract and then full-text selection in the data management application Rayyan(85). Cohen's kappa(86) was calculated to quantify interrater reliability. With assistance from a third reviewer, disagreements were settled after each selection step. The list of citations in the articles identified through full-text selection was also searched with CitationChaser(87). For articles that contained only aggregate information on cholesteatoma growth rate, corresponding authors were contacted to request anonymized individual participant data (time elapsed between surgery and measurement(s), basic demographic features, surgery type, and cholesteatoma size, preferably as the largest diameters in 2 dimensions) via email.

7.3.4. Data extraction

Two independent authors extracted individual growth data from the studies identified through the search and data request process and entered them into a prespecified Excel spreadsheet(88) containing the following columns: first author surname, publication year, demographic characteristics (age, sex, number of cases), age at and time passed since surgery, surgical procedure, measurement method, size, cholesteatoma location and if available specifications of imaging protocols. In articles where data was only available as diagrams, measurements were extracted with the WebPlotDigitizer tool(94).

7.3.5. Risk of Bias and Quality of Evidence Assessment

Risk of bias was independently assessed by the previously mentioned two authors with the JBI Critical Appraisal for Case Series(95). Disagreements were discussed for conflict resolution, and the final results were illustrated using the Risk-of-bias VISualization web application(90).

7.3.6. Synthesis methods

Data analysis and modeling were carried out using R(96) using the lme4(97), lmerTest(98), and sjPlot(99) packages.

As previously described, cholesteatoma growth measurements were available either as direct or as indirect data; for the latter, the original size of intraoperative residuals was unknown. For growth estimation, we ran the model with four hypothetical, radiologically undetectable starting points: 0 mm, 0.33 mm, 0.66 mm, and 1 mm(100, 101). As indirect and direct measurements are two distinct groups and thus may cause systematic differences, they were introduced as fixed effects in our models, and further sensitivity analyses limited to direct measurements were carried out to quantify robustness, to make up for the significantly smaller sample size. We chose to carry out growth modeling not only collectively for all data but also separately for the following covariates to reduce bias: solely imaging-based measurements and direct growth data.

We calculated growth rates from cholesteatoma size measurements described in three formats. First, as two-dimensional values, where the larger value was used as an effective diameter. As a second option, area estimates, from which the diameter of an equivalent circle was derived, or thirdly, volume estimates, from which the diameter of an equivalent sphere was calculated(102). We then used the resulting diameters to compute monthly growth rates by dividing the growth in diameter by the time elapsed in months. As growth rates tend to be positive and right-skewed, we performed a log-transformation to stabilize variance and improve normality in accordance with guidelines for log-normal biological process modeling(103, 104). Thus, in our final models, exponential fixed-effects coefficients depict multiplicative changes in the mean monthly growth rate.

To address heterogeneity, we fitted linear mixed-effects models with restricted maximum likelihood estimation and patient-specific random intercepts nested within studies(105, 106, 107). The lme4 package implements well-established numerical approaches for estimating hierarchical models; thus, we used this package for modeling(97). Covariates such as age at surgery, sex, indirect/direct measurement, and surgical technique were modelled separately when differences in variable availability made it necessary. We obtained confidence intervals for fixed-effect estimates according to recommendations, using profile likelihood(97, 108). We summarized model fit as recommended by Nakagawa and Schielzeth(109) and implemented in the MuMIn package(110), using marginal and conditional R^2 values. We

evaluated model assumptions by inspecting residual distributions and fitted residual relationships.

We conducted a Monte-Carlo simulation to approximate the time required for cholesteatomas to reach clinically relevant sizes. To describe the underlying distribution of lesion expansion, we fit an intercept-only mixed-effects model to the log-transformed growth rates. According to established guidelines of parametric bootstrapping and Monte Carlo simulation(111, 112, 113), the fixed-effect estimate, its standard error, and residual variance were used to define a log-normal data-generating process. We generated 10,000 independent Monte Carlo draws by sampling log-growth rates from a normal distribution centred on the fixed-effect estimate with variance equal to the sum of its squared standard error and the residual variance for both target diameters, 3 mm and 5 mm, individually. Utilizing deterministic transformation, these values were exponentiated and converted into expected times to reach the diameter stated earlier. Rather than replicating a specific study design, these methods result in a distribution of plausible growth trajectories. The thus yielded distributions were visualised through density-based illustrations and delineated according to empirical quantiles.

We are aware that this method does not accurately model real-life, three-dimensional cholesteatoma growth dynamics because it presumes a circular, bidimensional expansion interpreted as diameter expansion. However, our method proved to be practical and reliable for summarizing heterogeneously reported measurements.

8. RESULTS

8.1. Study I

8.1.1. Search and selection, characteristics of the included studies

As pictured in the PRISMA flowchart in **Figure 2**, we have identified 13 articles (114-126) during the full-text selection and reference search, which were all included in the systematic review section, and 7 (114-120) included data sufficient for our meta-analysis. Their characteristics are listed in **Table 1**. All studies were based on retrospective chart reviews, and outcomes included hearing and the incidence of open- and closed-type cholesteatoma. In total, we were able to include 643 patients (33,6% female, 6 months – 16 years) in the systematic review section.

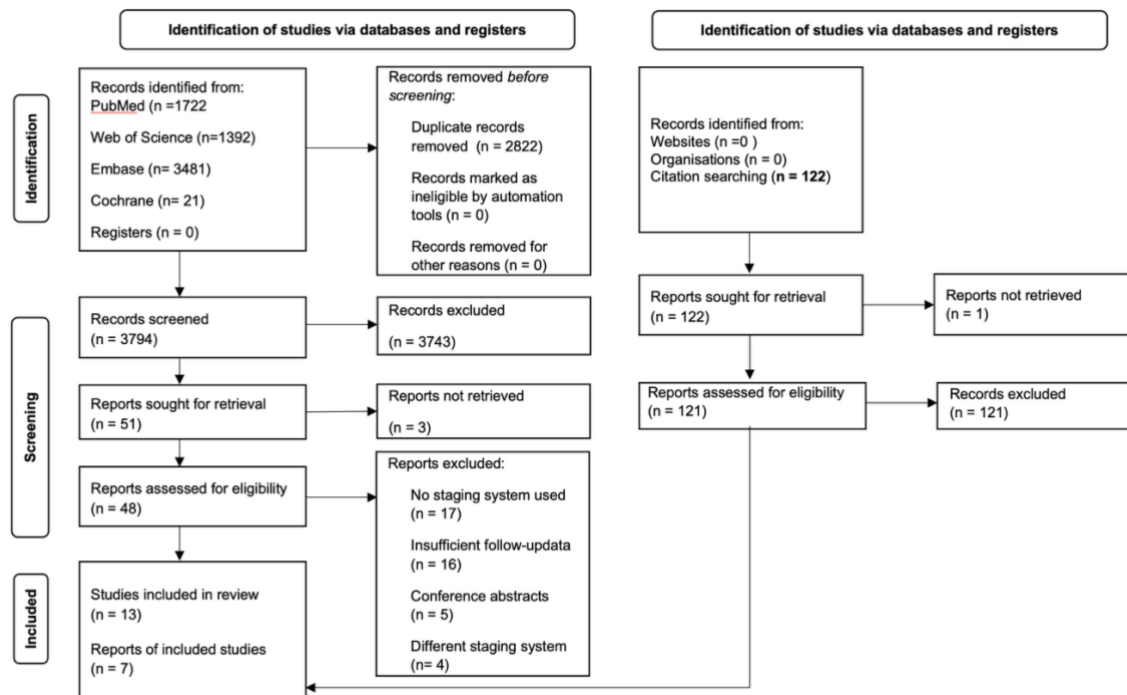


Figure 2 PRISMA flowchart of the selection process for Study I, which started with 6,616 articles and resulted in 13 articles in the review and 7 in the meta-analysis section.

	Participants (% of females, age range)	Intervention	Outcomes	Exclusion criteria (in addition to revision surgery and those listed by Levenson et al, 1986)	Follow-up range
Cho et al, 2016(114)	93 CC (31.2% F, 1-17 yrs)	transcanal myringotomy, tympanoplasty, CWU/CWD mastoidectomy	age at operation, location, number of patients per year, symptoms, operative procedures, recurrence and complication rate		at least 12 months
Inokuchi et al, 2010(115)	23 CC (48% F, 2-37 yrs)	translental tympanotomy, atticotomy and scutumplasty without mastoidectomy, CWU/CWD mastoidectomy	location, symptoms, residual rate, hearing improvement		at least 12 months
Kim et al, 2018(116)	12 CC involving anterior surface of the malleus and tensor tympani tendon (2-10 yrs, 33% F)	total endoscopic ear surgery, endoscope assisted procedures	hearing, postoperative complications, residual or recurrent disease	no involvement of the anterior surface of the malleus and tensor tympani tendon, stage IV	3.5–38.0 months
Kobayashi et al, 2015(117)	12 CC (25% F, 1-6 years)	TEES	hearing improvement, type, size and location of cholesteatoma, complications, and recurrence	mastoid involvement (stage IV)	3-51 months, mean 23.1 months
Lee et al, 2014(118)	36 CC (36% F, 0.5-6 yrs)	cholesteatoma removal with or without mastoidectomy	age at operation, location and type of cholesteatoma, length of hospitalization residual disease, postoperative complications, mean time between initial and second-look surgery	ossicular involvement and mastoid extension (stage III and IV)	12-56 months
Park et al, 2018(119)	25 CC (17 months - 9 years, 24% F)	TEES	age at operation, location, size and type of cholesteatoma, hearing improvement, residual disease, postoperative complications	mastoid involvement (stage IV)	mean 24 months, 12.2 - 37.3 months

	Participants (% of females, age range)	Intervention	Outcomes	Exclusion criteria (in addition to revision surgery and those listed by Levenson et al, 1986)	Follow-up range
Takagi et al, 2014(120)	71 CC (40,8% F, 1 - 23 years)	transcanal or combined transcanal and transmastoid approach, planned two-stage operation, CWD mastoidectomy	symptoms, type and location of cholesteatoma, rate of residual disease		12 months to 6 years, mean period 2.1 years
Jenks et al, 2022(121)	65 CC (29.2% F, 1.2-16 yrs)	TEES	location, type, surgery characteristics, residual rate, hearing improvement	stage IV	9-109.2 months
Kim et al, 2019(122)	115 CC (37.4% F, ≤15 years)	transcanal tympanoplasty, tympanomastoidectomy, tympanoplasty with atticotomy	location, type and symptoms of cholesteatoma, age at diagnosis, residual rate		min 24 months (mean 55.4 months)
Park et al, 2009(123)	35 CC (≤15 years, 22.9% F)	tympanoplasty, epitympanoplasty, CWU/CWD mastoidectomy, ossiculoplasty with PORP placement	CT findings, surgical findings, recurrence rate, hearing assessment		mean 47 months, 9-128 months
Song et al, 2019(124)	38 CC (0.8-17.4 years, 47.4% F)	cholesteatoma removal with or without mastoidectomy	size, type and location of cholesteatoma, rate of residual disease, hearing assessment		mean 30 months, 3-88 months
Stapleton et al, 2012(125)	82 CC (0.3-15.3 yrs, 31%F)	transcanal tympanoplasty, endaural or postauricular tympanoplasty, CWU tympanomastoidectomy, ossicular reconstruction,	mean age at diagnosis, location, rate of residual disease and complications, hearing assessment		mean 4.3 years, 6 months - 12 years

	Participants (% of females, age range)	Intervention	Outcomes	Exclusion criteria (in addition to revision surgery and those listed by Levenson et al, 1986)	Follow-up range
		second, third and fourth look surgery for 87%			
Yamatodani et al, 2013(126)	26 CC (42% F, ≤15 years)	mastoidectomy, myringoplasty, staged tympanoplasty, ossiculoplasty	type and location of cholesteatoma, rate of residual disease, hearing assessment		10-146 months (median 38 months)
total			643 CC (33,6% F, 0.5-16 yrs)		

Table 1. Baseline characteristics included articles for Study I

8.1.2. Quantitative and qualitative analyses

8.1.2.1. Primary Outcome – Proportion of Residual Disease

In our meta-analysis, 259 patients were included from 7 studies with 33 residual cases across 4 stages. The forest plot illustrating the results of the meta-analysis shows the proportion of residual disease in each stage (**Figure 2**). For all stages, the confidence intervals(CI) of residual disease proportion proved to be wide (stage I: 0,01-0,33; stage II: 0,09-0,38 in; stage III: 0,00-0,61; stage IV: 0,01-0,81) with high p values (stage I: 1.00; stage II: 0.99; stage III: 1.00, stage IV: 0.28). Intergroup difference assessed through χ^2_3 test showed no significant intergroup difference ($\chi^2_3=3,17$ $p=0,37$) and heterogeneity measured with I^2 suggested that exact heterogeneity was difficult to evaluate (stage I-III: 0%, stage IV: 22%, overall 0).

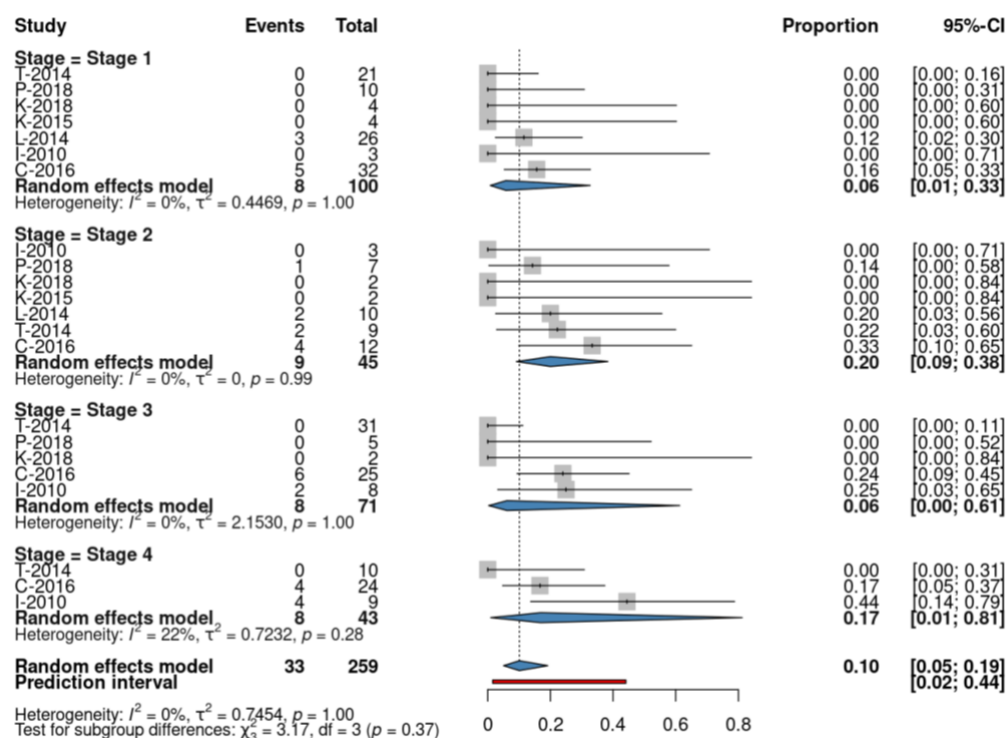


Figure 2 Forest plot showing the proportion of residual disease from the total number of patients after 1 year in four stages of the Potsic staging system for congenital cholesteatoma.

8.1.2.2. Secondary Outcomes – Audiological Results

9 articles (115-117, 119, 121, 123-126) included audiological results (**Table 2**), all using alternative reporting methods to each other and those of the Committee on Hearing and Equilibrium(127), thus, we were not able to summarize them.

Article (author, year)	Hearing Results	Examined thresholds on audiograms (kHz)	Results reported in the articles	Note
Cho et al, 2016(114)	not available			
Inokuchi et al, 2010(115)	staged pre/postoperative PTA for 19/23 patients	0.5, 1, 2	Stage II, III, IV difference not statistically significant; Jonckheere test showed significant relationship between stage and postoperative PTA	not reported whether results were base on bone/air conduction
Jenks et al, 2022(121)	staged pre/postoperative PTA, ABG for the majority of patients	0.5, 1, 2, 4	Pre- and postoperative air conduction PTA and ABG were different among Potsic I-III groups, with worse pre- and postoperative hearing results measured among Potsic stage III cases	
Kim et al, 2018(116)	unstaged pre/postoperative PTA(air) and PTA(bone) for 8/12 pts			
Kim et al, 2019(122)	not available			
Kobayashi et al, 2015(117)	IPD, staged pre/postoperative PTA for 4 patients	0.5, 1, 2	No ear showed any deterioration in hearing acuity, pure-tone audiometry performed in only seven patients	not reported whether results were base on bone/air conduction
Lee et al, 2014(118)	not available			
Park et al, 2009(123)	staged pre/postoperative ABG for 22/35 patients	0.5, 1, 2, 3	In preop ABG gap a trend of the increase with advanced disease stage was detected, postop statistically significant improvement was not detected	

Article (author, year)	Hearing Results	Examined thresholds on audiograms (kHz)	Results reported in the articles	Note
Park et al, 2018(119)	pre/postoperative audiogram in 1 case			
Song et al, 2019(124)	preoperative PTA	not specified		
Stapleton et al, 2012(125)	unstaged pre/postoperative PTA for 80/82 patients			
Takagi et al, 2014(120)	not available			
Yamatodani et al, 2013(126)	staged pre/postoperative AC for 14/26 patients	0.5, 1, 2, 3	Trend toward decreased rates of hearing improvement was associated with cholesteatomas of more advanced stage	
Committee on Hearing and Equilibrium Guidelines(127)	mean, standard deviation and range of postoperative ABG, number of decibels of closure of the ABG (both at least 1 year after treatment), the change in high-tone bone-conduction level in decibels of hearing-loss (6 or more weeks after treatment) for each case	0.5, 1, 2, 3		

Table 2. Documentation and calculation methods of hearing outcomes in Study I. *PTA = pure tone average, ABG = air-bone gap, IPD = individual patient data, AC = air conduction*

Three studies (115, 117, 125) found a statistically significant relationship between stage and hearing improvement, whereas two others(116, 123) reported no significant change in hearing results. One article reported a more modest rate of audiological betterment for patients with higher-stage cholesteatomas(126), and though no statistical analysis was performed, worse hearing outcomes were described in one other analysis(121).

8.1.2.3. Additional Outcomes – Cholesteatoma Location, Mean Age at Diagnosis or Surgery

10 articles (115-125) reported individual data on cholesteatoma location, which we summarized in **Figure 4**. Where two or more locations were stated, rather than creating combined groups, we added them to preexisting ones separately.

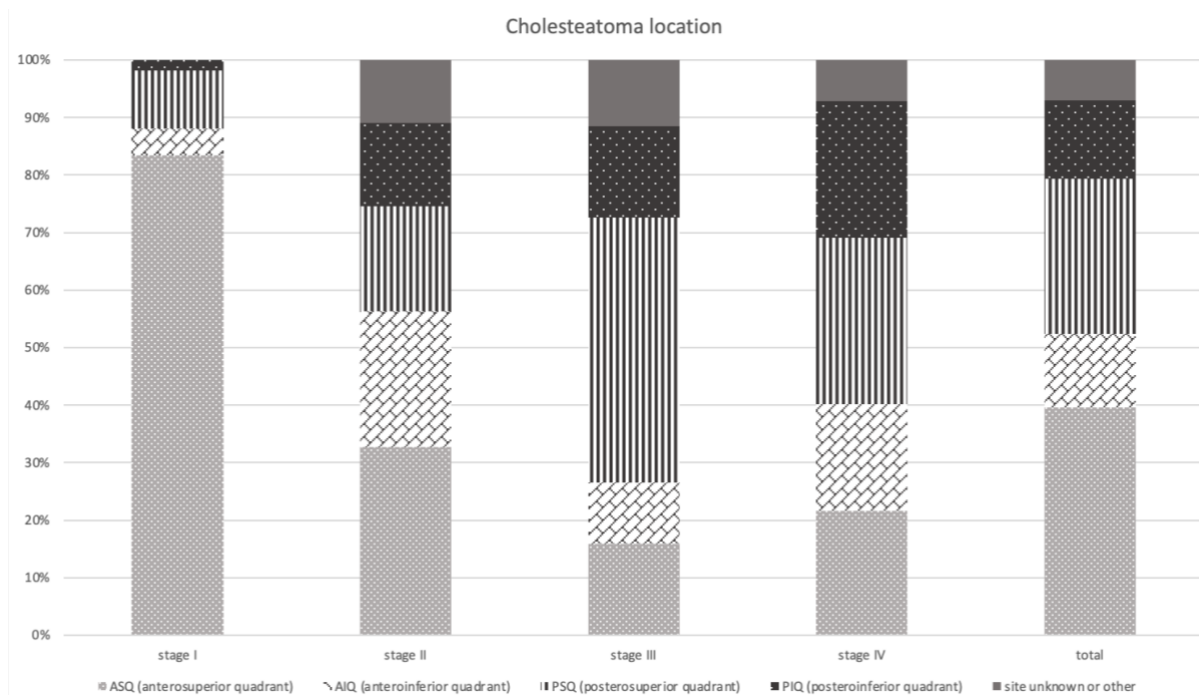


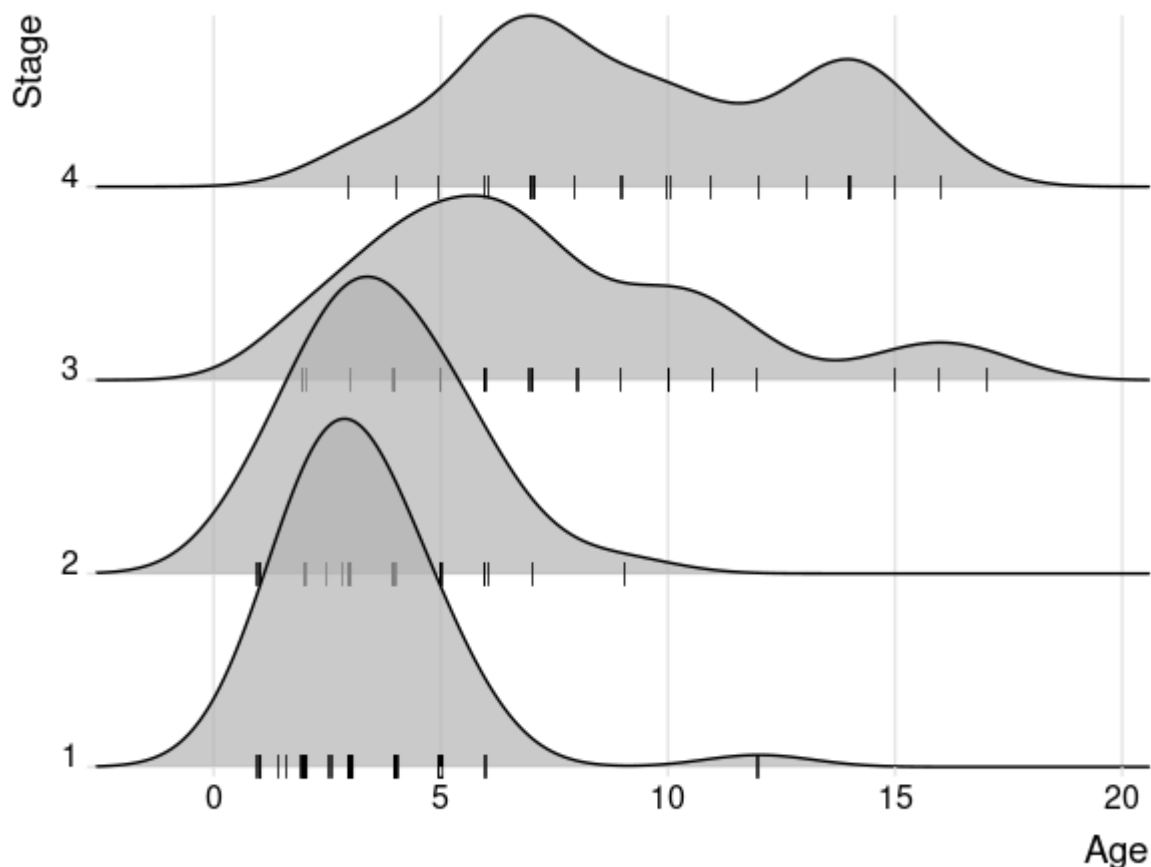
Figure 4 Bar chart depicting the quadrants of the tympanic membrane cholesteatomas are most commonly visible through in each stage as documented in the key articles

Upon summarizing, the anterosuperior quadrant was most frequently affected (214 cases, 38%), followed by the posterosuperior quadrant (163 cases, 29%). Other locations (posteroinferior quadrant (45 cases, 8%), anterior quadrans (35 cases, 6,2%), posterior quadrants (29 cases, 5,2%), anteroinferior quadrant (29 cases, 5,2%), atticus or epitympanic space (15 cases, 2,7%), mastoid cavity (9 cases, 1,6%), superior quadrants (2 cases, 0,4%), and

central quadrant (not specified) (1 case, 0,2%)) were less commonly affected. For 22 patients (3,9%), multiple, unspecified quadrants were reported.

Eight reports (114, 116-120, 124, 126) had individual or pooled data on mean age at diagnosis or surgery. In five (114-118), individual data were given, and three (121, 124, 126) included the mean age at each stage. In order to summarize pooled results, we multiplied the mean age by the number of patients in each stage. With this method, we found a tendency of older age with more advanced stage: 3,5 years in stage I (129 patients), 4,3 years in stage II (53 patients), 7,5 years in stage III (90 patients), and 9,4 years in stage IV (35 patients) (**Figure 5**).

Figure 5 Mean age (years) at staging for patients diagnosed with congenital



cholesteatoma.

8.1.3. Risk of Bias Analysis

Risk of bias analysis with the QUIPS tool(89) revealed a high risk of bias for all included articles (**Figure 6**). Articles proved to be biased in 3 domains, namely reasons for interrupted follow-up, staging procedure, and identifying confounders.

		Risk of bias domains						
		D1	D2	D3	D4	D5	D6	Overall
Study	Cho et al., 2016							
	Inokuchi et al., 2010							
	Jenks et al., 2022							
	Kim et al., 2018							
	Kim et al., 2019							
	Kobayashi et al., 2015							
	Lee et al., 2014							
	Park et al., 2009							
	Park et al., 2018							
	Song et al., 2019							
	Stapleton et al., 2012							
	Yamatodani et al., 2013							
	Takagi et al., 2014							
		Domains: D1: Bias due to participation. D2: Bias due to attrition. D3: Bias due to prognostic factor measurement. D4: Bias due to outcome measurement. D5: Bias due to confounding. D6: Bias in statistical analysis and reporting.						Judgement High Moderate Low

Figure 6 Visualization of the risk of bias assessment for Study I using the QUIPS tool. The grade of bias risk was quantified from low to high in each domain of the questionnaire, and overall, all studies proved to have a high risk of bias.

We created contour-enhanced funnel plots to visualise publication bias (**Figure 7**). As recommended by Harrer et al(92), Egger's test(128) was waived because the number of articles included did not exceed 10.

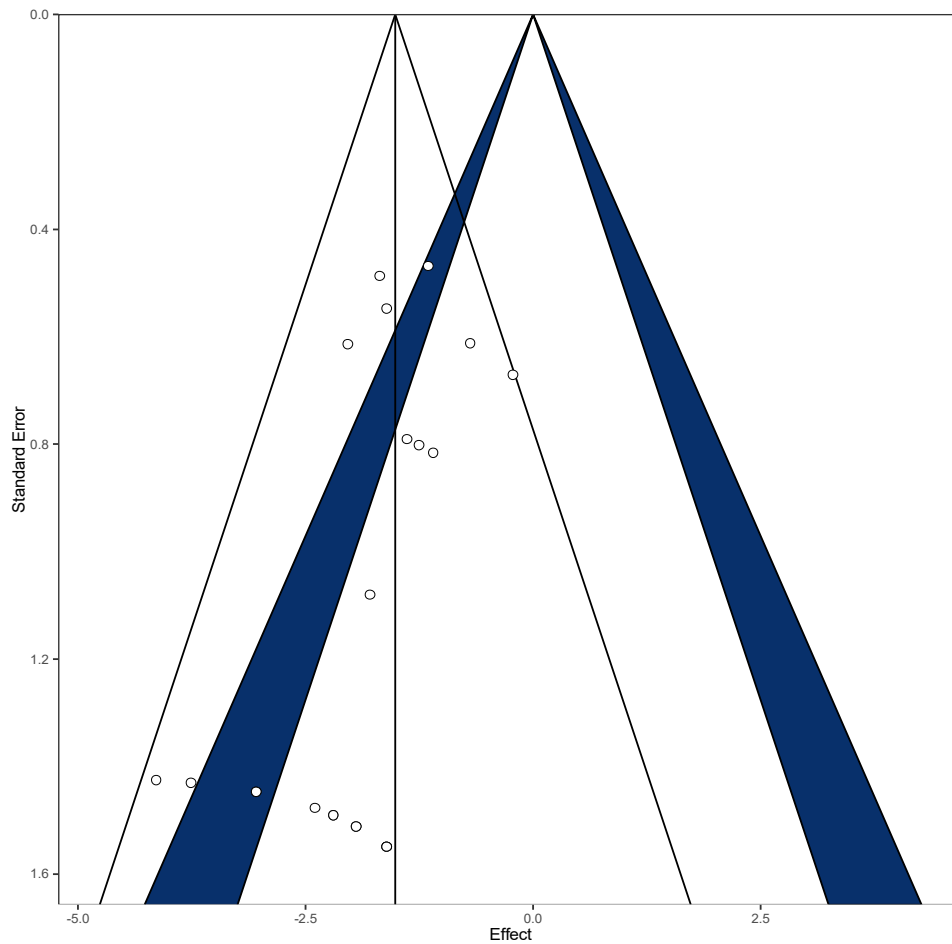


Figure 7. Contrast-enhanced funnel plot to visualise publication bias (i.e. studies with small studies – high standard error – not being published). Study size is shown on the y-axis through standard error, and effect size is on the x-axis, the dark blue triangles represent an ideal scenario with no bias.

8.2. Study II

8.2.1. Search and selection, characteristics of the included studies

Through our systematic search, we identified 11 articles (49, 129-138) (*Figure 8, Table 3*) reporting growth data of 163 patients (mean age 28,3 years, range 4-72 years, data on sex provided for 42,3%, 19,6% female, 38% male), amounting to a total of 248 data points (170 indirect, 78 direct measurements). After requesting individual participant data, the team at Université Paris Cité Department of Pediatric Otolaryngology shared anonymized measurements of 52 patients previously included in 3 separate studies (49, 129-130). Most studies were retrospective, and many included heterogeneous data from various surgical procedures and imaging protocols (*Table 4*).

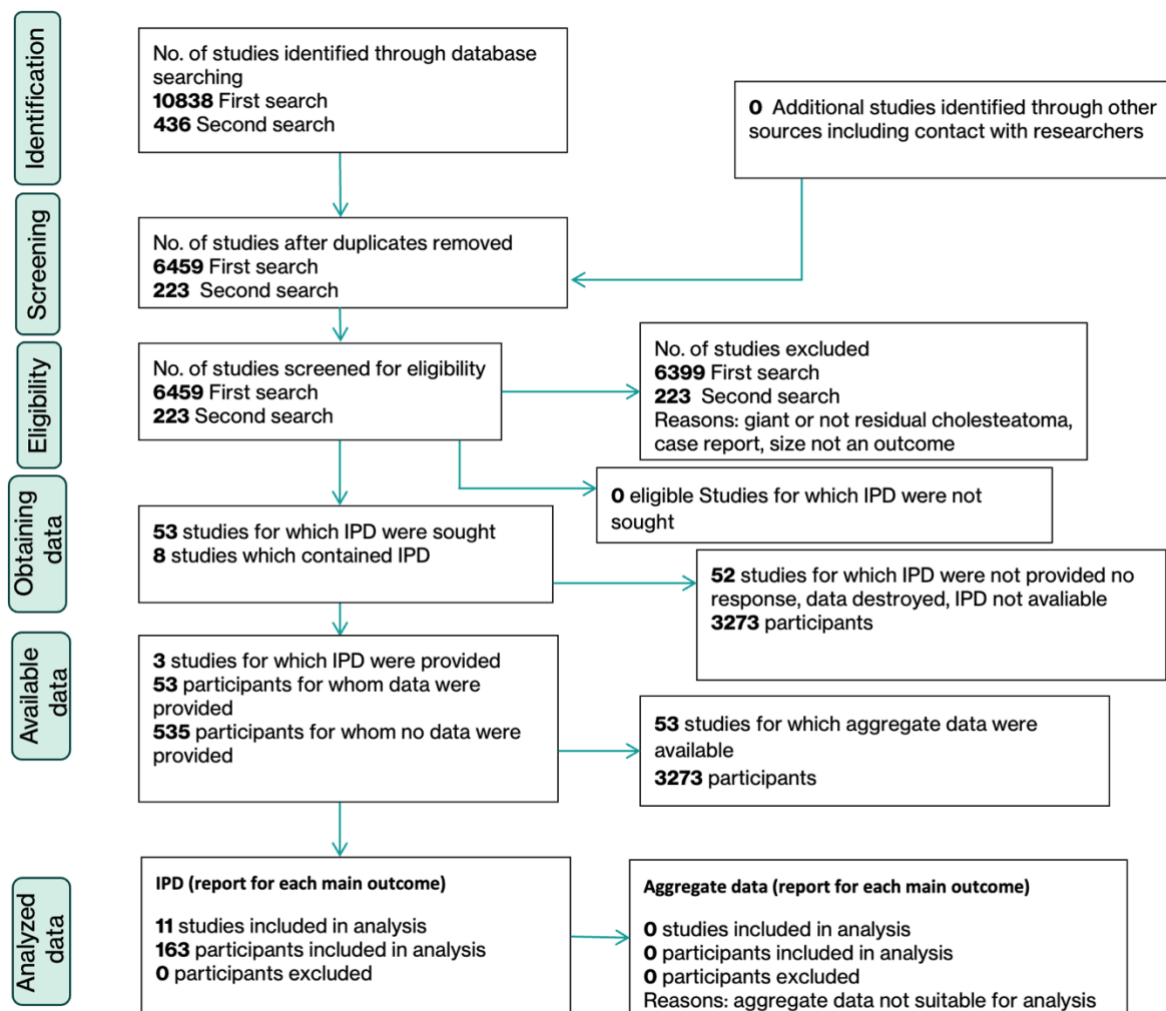


Figure 8 PRISMA flowchart of the selection process for Study II

First author, year of publication (Country)	Study method (OCEBM rate of evidence)	No. of cases (female %, age, data on previous operations)	No. of cases with growth data (no. of datapoints, indirect/direct)	Measurement method	Follow-up length	Mean growth rate
Baoudouin et al., 2023 (France)(129)	Retrospective study (4)	140 (NA, 9.2±3.7 years, various techniques)	*	Non-EPI DWI MRI	3.2±2.2 years	Not calculated
Daoudi et al., 2023 (France)(50)	Retrospective study (4)	224 (30% F, 2-18 years)	*	Non-EPI DWI MRI	27 ± 24 months	Not calculated
Delrue et al., 2019 (Belgium)(130)	Retrospective clinical record study (4)	48 (50% F, 14-84 years, post subtotal petrosectomy)	10 (10, 10/0)	EPI and non-EPI DW MRI, long and short axis diameter in coronal view	0.5-13 years (mean 3.9)	0.54 mm ² /month
De Foer et al., 2008 (Netherlands)(131)	Prospective and blinded study (3)	32 (31% F, 7-71 years, post CWU mastoidectomy)	2 (2, 2/0)	Intraoperative findings	11.2-40.3 months (mean 25.2)	Not calculated
Gristwood et al., 1976 (Australia)(132)	Prospective cohort study (3)	141 (50% F, 6-83 years, various techniques)	23 (29, 24/5)	Intraoperative findings	At most 6 years	epitymanic: doubles diameter every 10 mo, mastoid: doubles diameter every 25 mo
Hellingman et al., 2019 (The Netherlands)(133)	Retrospective case series (4)	10 (70%F, 12-72 years, post subtotal petrosectomy)	10 (62, 13/49)	MRI (not specified)	8-186 months (mean 59)	25.6mm ³ /month

Lecler et al., 2015 (France)(134)	Prospective monocentric consecutive study (3)	22 (9%F, 4-18 years)	7 (10, 10/0)	Non-EPI DWI and contrast enhanced MRI	At least 12 months	Not calculated
Pai et al., 2019 (United Kingdom)(135)	Retrospective case review (4)	12 (NA, 4-66 years, various techniques)	34 (34, 34/0)	Non-EPI DWI MRI	3.0 – 42.8 (Mean 8.1 years, median 6.1)	4mm/year (median 2, range 0 – 18)
Simon et al., 2024 (France)(136)	Retrospective observational study (4)	223 (30%, 8.4±4.3 years, various techniques)	*	Non-EPI DWI MRI	95 months ± 26.2 (range 60-186)	Not calculated
Smith et al., 2020 (United Kingdom)(137)	Retrospective longitudinal study	17 (41%F, 10-72 years)	17 (38, 17/21)	Non-EPI DWI MRI	33 months (range 6-91)	0,6 mm/year (-0,2 mm – 19.9 mm / year)
van der Toom et al., 2022 (Belgium)(138)	Retrospective case review	271 (39% F, post CWU BOT with mastoid obliteration)	8 (11, 8/3)	Non-EPI DWI MRI	60 months (IQR 56-62)	1,8 mm/8 months

Table 3 Baseline characteristics of included articles for Study II

8.2.2. Quantitative and qualitative analyses

8.2.2.1. *Biological Predictors of Growth – Age at Surgery, Sex*

As a result of linear mixed-effects modeling, age at surgery did not prove significant in predicting growth rate (1% decrease per year; 95% CI: -3% to +1%, $p = 0.18$, marginal $R^2 = 0.017$, conditional $R^2 = 0.31$). These results show that most variability may be due to random effects. This part of the analysis was limited by scarce data.

When examining sex as a predictor, male sex was associated with an approximately 19% faster growth in diameter each month (95% CI: 0% to 42%, $p = 0.054$) (**Figure 9, 10, 11**).

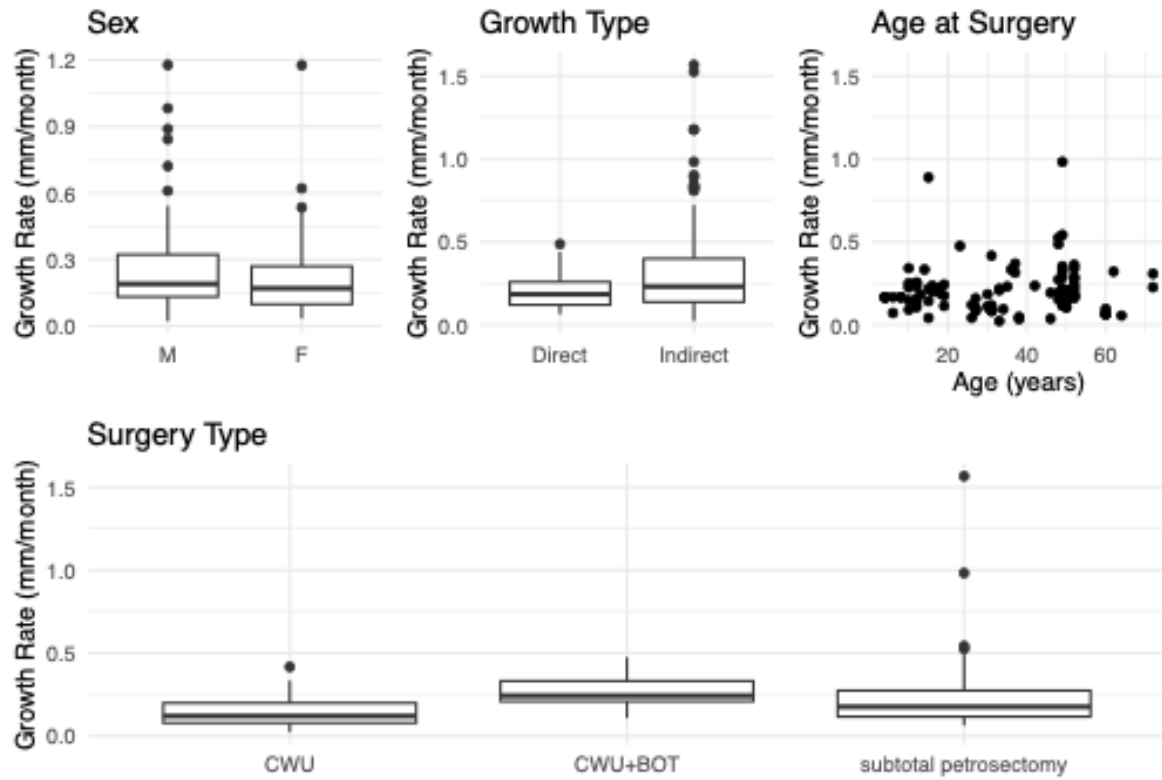


Figure 9 Summarization of observed relationships with the initial size of indirect cholesteatomas set to 0 mm: top row includes sex, growth type, and age; bottom row shows effects of surgical type. mm: millimetre, M: male, F: female, CWU: canal wall up, CWU+BOT: canal wall up with bony obliteration

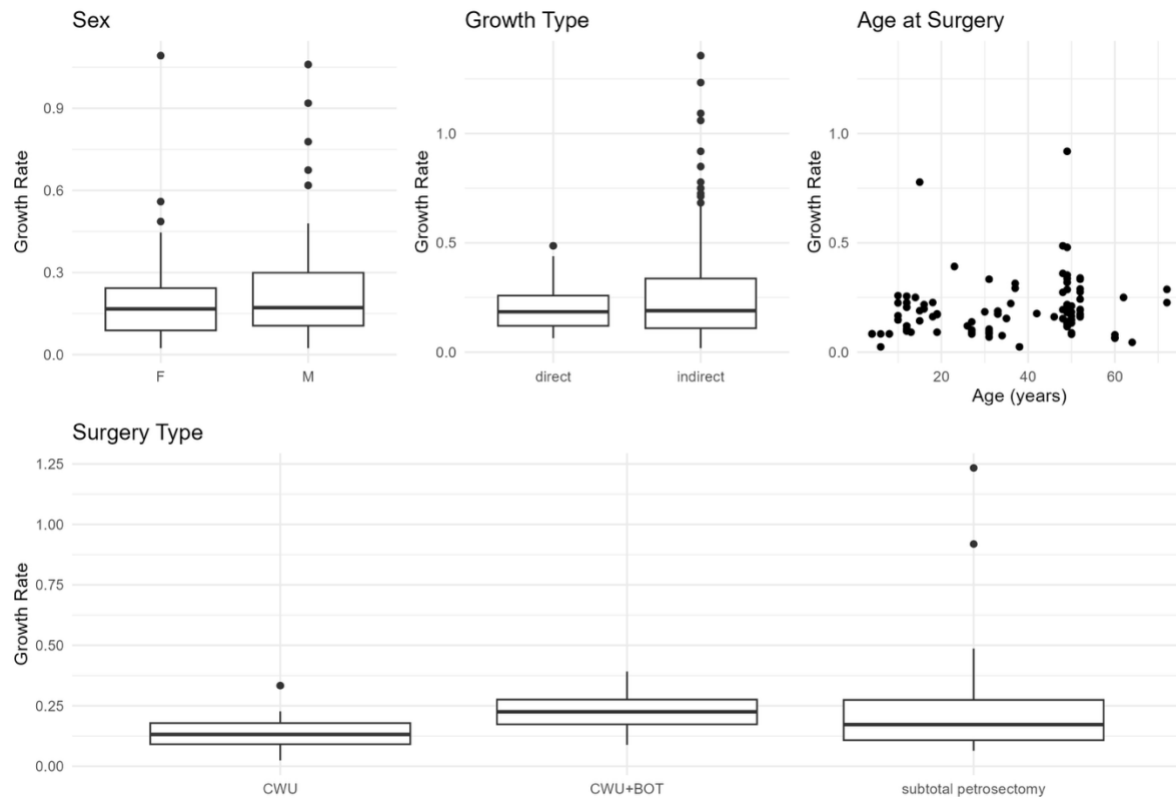


Figure 10 Summarization of observed relationships with the initial size of indirect cholesteatomas set to 1 mm: top row includes sex, growth type, and age; bottom row shows effects of surgical type. mm: millimetre, M: male, F: female, CWU: canal wall up, CWU+BOT: canal wall up with bony obliteration

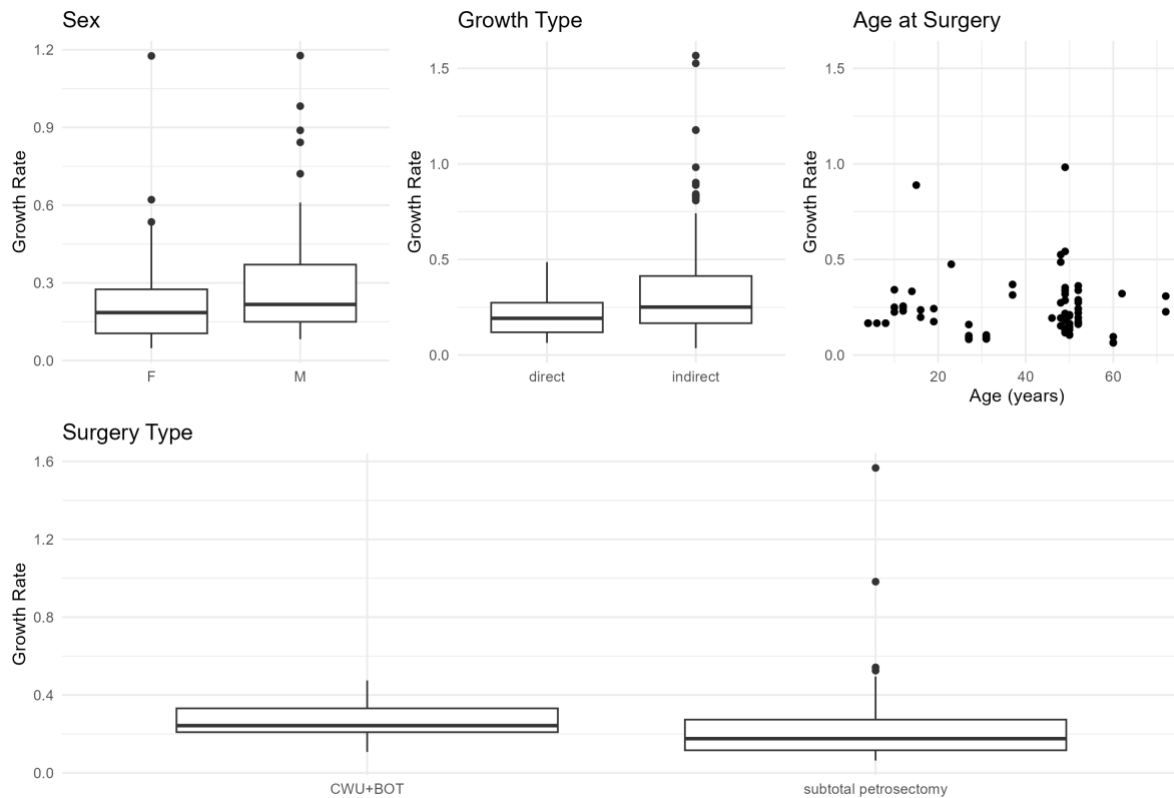


Figure 11 Summarization of observed relationships with the initial size of indirect cholesteatomas set to 0 mm and including only radiological measurements: top row includes sex, growth type, and age; bottom row shows effects of surgical type. mm: millimetre, M: male, F: female, CWU+BOT: canal wall up with bony obliteration

8.2.2.2. Growth Type

When comparing direct and indirect growth rates in another model, when presuming 0 mm as an initial size for indirect data points, directly measured cholesteatomas exhibited a significant, 25% slower growth rate (25%) compared to indirect measurements (95% CI: 6% to 47%, $p = 0.01$, marginal $R^2 = 0.029$, conditional $R^2 = 0.28$) (**Figure 9**). When indirect datapoints were assumed to be 1 mm in diameter instead, the difference between groups was no longer significant (95% CI: 6% to 47%, $p = 0.191$, marginal $R^2 = 0.035$, conditional $R^2 = 0.59$) (**Figure 10**). Considering the uncertainty mentioned in the methods concerning indirect starting size, models were also created with initial sizes of 0.33 and 0.66 mm, and to decrease bias, including only radiological measurement, assuming a starting size of 0 mm.

8.2.2.3. Surgical Procedure

Patients followed after canal wall up procedures with bony obliteration technique (CWU + BOT) exhibited a statistically nonsignificant, 20% increased growth rate compared to patients who underwent only CWU (95% CI: -7% to +54%, $p = 0.14$). When comparing CWU to patients who previously had subtotal petrosectomies (STP), the latter was associated with a significant, 36% higher growth rate (95% CI: 6% to 75%, $p = 0.01$, marginal $R^2 = 0.031$, conditional $R^2 = 0.29$) (**Figure 9, 10, 11**).

8.2.2.4. Simulation Study

To calculate optimal timing for imaging or second-look surgery, simulated growth durations were generated. When presuming 0 mm for indirect starting size, 3 mm (non-EPI DWI MRI threshold) in diameter was reached or surpassed by 95% of cholesteatomas within 28 months and 5 mm (feasible to locate during second-look surgery) was reached or surpassed by 95% of cholesteatomas within 47 months (**Figure 12**). When indirect starting size was increased to 1 mm, a diameter of 3 mm was reached or surpassed only at 35 months, and 5 mm was reached or surpassed at 58 months (**Figure 13**). When only using radiological measurements, the time span was 27 months for 3 mm and 46 months for 5 mm in 95% of cases (**Figure 14**).

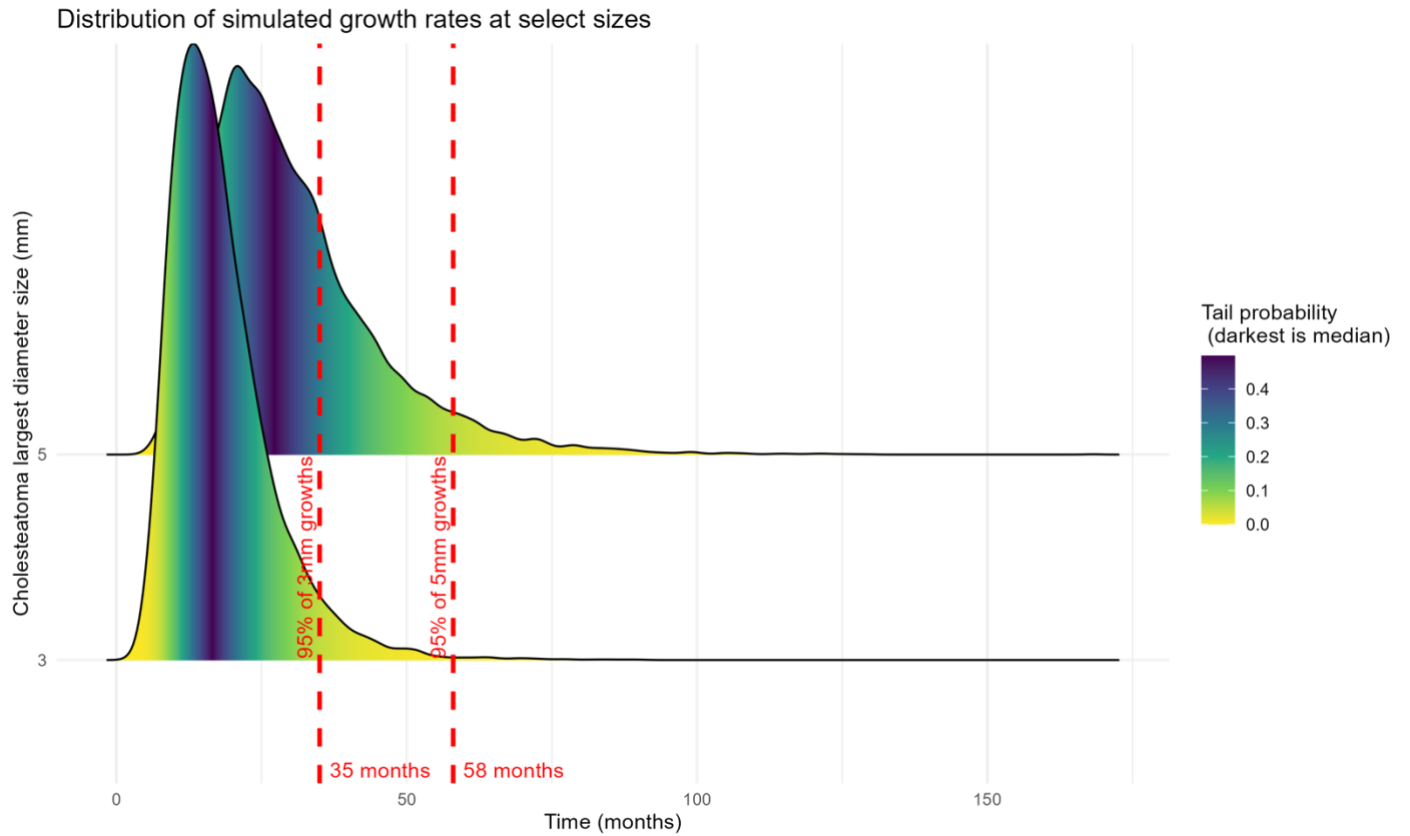


Figure 12 Ridge density plot of simulated time (months) required to reach 3 mm and 5 mm cholesteatoma growth targets, with the initial size of indirect cholesteatomas set to 0 mm. The figure shows the distribution of the likelihood of cholesteatomas reaching a size of 3 or 5 millimetres by a specific time point. Dashed red lines indicate 95th percentiles for each target.

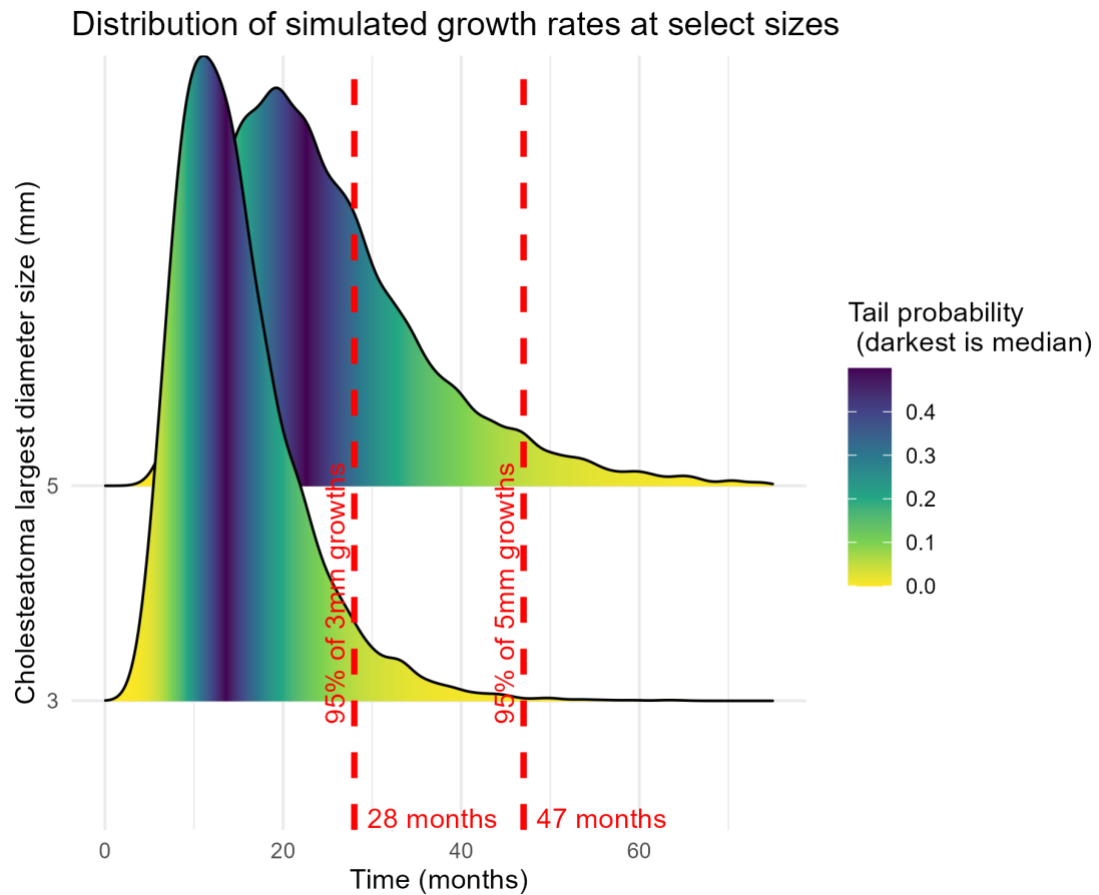


Figure 13 Ridge density plot of simulated time (months) required to reach 3 mm and 5 mm cholesteatoma growth targets, with the initial size of indirect cholesteatomas set to 1 mm. The figure shows the distribution of the likelihood of cholesteatomas to reach a size of 3 or 5 millimetres by a specific timepoint. Dashed red lines indicate 95th percentiles for each target.

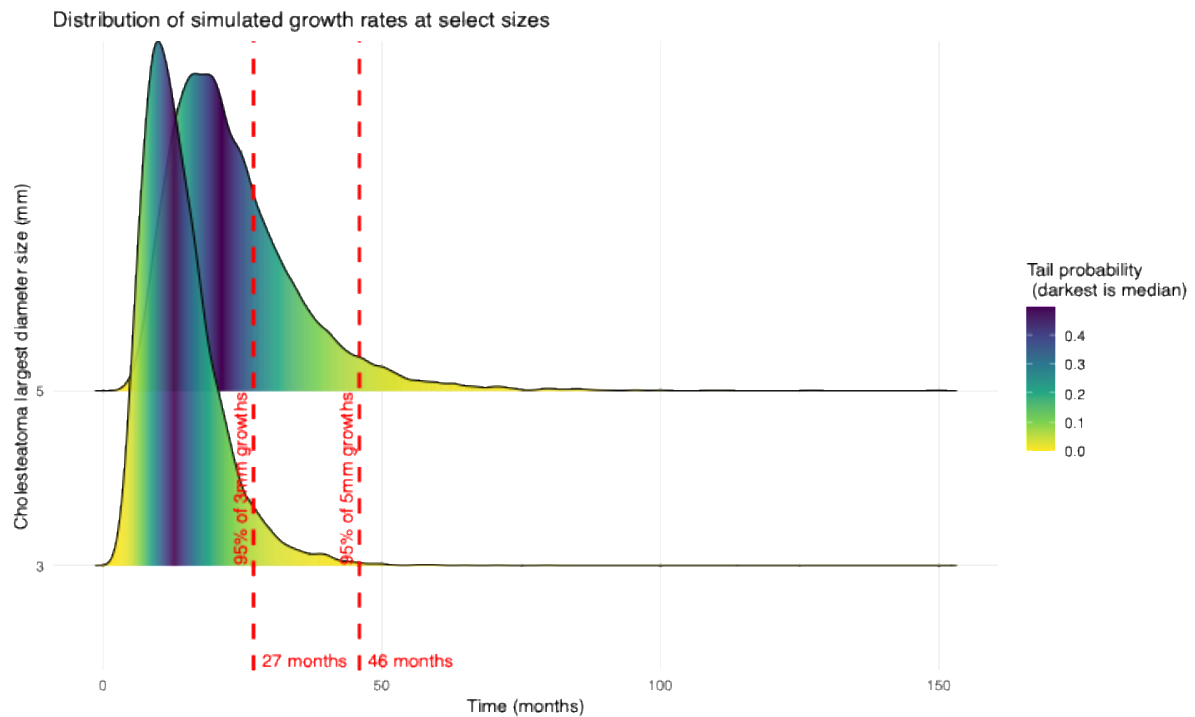


Figure 14 Ridge density plot of simulated time (months) required to reach 3 mm and 5 mm cholesteatoma growth targets, with the initial size of indirect cholesteatomas set to 0 mm and including only radiological measurements. The figure shows the distribution of the likelihood of cholesteatomas to reach a size of 3 or 5 millimetres by a specific timepoint. Dashed red lines indicate 95th percentiles for each target

8.2.3. Risk of Bias Assessment

Owing to heterogeneous imaging protocols, lack of data on consecutiveness and patient demographics, 10/11 key articles received a high risk of bias rating based on the domains of the JBI tool for case series(95) (*Figure 15*).

Study	Risk of bias										Overall
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	
Hellingman et al., 2019	+	+	+	×	×	×	×	+	+	+	×
van der Toom et al. 2022	+	+	+	+	+	+	+	+	+	+	+
Gristman et al., 1976	+	×	?	+	+	+	+	+	×	+	×
Smith et al. 2020	+	+	+	×	×	+	+	+	×	+	×
DeFoer et al., 2008	+	+	+	+	×	+	+	+	×	+	×
Delrue et al., 2018	+	+	+	+	+	×	+	+	+	+	×
Pai et al., 2019	+	+	+	×	+	×	+	+	+	+	×
Lecler et al., 2015	+	+	?	+	+	×	×	+	+	+	×
Daoudi et al., 2023	+	×	+	×	+	+	+	+	+	+	×
Baudouin et al., 2023	+	×	+	+	+	+	+	+	+	+	×
Simon et al., 2024	+	×	+	+	+	+	+	+	+	+	×

D1: Inclusion criteria defined
D2: Standard measurement method
D3: Valid diagnosis
D4: Consecutiveness
D5: Completeness
D6: Patient demographics included
D7: Clinical information included
D8: Follow up information
D9: Disease demographic
D10: Statistical analysis

Judgement
× High
+ Low
? No information

Figure 15 Visualization of the risk of bias assessment for Study II using the JBI tool(95).

9. DISCUSSION

9.1. Summary of findings, international comparisons (including all studies)

Cholesteatoma is an expansive growth of squamous epithelium inside the middle ear, which can either originate from a retraction pocket in the tympanic membrane (“acquired cholesteatoma”) or, in a significantly smaller portion of cases, the condition is congenital(34). Contemporary therapeutic options are all surgical, with a wide array of procedures involving varied invasiveness, their indications based mainly on disease extension. Since recidivism (recurrence or residual disease) affects a large portion of patients, long-term follow-up is essential. In this work, we investigated the possibilities of supporting cholesteatoma management based on disease extension.

In the first study based on individual data from 259 patients with substantial (minimum 1 year) follow-up after primary surgery for congenital cholesteatoma, the difference in residual disease proportion was not statistically significant between Potsic stages. Disease tended to be more extensive as patient age increased, and the most frequent location was behind the anterosuperior quadrant of the tympanic membrane. Audiological outcomes could not be summarized due to a lack of uniform reporting.

During our second project, through collecting all available individually reported cholesteatoma growth data from the literature and creating a residual disease detectability model, we found that 95% of cholesteatomas reach or surpass 3 mm in diameter (lowest size to be detected with optimal specificity and sensibility with non-EPI DWI MRI) after 28-35 months of follow-up after surgery, while the same detection time window for a 5 mm diameter is 47-58 months.

9.1.1. Congenital cholesteatoma staging

As congenital cholesteatoma has a low prevalence (most studies that surfaced in our search include fewer than 100 patients), uniform reporting is essential to create a higher level of evidence. Staging systems are especially helpful for this, and a system created especially for congenital cholesteatoma by Potsic and colleagues(54) is one of the most widely used staging systems. These tools may also facilitate clinical decision-making when selecting the appropriate surgical procedure, thus minimizing the time our youngest patients spend in the hospital. When describing the Potsic staging system for the first time, the authors also included 4 principles as goals for their own staging system: simplicity, stages being clearly defined and well-balanced, and prognostic for later outcomes such as residual disease. Three of our key articles assessed prognostic accuracy in their respective cohorts, finding an association between

advanced stage and a higher probability of residual cholesteatoma(139, 140, 141), while two reported no such connection(124, 142). However, when pooling their results, we found that the difference in the proportion of residual disease between stages was not statistically significant.

9.1.2. Congenital cholesteatoma location

During our first project, when grouping congenital cholesteatomas by the quadrant of the tympanic membrane through which they were visualised, the most common location was the anterosuperior quadrant, closely followed by the posterosuperior quadrant, which is in line with previous publications(143, 144, 145). Inkouchi et al.(139), while analyzing an international cohort, found that patients in East Asia were more likely to have more extensive disease. Our data, though mostly collected from articles published in this region, also showed a predominance of the anterosuperior quadrant being affected.

9.1.3. Biological predictors of growth

When analyzing residual cholesteatoma growth in the second study, we chose to assess basic demographic features such as age and previous surgical procedures.

In middle ear surgery, there is a long-standing presumption, mostly rooted in clinical experience and retrospective studies, that cholesteatoma is more aggressive in children. Previous publications reported larger extension upon diagnosis, more drastic bony erosion, and different biochemical properties compared to those in adults(146, 147, 148, 149, 150). However, in our second study, we found no significant correlation between age at surgery and residual disease growth. A recent analysis of MRI follow-up results involving 664 patients also found that for patients younger than 12 years, the time between surgery and discovering residuals was not shorter than that in adults; however, the risk of developing residual disease in this group was higher(51).

Another factor of interest is the characteristics of the cavity where residual disease forms and whether these spatial relations influence growth rate(151). These are determined by previous surgical procedures: after mastoidectomy, patients are left with an aerated mastoid cavity, whereas after bony obliteration or subtotal petrosectomy, these spaces are filled with bone pâté or autologous fat. In our cohorts (notably heterogeneous, non-randomized, and small groups with an asymmetric distribution), a multivariate analysis found no clinically significant differences in growth dynamics across these spaces. In a recent retrospective comparative study, Kemps et al.(152) found that when comparing bony obliteration and subtotal

petrosectomy follow-up results, residual cholesteatomas were discovered earlier in the first group, although statistical significance was not determined.

Although the data available to us were limited, it would also be worthwhile to investigate whether previously implanted synthetic matter (such as ossicular prostheses made of titanium, silicone sheets placed to prevent scar tissue formation, or autologous bone columellas) influences residual growth.

9.1.4. Cholesteatoma follow-up

To our knowledge, no other cholesteatoma growth model exists, and no internationally approved protocol has been established to this point for cholesteatoma follow-up. However, there is consensus in the literature that, because a large proportion of residual cholesteatomas appear multiple years postoperatively, an extended follow-up period is needed, and early imaging studies should be interpreted with the possibility of false-negative results in mind. (50, 51, 136, 138). Concerns of complications were raised about the delayed follow-up. Nevertheless, according to an analysis conducted during the SARS-CoV-2 pandemic(153), the incidence of major complications did not increase despite longer waiting periods.

In our first project, we found several sources that presented cases with follow-up periods shorter than one year, and during the selection process for our second article, we also found instances where imaging was conducted mere months after surgery. Thus, to reduce bias, we decided not to include these in our analyses.

However, as previously mentioned, some patients have a higher risk of developing residual disease, such as ossicular erosion(154), intraoperative bleeding(155, 156), and extension to hard-to-access areas such as the sinus tympani. Since no standard assessment tool exists for these in cholesteatoma surgery, physicians should gauge risk individually for patients, and in select patients, it might be advisable to diverge from established clinical practice with earlier follow-up MRIs.

Non-EPI DWI MRI with ADC mapping has excellent sensitivity (87%-100%) and specificity (83%-100%) for cholesteatoma as small as 2-3 mm (48, 157, 158, 159). However, autografts introduced previously (cartilage grafts or bone columella were previously shown to influence specificity(160, 161). Taking this into account, when specifying detection thresholds in our cholesteatoma growth model, we chose 3 millimetres for radiological follow-up, and considering our clinical experiences (such as re-exploring a previously obliterated mastoid cavity), we defined 5 millimetres as the limit for operative follow-up. Complying with

established statistical methods (162), the time elapsed between imaging and detection was calculated when 95% of cholesteatomas could be detected.

The majority of size measurements in the database for the second study were based on imaging studies. While this group was already heterogeneous, there were 5 other cholesteatomas, which were measured intraoperatively using surgical instruments with known dimensions(132). To limit intragroup variance, we conducted an analysis omitting these measurements, which yielded results similar to our original model (95% of cholesteatomas reaching or surpassing 3 mm at 27 months and 5 mm at 46 months).

As previously mentioned, we divided our data points into direct and indirect measurements based on whether the exact original size was reported. In the latter group, where we had to assume initial measurements, we created several models with different dimensions: 0 mm, 0.33 mm, 0.66 mm, and 1 mm. When comparing our results, we found that adopting 0 mm as the original size for indirectly measured cholesteatomas, the variance of growth rates in this group was higher, and a significant difference between directly and indirectly measured growth rates was detected. When running the analysis with larger diameters, variance and the difference in growth rate diminished, and although a small difference remained, it was not clinically significant. Based on these results, one could speculate that most intraoperative residuals in this cohort may have been closer to 1 mm in size.

Having no definite starting sizes undoubtedly renders indirectly measured data points less reliable. However, since the method of indirect measurements being acquired is much closer to mainstream practice than subsequent imaging of the same lesion, we still found it important to include them in our analysis.

9.2. Strengths (including all studies)

Both articles followed strict, renowned methodological guidelines and protocols with minimal, documented deviation. To our knowledge, these analyses were the first to summarize substantial data, in the first case to estimate the prognostic capabilities of the widely-used Potsic staging system, and for the second project, to create an evidence-based simulation model of cholesteatoma growth.

9.3. Limitations (including all studies)

Despite the above-mentioned strengths, both articles have several limitations. Most of our data sources were retrospective studies, which included heterogeneous cohorts and sometimes little data regarding previous procedures, follow-up, patient demographics, potential

confounders, and imaging protocols. Due to diverse reporting, we were unable to synthesize summarized data on hearing improvement in the first project, and in the second, we had to resort to using area and volume estimates, which do not fully grasp more complex cholesteatoma expansion patterns and thus may lead to deviations from real-world processes.

10. CONCLUSIONS

Based on our findings, although the Potsic system is exceptional in theory, based on data currently available in the literature, its prognostic value cannot be confirmed. As for cholesteatoma follow-up, according to the data at hand and contrasting current clinical practice, in the future, a delayed follow-up imaging might be warranted for average-risk, grown-up cholesteatoma patients after surgery. However, both projects were based on retrospectively collected, heterogeneous data and thus, further large-scale prospective analyses are needed with rigorous follow-up and reporting to confirm these results.

11. IMPLICATIONS FOR PRACTICE

Although staging systems, especially one so logically built as the Potsic staging system, can be excessively helpful in everyday medical practice, based on the data available in the literature, we could not verify whether this staging system correctly estimates cholesteatoma prognosis.

Based on our cholesteatoma growth model, in average-risk adult patients, the ideal timing for imaging follow-up of residual cholesteatomas may be slightly later than current clinical practice would dictate, approximately 2 years postoperatively.

12. IMPLICATIONS FOR RESEARCH

Cholesteatoma follow-up is a long-term commitment for physicians and patients alike. Further large-scale prospective studies are needed to give us definitive answers on the congenital cholesteatoma recidivism rate and follow-up protocols. Documenting residual cholesteatoma sizes and the exact time of discovery in homogenous patient groups would be helpful to create a more realistic model of cholesteatoma growth.

13. FUTURE PERSPECTIVES, IMPLEMENTATION FOR POLICYMAKERS

In the future, more specific and sensitive imaging methods might emerge, enabling closer follow-up, although access might still prove challenging. To forward the field of middle ear surgery, it is essential for middle ear surgeons to ensure meticulous documentation and long follow-up periods for cholesteatoma patients. Although cholesteatoma may be slow growing, it can potentially result in life-threatening complications. Therefore, policymakers should make it an utmost priority to ensure that all patients are able to progress through the appropriate follow-up protocols on time while also minimizing unnecessary procedures and examinations.

14. REFERENCES

1. Yung M, Tono T, Olszewska E, Yamamoto Y, Sudhoff H, Sakagami M, et al. EAONO/JOS Joint Consensus Statements on the Definitions, Classification and Staging of Middle Ear Cholesteatoma. *The journal of international advanced otology*. 2017;13(1):1-8.
2. Müller J. Ueber den feinen Bau und die Formen der krankhaften Geschwülste. (No Title). 1838.
3. Renner B, Craveiro AV, Balk M, Allner M, Sievert M, Mueller SK, et al. EAONO/JOS classification for acquired cholesteatoma: evaluating the impact of the number of affected sites on treatment and outcomes. *European Archives of Oto-Rhino-Laryngology*. 2023.
4. Melariri H, Balakrishna Y, Mukhtar A, Joseph E, Labuschagne S, Hapunda-Chibanga R, et al. The Global Burden of Cholesteatoma: A Systematic Review and Meta-analysis. *Otolaryngology–Head and Neck Surgery*. 2026;174(1):45-56.
5. Bennett M, Warren F, Jackson GC, Kaylie D. Congenital cholesteatoma: theories, facts, and 53 patients. *Otolaryngologic Clinics of North America*. 2006;39(6):1081-94.
6. Tomlin J, Chang D, McCutcheon B, Harris J. Surgical technique and recurrence in cholesteatoma: a meta-analysis. *Audiol Neurotol*. 2013;18(3):135-42.
7. Harris A, Mettias B, Lesser T. Pooled analysis of the evidence for open cavity, combined approach and reconstruction of the mastoid cavity in primary cholesteatoma surgery. *The Journal of Laryngology & Otology*. 2016;130(3):235-41.
8. van der Toom HF, van der Schroeff MP, Pauw RJ. Single-stage mastoid obliteration in cholesteatoma surgery and recurrent and residual disease rates: a systematic review. *JAMA Otolaryngology–Head & Neck Surgery*. 2018;144(5):440-6.
9. Britze A, Møller M, Ovesen T. Incidence, 10-year recidivism rate and prognostic factors for cholesteatoma. *The Journal of Laryngology & Otology*. 2017;131(4):319-28.
10. Kerckhoffs KG, Kommer MB, van Strien TH, Visscher SJ, Bruijnzeel H, Smit AL, et al. The disease recurrence rate after the canal wall up or canal wall down technique in adults. *The Laryngoscope*. 2016;126(4):980-7.
11. Jackler RK, Santa Maria PL, Varsak YK, Nguyen A, Blevins NH. A new theory on the pathogenesis of acquired cholesteatoma: mucosal traction. *The Laryngoscope*. 2015;125:S1-S14.
12. Wolfman DE, Chole RA. Experimental retraction pocket cholesteatoma. *Annals of Otology, Rhinology & Laryngology*. 1986;95(6):639-44.
13. Roland N, Phillips D, Rogers J, Singh S. The use of ventilation tubes and the incidence of cholesteatoma surgery in the paediatric population of Liverpool. *Clinical Otolaryngology & Allied Sciences*. 1992;17(5):437-9.
14. Marchioni D, Alicandri-Ciufelli M, Molteni G, Artioli FL, Genovese E, Presutti L. Selective epitympanic dysventilation syndrome. *The Laryngoscope*. 2010;120(5):1028-33.
15. Masaki M, Wright CG, Lee DH, Meyerhoff WL. Experimental cholesteatoma: epidermal ingrowth through tympanic membrane following middle ear application of propylene glycol. *Acta oto-laryngologica*. 1989;108(1-2):113-21.
16. Kuijpers W, Vennix P, Peters T, Ramaekers F. Squamous metaplasia of the middle ear epithelium. *Acta oto-laryngologica*. 1996;116(2):293-8.
17. Michaels L, Soucek S. Auditory epithelial migration on the human tympanic membrane: II. The existence of two discrete migratory pathways and their embryologic correlates. *American journal of anatomy*. 1990;189(3):189-200.
18. Hüttenbrink K-B. A new theory interprets the development of a retraction pocket as a natural self-healing process. *European Archives of Oto-Rhino-Laryngology*. 2019;276(2):367-73.

19. Ghedia R, Ahmed J, Navaratnam A, Harcourt J. No evidence of cholesteatoma in untreated otitis media with effusion in children with primary ciliary dyskinesia. *International Journal of Pediatric Otorhinolaryngology*. 2018;105:176-80.
20. Pauna HF, Monsanto RC, Schachern P, Paparella MM, Chole RA, Cureoglu S. Evidence against the mucosal traction theory in cholesteatoma. *The Laryngoscope*. 2018;128(7):1663-7.
21. Michaels L. An epidermoid formation in the developing middle ear: possible source of cholesteatoma. *The Journal of otolaryngology*. 1986;15(3):169-74.
22. Teed RW. Cholesteatoma verum tympani: its relationship to the first epibranchial placode. *Archives of Otolaryngology*. 1936;24(4):455-74.
23. Tos M. A new pathogenesis of mesotympanic (congenital) cholesteatoma. *The Laryngoscope*. 2000;110(11):1890-7.
24. Kayhan FT, Mutlu C, Schachern PA, Le CT, Paparella MM. Significance of epidermoid formations in the middle ear in fetuses and children. *Archives of Otolaryngology–Head & Neck Surgery*. 1997;123(12):1293-7.
25. McGill TJ, Merchant S, Healy GB, Friedman EM. Congenital cholesteatoma of the middle ear in children: a clinical and histopathological report. *The Laryngoscope*. 1991;101(6):606-13.
26. Wang R-G, Hawke M, Kwok P. The epidermoid formation (Michaels' structure) in the developing middle ear. *The Journal of otolaryngology*. 1987;16(6):327-30.
27. Ferlito A. A review of the definition, terminology and pathology of aural cholesteatoma. *The Journal of Laryngology & Otology*. 1993;107(6):483-8.
28. Kuo C-L, Shiao A-S, Yung M, Sakagami M, Sudhoff H, Wang C-H, et al. Updates and knowledge gaps in cholesteatoma research. *BioMed research international*. 2015;2015(1):854024.
29. Haruyama T, Furukawa M, Kusunoki T, Onoda J, Ikeda K. Expression of IL-17 and its role in bone destruction in human middle ear cholesteatoma. *ORL*. 2010;72(6):325-31.
30. Kuo CL. Etiopathogenesis of acquired cholesteatoma: prominent theories and recent advances in biomolecular research. *The Laryngoscope*. 2015;125(1):234-40.
31. Bassiouny M, Badour N, Omran A, Osama H. Histopathological and immunohistochemical characteristics of acquired cholesteatoma in children and adults. *Egyptian Journal of Ear, Nose, Throat and Allied Sciences*. 2012;13(1):7-12.
32. Dambergs K, Sumeraga G, Pilmane M. Comparison of tissue factors in the ontogenetic aspects of human cholesteatoma. *Diagnostics*. 2024;14(6):662.
33. Preciado DA. Biology of cholesteatoma: special considerations in pediatric patients. *International journal of pediatric otorhinolaryngology*. 2012;76(3):319-21.
34. Castle JT. Cholesteatoma pearls: practical points and update. *Head and neck pathology*. 2018;12(3):419-29.
35. Takagi T, Gyo K, Hakuba N, Hyodo J, Hato N. Clinical features, presenting symptoms, and surgical results of congenital cholesteatoma based on Potsic's staging system. *Acta Oto-Laryngologica*. 2014;134(5):462-7.
36. Lee JA, Fuller SR, Nguyen SA, Meyer TA. Factors affecting complications and comorbidities in children with cholesteatoma. *International Journal of Pediatric Otorhinolaryngology*. 2020;135:110080.
37. Mustafa A, Kuçi S, Behramaj A. Management of cholesteatoma complications: Our experience in 145 cases. *Indian Journal of Otology*. 2014;20(2).
38. Milroy C, Slack R, Maw A, Bradfield J. Aural polyps as predictors of underlying cholesteatoma. *Journal of Clinical Pathology*. 1989;42(5):460-5.

39. Levenson MJ, Parisier SC, Chute P, Wenig S, Juarbe C. A review of twenty congenital cholesteatomas of the middle ear in children. *Otolaryngology - Head and Neck Surgery*. 1986;94(5):560-7.
40. Michaels L. Origin of congenital cholestecetoma from a normally occurring epidermoid rest in the developing middle ear. *International journal of pediatric otorhinolaryngology*. 1988;15(1):51-65.
41. Touska P, Connor SEJ. ESR Essentials: imaging of middle ear cholesteatoma—practice recommendations by the European Society of Head and Neck Radiology. *European Radiology*. 2025;35(4):2053-64.
42. Corrales CE, Blevins NH. Imaging for evaluation of cholesteatoma: current concepts and future directions. *Current Opinion in Otolaryngology & Head and Neck Surgery*. 2013;21(5):461-7.
43. Loubele M, Bogaerts R, Van Dijck E, Pauwels R, Vanheusden S, Suetens P, et al. Comparison between effective radiation dose of CBCT and MSCT scanners for dentomaxillofacial applications. *European journal of radiology*. 2009;71(3):461-8.
44. Saxby AJ, Jufas N, Kong JH, Newey A, Pitman AG, Patel NP. Novel radiologic approaches for cholesteatoma detection: implications for endoscopic ear surgery. *Otolaryngologic Clinics of North America*. 2021;54(1):89-109.
45. Keeler JA, Kaylie DM. Cholesteatoma: Is a second stage necessary? *The Laryngoscope*. 2016;126(7):1499-500.
46. Muzaffar J, Metcalfe C, Colley S, Coulson C. Diffusion-weighted magnetic resonance imaging for residual and recurrent cholesteatoma: a systematic review and meta-analysis. *Clinical Otolaryngology*. 2017;42(3):536-43.
47. Bazzi K, Wong E, Jufas N, Patel N. Diffusion-weighted magnetic resonance imaging in the detection of residual and recurrent cholesteatoma in children: a systematic review and meta-analysis. *International journal of pediatric otorhinolaryngology*. 2019;118:90-6.
48. Li PM, Linos E, Gurgel RK, Fischbein NJ, Blevins NH. Evaluating the utility of non-echo-planar diffusion-weighted imaging in the preoperative evaluation of cholesteatoma: A meta-analysis. *The Laryngoscope*. 2013;123(5):1247-50.
49. Patel TA, Etttyreddy A, Cheng T, Smith K, Sridharan SS, McCall AA. Cost-effectiveness of diffusion weighted MRI versus planned second-look surgery for cholesteatoma. *Annals of Otolaryngology, Rhinology & Laryngology*. 2024;133(7):665-71.
50. Daoudi H, Levy R, Baudouin R, Couloigner V, Leboulanger N, Garabédian EN, et al. Performance of non-EPI DW MRI for pediatric cholesteatoma follow-up. *Otolaryngology–Head and Neck Surgery*. 2024;170(1):221-9.
51. Eggink MC, de Wolf MJ, Ebbens FA, de Win MM, Dikkers FG, van Spronsen E. MRI-DWI detection of residual cholesteatoma: moving toward an optimum follow-up scheme. *European Archives of Oto-Rhino-Laryngology*. 2025;282(2):659-68.
52. Sanna M, Pandya Y, Mancini F, Sequino G, Piccirillo E. Petrous bone cholesteatoma: classification, management and review of the literature. *Audiol Neurotol*. 2011;16(2):124-36.
53. Linder TE, Shah S, Martha AS, Rösli C, Emmett SD. Introducing the "ChOLE" Classification and Its Comparison to the EAONO/JOS Consensus Classification for Cholesteatoma Staging. *Otol Neurotol*. 2019;40(1):63-72.
54. Potsic WP, Samadi DS, Marsh RR, Wetmore RF. A staging system for congenital cholesteatoma. *Archives of Otolaryngology - Head and Neck Surgery*. 2002;128(9):1009-12.
55. Marchand G, Chatelet F, Atallah S, Célérier C, Leboulanger N, Couloigner V, et al. EAONO/JOS, STAMCO, ChOLE & Potsic Staging of 271 Pediatric Cholesteatoma: Evidence-Based Mod-Pot Staging System. *The Laryngoscope*. 2025;135(2):908-19.

56. Kostadinov F, Schlegel-Wagner C, Linder T. A tailored approach in cholesteatoma surgery. *European Archives of Oto-Rhino-Laryngology*. 2024;281(10):5189-98.
57. Hulka GF, McElveen Jr JT. A randomized, blinded study of canal wall up versus canal wall down mastoidectomy determining the differences in view of middle ear anatomy and pathology. *LWW*; 1998. p. 574-8.
58. Khalil HS, Windle-Taylor PC. Canal wall down mastoidectomy: A long term commitment to the outpatients? *BMC Ear, Nose and Throat Disorders*. 2003;3(1):1.
59. Das S, Dutta M, Panja T, Sinha R. Chronic draining ear and cholesteatoma recidivism: A retrospection from clinical, imaging, and surgical perspectives. *Turkish archives of otorhinolaryngology*. 2019;57(3):133.
60. Coker NJ, Jenkins HA, Fisch U. Obliteration of the middle ear and mastoid cleft in subtotal petrosectomy: indications, technique, and results. *Annals of Otology, Rhinology & Laryngology*. 1986;95(1):5-11.
61. Sanna M, Dispenza F, Flanagan S, De Stefano A, Falcioni M. Management of chronic otitis by middle ear obliteration with blind sac closure of the external auditory canal. *Otology & neurotology*. 2008;29(1):19-22.
62. Sajjadi H. Endoscopic middle ear and mastoid surgery for cholesteatoma. *Iranian journal of otorhinolaryngology*. 2013;25(71):63.
63. Solis-Pazmino P, Siepmann T, Scheffler P, Ali N-E-S, Lincango-Naranjo E, Valdez TA, et al. Canal wall up versus canal wall down mastoidectomy techniques in the pediatric population with cholesteatoma: A systematic review and meta-analysis of comparative studies. *International Journal of Pediatric Otorhinolaryngology*. 2023;173:111658.
64. Lima AF, Moreira FC, Menezes AS, Costa IE, Azevedo C, Breda MS, et al. Is pediatric cholesteatoma more aggressive in children than in adults? A comparative study using the EAONO/JOS classification. *International journal of pediatric otorhinolaryngology*. 2020;138:110170.
65. Abraham L, Philip A, Lepcha A, Augustine AM, Mathews SS, Paul RR, et al. A comparative study of outcomes and quality of life in canal wall up mastoidectomies and canal wall down mastoidectomies. *Indian Journal of Otolaryngology and Head & Neck Surgery*. 2022;74(Suppl 1):600-7.
66. Mosher HP. A method of filling the excavated mastoid with a flap from the back of the auricle. *The Laryngoscope*. 1911;21(12):1158-63.
67. van Dinther JJ, Vercruysse J-P, Camp S, De Foer B, Casselman J, Somers T, et al. The bony obliteration tympanoplasty in pediatric cholesteatoma: long-term safety and hygienic results. *Otology & Neurotology*. 2015;36(9):1504-9.
68. Gantz BJ, Wilkinson EP, Hansen MR. Canal wall reconstruction tympanomastoidectomy with mastoid obliteration. *The Laryngoscope*. 2005;115(10):1734-40.
69. Walker PC, Mowry SE, Hansen MR, Gantz BJ. Long-Term Results of Canal Wall Reconstruction Tympanomastoidectomy. *Otology & Neurotology*. 2014;35(1):e24-e30.
70. van der Toom HFE, van der Schroeff MP, Metselaar M, van Linge A, Vroegop JL, Pauw RJ. Treatment Outcome of the Bony Obliteration Tympanoplasty Versus Nonobliterative Techniques in Cholesteatoma Surgery: A Retrospective Analysis. *Otology & Neurotology*. 2021;42(9):1366-74.
71. Wilkie M, Chudek D, Webb C, Panarese A, Banhegyi G. Canal wall down mastoidectomy with obliteration versus canal wall up mastoidectomy in primary cholesteatoma surgery. *The Journal of Laryngology & Otology*. 2019;133(12):1074-8.
72. Salem J, Bakundukize J, Milinis K, Sharma SD. Mastoid obliteration versus canal wall down or canal wall up mastoidectomy for cholesteatoma: Systematic review and meta-analysis. *American Journal of Otolaryngology*. 2023;44(2):103751.

73. Illes K, Meznerics FA, Dembrovszky F, Fehervari P, Bánvölgyi A, Csupor D, et al. Mastoid obliteration decreases the recurrent and residual disease: systematic review and meta-analysis. *The Laryngoscope*. 2023;133(6):1297-305.
74. Niwa H, Utsunomiya T, Kuyama Y, Makiyama Y. A Novel Strategy for Conservative Management of External Auditory Canal Cholesteatoma: Employing 5-Fluorouracil in Ambulatory Care for Select Patients. *Archives of Otorhinolaryngology-Head & Neck Surgery (AOHNS)*. 2023.
75. Schürmann M, Goon P, Sudhoff H. Review of potential medical treatments for middle ear cholesteatoma. *Cell Communication and Signaling*. 2022;20(1):148.
76. Chen JX, Yu SE, Ding AS, Lee DJ, Welling DB, Carey JP, et al. Augmented reality in otology/neurotology: a scoping review with implications for practice and education. *The Laryngoscope*. 2023;133(8):1786-95.
77. Uchida M, Matsumoto Y, Morioka S, Hori R, Mizutari K. Efficacy of image-guided percutaneous endoscopic ear surgery: a novel augmented reality-assisted minimally invasive surgery. *Otology & Neurotology*. 2024;10.1097.
78. Minoda R, Miwa T. Non-microscopic Middle Ear Cholesteatoma Surgery: A Case Report of a Novel Head-Up Approach. *Otology & Neurotology*. 2019;40(6):777-81.
79. Zhang B-Y, Ho VW-Y, Tsai T-Y, Chan K-C. An early report of exoscope-assisted otologic surgery. *Journal of the Chinese Medical Association*. 2023;86(5):523-8.
80. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
81. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred reporting items for a systematic review and meta-analysis of individual participant data: the PRISMA-IPD statement. *Jama*. 2015;313(16):1657-65.
82. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*. Cochrane Database of Systematic Reviews. 2022.
83. Haby M, Barreto J, Torres M, Peiris S, Reveiz L. What are the best methodologies for rapid reviews of the research evidence for EIDM in health policy and practice? An overview of systematic reviews and primary studies (Protocol). *Res Synth Methods*. 2022;15(1):1-13.
84. Team TE. *EndNote*. Philadelphia, PA, USA: Clarivate; 2013.
85. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210.
86. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)*. 2012;22(3):276-82.
87. Haddaway NR, Grainger MJ, Gray CT. Citationchaser: A tool for transparent and efficient forward and backward citation chasing in systematic searching. *Research Synthesis Methods*. 2022;13(4):533-45.
88. Corporation M. *Microsoft Excel*. 2018.
89. QUAPAS: An Adaptation of the QUADAS-2 Tool to Assess Prognostic Accuracy Studies. *Annals of Internal Medicine*. 2022;175(7):1010-8.
90. McGuinness LA, Higgins JP. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. *Research synthesis methods*. 2021;12(1):55-61.
91. Jeremy Howick IC, Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, and Hazel Thornton. *Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document) 2011* [Available from: <https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence>].

92. Harrer M, Pim Cuijpers, Furukawa Toshi A, and David D Ebert. *Doing Meta-Analysis With R: A Hands-On Guide*. 1st ed. ed. London: Boca Raton, FL; London: Chapman & Hall/CRC Press.; 2021.
93. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Stat Med*. 2003;22(17):2693-710.
94. Rohatgi A. WebPlotDigitizer tool (v4). 2025.
95. Munn Z, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A, et al. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBI evidence synthesis*. 2020;18(10):2127-33.
96. Team RC. *R: A Language and Environment for Statistical Computing (Version 4.4.2)*. Vienna, Austria: R Foundation for Statistical Computing; 2024.
97. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *Journal of statistical software*. 2015;67:1-48.
98. Kuznetsova A, Brockhoff PB, Christensen RH. lmerTest package: tests in linear mixed effects models. *Journal of statistical software*. 2017;82:1-26.
99. Lüdtke D. sjPlot-data visualization for statistics in social science. Zenodo. 2021.
100. Vercruyse JP, De Foer B, Somers T, Casselman J, Offeciers E. Magnetic resonance imaging of cholesteatoma: An update. *B-ENT*. 2009;5(4):233-40.
101. Williams M, Ayache D. Imagerie des otites chroniques de l'adulte. *Journal de radiologie*. 2006;87(11):1743-55.
102. Weibel C. Nilpotence and K-theory. *Journal of Algebra*. 1979;61(2):298-307.
103. Bland JM, Altman DG. Transformations, means, and confidence intervals. *BMJ: British Medical Journal*. 1996;312(7038):1079.
104. Limpert E, Stahel WA, Abbt M. Log-normal distributions across the sciences: keys and clues: on the charms of statistics, and how mechanical models resembling gambling machines offer a link to a handy way to characterize log-normal distributions, which can provide deeper insight into variability and probability—normal or log-normal: that is the question. *BioScience*. 2001;51(5):341-52.
105. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;963-74.
106. Pinheiro JC, Bates DM. *Mixed-effects models in S and S-PLUS*: Springer; 2000.
107. Gelman A, Hill J. *Data analysis using regression and multilevel/hierarchical models*: Cambridge university press; 2007.
108. Venzon D, Moolgavkar S. A method for computing profile-likelihood-based confidence intervals. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*. 1988;37(1):87-94.
109. Nakagawa S, Schielzeth H. A general and simple method for obtaining R² from generalized linear mixed-effects models. *Methods in ecology and evolution*. 2013;4(2):133-42.
110. Bartoń K. MuMIn: Multi-Model Inference. R package version 1.47. 5. 2023. 2023.
111. Efron B, Tibshirani RJ. *An introduction to the bootstrap*: Chapman and Hall/CRC; 1994.
112. Davison A, Hinkley D. *Bootstrap Methods and Their Application*, Cambridge Univ. Press, Cambridge. 1997.
113. Christian P. Robert GC. *Monte Carlo Statistical Methods*. 2 ed: Springer New York, NY; 2004. XXX, 694 p.
114. Cho HS, Kim HG, Jung DJ, Jang JH, Lee SH, Lee KY. Clinical Aspects and Surgical Outcomes of Congenital Cholesteatoma in 93 Children: Increasing Trends of Congenital Cholesteatoma from 1997 through 2012. *J Audiol Otol*. 2016;20(3):168-73.

115. Inokuchi G, Okuno T, Hata Y, Baba M, Sugiyama D. Congenital cholesteatoma: posterior lesions and the staging system. *Ann Otol Rhinol Laryngol*. 2010;119(7):490-4.
116. Kim BJ, Kim JH, Park MK, Lee JH, Oh SH, Suh MW. Endoscopic visualization to the anterior surface of the malleus and tensor tympani tendon in congenital cholesteatoma. *Eur Arch Otorhinolaryngol*. 2018;275(5):1069-75.
117. Kobayashi T, Gyo K, Komori M, Hyodo M. Efficacy and Safety of Transcanal Endoscopic Ear Surgery for Congenital Cholesteatomas: A Preliminary Report. *Otol Neurotol*. 2015;36(10):1644-50.
118. Lee SH, Jang JH, Lee D, Lee HR, Lee KY. Surgical outcomes of early congenital cholesteatoma: minimally invasive transcanal approach. *Laryngoscope*. 2014;124(3):755-9.
119. Park JH, Ahn J, Moon IJ. Transcanal Endoscopic Ear Surgery for Congenital Cholesteatoma. *Clin Exp Otorhinolaryngol*. 2018;11(4):233-41.
120. Takagi T, Gyo K, Hakuba N, Hyodo J, Hato N. Clinical features, presenting symptoms, and surgical results of congenital cholesteatoma based on Potsic's staging system. *Acta Otolaryngol*. 2014;134(5):462-7.
121. Jenks CM, Purcell PL, Federici G, Villari D, Presutti L, James AL, et al. Transcanal Endoscopic Ear Surgery for Congenital Cholesteatoma: A Multi-institutional Series. *Otolaryngol Head Neck Surg*. 2022;167(3):537-44.
122. Kim H, Yoo SY, Choung YH, Park HY. Is transcanal tympanoplasty an appropriate surgical treatment for congenital middle ear cholesteatoma with ossicular involvement? *Int J Pediatr Otorhinolaryngol*. 2019;116:102-6.
123. Park KH, Park SN, Chang KH, Jung MK, Yeo SW. Congenital middle ear cholesteatoma in children; retrospective review of 35 cases. *Journal of Korean medical science*. 2009;24(1):126-31.
124. Song IS, Han WG, Lim KH, Nam KJ, Yoo MH, Rah YC, et al. Clinical Characteristics and Treatment Outcomes of Congenital Cholesteatoma. *J Int Adv Otol*. 2019;15(3):386-90.
125. Stapleton AL, Egloff AM, Yellon RF. Congenital cholesteatoma: predictors for residual disease and hearing outcomes. *Arch Otolaryngol Head Neck Surg*. 2012;138(3):280-5.
126. Yamatodani T, Mizuta K, Hosokawa K, Takizawa Y, Sugiyama K, Nakanishi H, et al. Congenital middle ear cholesteatoma: Experience from 26 surgical cases. *Annals of Otolaryngology, Rhinology and Laryngology*. 2013;122(5):316-21.
127. Edwin M. Monsell M, PhD, Chairman; Thomas A. Balkany, MD; George A. Gates, MD; Robert A. Goldenberg, MD; William L. Meyerhoff, MD, PhD; John W. House, MD, Consultant. Committee on Hearing and Equilibrium guidelines for the evaluation of results of treatment of conductive hearing loss. American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc. *Otolaryngol Head Neck Surg*. 1995;113(3):186-7.
128. Sterne JAC, Egger M, Smith GD. Investigating and dealing with publication and other biases in meta-analysis. *BMJ*. 2001;323(7304):101-5.
129. Baudouin R, Simon F, Levy R, Breton S, Alciato L, Talab E, et al. Early Magnetic Resonance Imaging to Diagnose Residual Cholesteatoma in Children and Benefit of Radiological Rereview. *Otolaryngol Head Neck Surg*. 2023.
130. Delrue S, De Foer B, van Dinther J, Zarowski A, Bernaerts A, Vanspauwen R, et al. The Value of Diffusion-Weighted MRI in the Long-term follow-up After Subtotal Petrossectomy for Extensive Cholesteatoma and Chronic Suppurative Otitis Media. *Otol Neurotol*. 2019;40(1):e25-e31.
131. De Foer B, Vercruysse J-P, Bernaerts A, Deckers F, Pouillon M, Somers T, et al. Detection of postoperative residual cholesteatoma with non-echo-planar diffusion-weighted magnetic resonance imaging. *Otology & Neurotology*. 2008;29(4):513-7.

132. Gristwood R, Venables W. Growth rate and recurrence of residual epidermoid cholesteatoma after tympanoplasty. *Clinical Otolaryngology & Allied Sciences*. 1976;1(2):169-82.
133. Hellingman CA, Logher JL, Kammeijer Q, Waterval JJ, Ebbens FA, van Spronsen E. Measuring growth of residual cholesteatoma in subtotal petrosectomy. *Acta Oto-Laryngologica*. 2019;139(5):415-20.
134. Lecler A, Lenoir M, Peron J, Denoyelle F, Garabedian EN, Pointe HD, et al. Magnetic resonance imaging at one year for detection of postoperative residual cholesteatoma in children: Is it too early? *Int J Pediatr Otorhinolaryngol*. 2015;79(8):1268-74.
135. Pai I, Crossley E, Lancer H, Dudau C, Connor S. Growth and late detection of post-operative cholesteatoma on long term follow-up with diffusion weighted magnetic resonance imaging (DWI MRI): a retrospective analysis from a single UK centre. *Otology & Neurotology*. 2019;40(5):638-44.
136. Simon F, Remangeon F, Loundon N, Leboulanger N, Couloigner V, Garabédian N, et al. Pediatric cholesteatoma follow-up: residual and recurrence in 239 cases with over 5-year hindsight. *The Laryngoscope*. 2024;134(11):4789-98.
137. Smith WK, Naidu L, Subrahmanyam HK. The use of serial non EPI DWI MRI scans to determine the growth of cholesteatoma. *Bengal Journal of Otolaryngology and Head Neck Surgery*. 2020;28(3):215-20.
138. van der Toom HF, van Dinther JJ, Zarowski A, Baazil AH, De Foer B, Bernaerts A, et al. Radiological follow-up after the bony obliteration tympanoplasty in detecting residual cholesteatoma: towards an optimal postoperative MR imaging protocol. *Otology & Neurotology*. 2022;43(1):e79-e87.
139. Inokuchi G, Okuno T, Hata Y, Baba M, Daisuke S. Congenital cholesteatoma: Posterior lesions and the staging system. *Annals of Otology, Rhinology and Laryngology*. 2010;119(7):490-4.
140. Park JH, Ahn J, Moon IJ. Transcanal Endoscopic Ear Surgery for Congenital Cholesteatoma. *Clinical and experimental otorhinolaryngology*. 2018;11(4):233-41.
141. Stapleton AL, Egloff AM, Yellon RF. Congenital cholesteatoma: predictors for residual disease and hearing outcomes. *Archives of otolaryngology--head & neck surgery*. 2012;138(3):280-5.
142. Kim BJ, Kim JH, Park MK, Lee JH, Oh SH, Suh MW. Endoscopic visualization to the anterior surface of the malleus and tensor tympani tendon in congenital cholesteatoma. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*. 2018;275(5):1069-75.
143. Cho HS, Kim HG, Da Jung Jung NA, Jang JH, Lee S-H, Lee K-Y. Clinical Aspects and Surgical Outcomes of Congenital Cholesteatoma in 93 Children: Increasing Trends of Congenital Cholesteatoma from 1997 through 2012. *Journal of audiology & otology*. 2016;20(3):168-73.
144. Potsic WP, Korman SB, Samadi DS, Wetmore RF. Congenital cholesteatoma: 20 Years' experience at the Children's Hospital of Philadelphia. *Otolaryngology - Head and Neck Surgery*. 2002;126(4):409-14.
145. Nelson JD. Chronic suppurative otitis media. *Pediatric Infectious Disease Journal*. 1988;7(6):446-8.
146. de Carvalho Dornelles C, da Costa SS, Meurer L, Rosito LPS, da Silva AR, Alves SL. Comparison of acquired cholesteatoma between pediatric and adult patients. *European archives of oto-rhino-laryngology*. 2009;266(10):1553-61.
147. Kalia M, Dass A, Singhal S, Gupta N. Comparative study of cholesteatoma in paediatric and adult patients. *The Journal of Laryngology & Otology*. 2022;136(8):765-8.

148. Molinari G, Reale M, Albera A, Russo FY, Di Lullo AM, Gaffuri M, et al. Follow-up strategies in pediatric cholesteatoma: a systematic review. *European Archives of Oto-Rhino-Laryngology*. 2025;282(1):11-22.
149. Kuo C-L, Shiao A-S, Yung M, Sakagami M, Sudhoff H, Wang C-H, et al. Updates and knowledge gaps in cholesteatoma research. *BioMed research international*. 2015;2015(NA):854024-.
150. Jackson R, Addison A, Prinsley P. Cholesteatoma in children and adults: are there really any differences? *The Journal of Laryngology & Otology*. 2018;132(7):575-8.
151. Hinohira Y, Gyo K, Yanagihara N, Bredberg G, Alsterborg E. Effects of mastoid cavity obliteration on the growth of experimentally produced residual cholesteatoma. *Acta Otolaryngol*. 1998;118(1):101-4.
152. Kemps G, Geven L, Kunst H, Mylanus E, Mulder J, Lanting C, et al. Surgical Treatment for Troublesome Mastoid Cavities: Canal Wall Reconstruction With Bony Obliteration Versus Subtotal Petrossectomy. *Otology & Neurotology*. 2024;45(3):273-80.
153. Hussain MH, Mair M, Mahmood S, Sakagiannis G, Rojoa DM, Raheman FJ, et al. Delays in surgery for cholesteatoma due to COVID-19: is there an impact on rates of recidivism and major complications? *European Archives of Oto-Rhino-Laryngology*. 2021;278(9):3291-7.
154. Rosenfeld RM, Moura RL, Bluestone CD. Predictors of residual-recurrent cholesteatoma in children. *Archives of Otolaryngology–Head & Neck Surgery*. 1992;118(4):384-91.
155. le Nobel GJ, Cushing SL, Papsin BC, James AL. Intraoperative bleeding and the risk of residual cholesteatoma: a multivariate analysis. *Otology & Neurotology*. 2017;38(4):529-34.
156. Volgger V, Lindeskog G, Krause E, Schrötzlmair F. Identification of risk factors for residual cholesteatoma in children and adults: a retrospective study on 110 cases of revision surgery. *Brazilian Journal of Otorhinolaryngology*. 2020;86(2):201-8.
157. Jindal M, Riskalla A, Jiang D, Connor S, O'Connor AF. A systematic review of diffusion-weighted magnetic resonance imaging in the assessment of postoperative cholesteatoma. *Otology & Neurotology*. 2011;32(8):1243-9.
158. Lingam RK, Bassett P. A meta-analysis on the diagnostic performance of non-echoplanar diffusion-weighted imaging in detecting middle ear cholesteatoma: 10 years on. *Otology & Neurotology*. 2017;38(4):521-8.
159. Geoffray A, Guesmi M, Nebbia JF, Leloutre B, Bailleux S, Maschi C. MRI for the diagnosis of recurrent middle ear cholesteatoma in children—can we optimize the technique? Preliminary study. *Pediatric radiology*. 2013;43(4):464-73.
160. Kálmán J, Horváth T, Liktó B, Dános K, Tamás L, Gódegy M, et al. Limitations of non-echo planar diffusion weighted magnetic resonance imaging (non-EPI MRI) in cholesteatoma surveillance after ossicular chain reconstruction. A prospective study. *Auris Nasus Larynx*. 2021;48(4):630-5.
161. Walters H, Lee-Warder L, Mentias Y, Arullendran P. Cartilage grafts mimicking cholesteatoma recurrence on diffusion-weighted magnetic resonance imaging: a case series. *The Journal of Laryngology & Otology*. 2023;137(8):938-41.
162. Hazra A. Using the confidence interval confidently. *Journal of thoracic disease*. 2017;9(10):4125.

15. BIBLIOGRAPHY

15.1. Publications related to the thesis

Körmendy, KB ; Shenker-Horváth, K ; Shulze Wenning, A. ;

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Modeling residual cholesteatoma growth rate: a meta-analysis of individual participant data. 2026, Eur Arch Otorhinolaryngol.

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15.2. Publications not related to the thesis

Körmendy KB, Illés K, Bajor B, Kálmán J, Sükösd H, Horváth T

Endoscopic control of difficult-to-access sites during microscopic cholesteatoma surgery. 2025, Ear Nose Throat J.

Q3, IF: 0,7

Budai BK, Stollmayer R, Ronaszeki AD, Körmendy KB, Zsombor Z, Palotás L, Fejér B, Szendrői A, Székely E, Maurovich-Horvat P, Kaposi PN (2022)

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Predicting residual cholesteatoma with the Potsic staging system still lacks evidence: a systematic review and meta-analysis

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Abstract

Purpose To investigate the rate of residual disease in the Potsic staging system for congenital cholesteatomas.

Methods A protocol registration was published on PROSPERO (CRD42022383932), describing residual disease as a primary outcome and hearing improvement as secondary. A systematic search was performed in four databases (PubMed, Embase, Cochrane Library, Web of Science) on December 14, 2022. Articles were included if cholesteatomas were staged according to the Potsic system and follow-up duration was documented. Risk of bias was evaluated using the Quality In Prognosis Studies (QUIPS) tool. In the statistical synthesis a random effects model was used. Between-study heterogeneity was assessed using I^2 .

Results Thirteen articles were found to be eligible for systematic review and seven were included in the meta-analysis section. All records were retrospective cohort studies with high risk of bias. Regarding the proportions of residual disease, analysis using the χ^2 test showed no statistically significant difference between Potsic stages after a follow-up of minimum one year (stage I 0.06 (confidence interval (CI) 0.01–0.33); stage II 0.20 (CI 0.09–0.38); stage III 0.06 (CI 0.00–0.61); stage IV: 0.17 (CI 0.01–0.81)). Postoperative and preoperative hearing outcomes could not be analyzed due to varied reporting. Results on cholesteatoma location and mean age at staging were consistent with those previously published.

Conclusion No statistically significant difference was found in the proportions of residual disease between Potsic stages, thus the staging system's applicability for outcome prediction could not be proven based on the available data. Targeted studies are needed for a higher level of evidence.

Keywords Congenital cholesteatoma · Potsic · Residual cholesteatoma

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Introduction

The most widely used staging system for congenital cholesteatoma is the one that was described by Potsic and colleagues in 2002 [1], which is based on the extension of the disease behind an intact tympanic membrane. A cholesteatoma limited to a single tympanic membrane quadrant is referred to as stage I, while a cholesteatoma mass behind two or more quadrants without ossicular chain involvement or mastoid extension is called stage II. Stage III means that the ossicular chain is affected but without mastoid involvement, and the cholesteatoma enters the mastoid space in stage IV disease.

There are numerous advantages to adopting a staging system in cholesteatoma management. Ideally, it could allow for more precise patient counseling about disease severity and the likelihood of experiencing residual cholesteatoma, help

comparing treatment results on a multi-institutional level, choose proper surgical approach, and assess the need for second-look surgery.

As congenital cholesteatoma is an uncommon disease, accounting for only 1–5% [2] of all cholesteatomas, mostly smaller case series were published in the literature, with some of them using the Potsic staging system to categorize patients [3]. As it was described when introduced, one of the dedicated goals of this staging system is outcome prediction [1]. However, the real prognostic value of this system in estimating the occurrence of residual disease remains uncertain. To obtain a higher level of evidence on the usefulness of the Potsic staging system, a joint data analysis of these studies is needed. Therefore, we aimed to assess whether the Potsic staging system was indeed indicative of the rate of residual disease and whether the extent of hearing improvement was also connected to the stage at presentation.

Methods

The following systematic review and meta-analysis was based on recommendations of the PRISMA 2020 guideline [4] and the Cochrane Handbook [5]. The protocol of the study was created using a PICO framework [6], has been registered on PROSPERO (registration number: CRD42022383932) and was adhered to in every step.

Inclusion and exclusion criteria

We included patients of any age and sex, diagnosed with congenital cholesteatoma (with or without symptoms) based on the Levenson criteria [7]. These criteria are the following: upon examination a pearly white mass can be observed medial to an intact tympanic membrane with a normal pars tensa and flaccida and no history of tympanic membrane perforation, no previous otologic procedures in the anamnesis, but previous occurrences of otitis media are allowed. Additional criteria for selected studies were that all patients were undergoing primary surgery, and afterwards followed up for more than 12 months, and their cholesteatoma was graded using the Potsic staging system. For the records selected for the systematic review section of our report we also included sources with a follow-up period shorter than 12 months to allow for a wider scope of publications on this rare entity that we studied.

We included published retrospective cohort studies and observational studies written in English, whereas conference abstracts, guidelines, systematic reviews of literature, meta-analyses, animal studies, case reports, case series and reports predating the publication of the Potsic staging system were excluded. Reports that included no information based on residual disease in each stage were likewise

excluded, together with patients whose outcome has been individually reported but were lost to follow-up within one year of surgery.

Information sources and search strategy

A systematic search was performed on December 14, 2022, in PubMed, Embase, Web of Science, and Cochrane Library using the following search key, without applying filters:

“Potsic” and stag* or system or classification or congenital or pediatric) AND cholesteatoma.

Reference lists of all identified studies found eligible during text selection were reviewed for additional reports using CitationChaser [8].

Selection process

After automatic and manual removal of duplicates using a citation manager program (EndNote 20, Clarivate Analytics, Philadelphia, PA, USA), title, abstract and full-text selection was performed by two independent review authors (BK and KSH) using the management program Rayyan [9]. After each selection step disagreements were resolved by a third reviewer (TH) and inter-rater reliability was measured with Cohen’s kappa calculation [10].

Data collection process

The aforementioned authors (BK and KSH) independently completed the data extraction using a predesigned Excel (Microsoft Corporation, Redmond, Washington, United States) datasheet. The following data were extracted from each eligible article if available: name of the first author, year of publication, basic demographic characteristics (proportion of females, age, number of patients), number of patients assigned to each stage, the number of residual cases in these stages, surgery technique, length of follow-up period mean, median, standard deviation and range measured in months, hearing outcomes, type and location of the cholesteatoma, exclusion and inclusion criteria. Disagreements on data extraction were resolved by discussion between the authors.

Data items

Our main outcome was the proportion of residual disease (defined as keratinizing squamous epithelium left behind in the tympanic or mastoid cavity serving as a focal point for new cholesteatoma growth) [11] in each Potsic stage. Secondary outcomes were preoperative cholesteatoma location behind the quadrants of the tympanic membrane, improvement in hearing measured by preoperative and post-operative pure tone average or air bone gap, and mean age

at diagnosis. Studies were ineligible if these outcomes were either not measured or measured but not reported.

Study risk of bias assessment

The two authors (KBK and KSH) performed the risk of bias assessment and visualized the results independently using the QUIPS tool [12]. Disagreements arising in the process were resolved through discussion.

Effect measures and synthesis methods

To calculate the proportions, in each Potsic stage we used the total number of patients and those with residual diseases to measure effect size. We then used a random intercept meta-logistic regression model to pool proportions where the stage was a moderator variable [13]. Knapp–Hartung adjustments [14] were applied to the parameter estimates to control for the uncertainty in between-study heterogeneity. We used the maximum likelihood method to estimate the random effect heterogeneity (τ^2). For the different stages where we assumed that subgroups had different τ^2 values as we anticipated differences in the between-study heterogeneity in the subgroups. We assessed the difference between

the subgroups with the Cochrane Q test [13]. I^2 was used to assess the between-study heterogeneity following the recommendations of Harrer et al. [13].

Reporting bias assessment

Funnel plots were applied to report and visualize publication bias.

Certainty assessment

Level of evidence was ranked using the Oxford Centre of Evidence Based Medicine (OCEBM) 2011 Levels of Evidence table [15], assisted by the OCEBM Background document [16].

Results

Study selection

Our selection process is detailed in a PRISMA flowchart pictured in Fig. 1. Inter-rater reliability according to Cohen's kappa was 0.94 for title and abstract selection, and 1.00 for

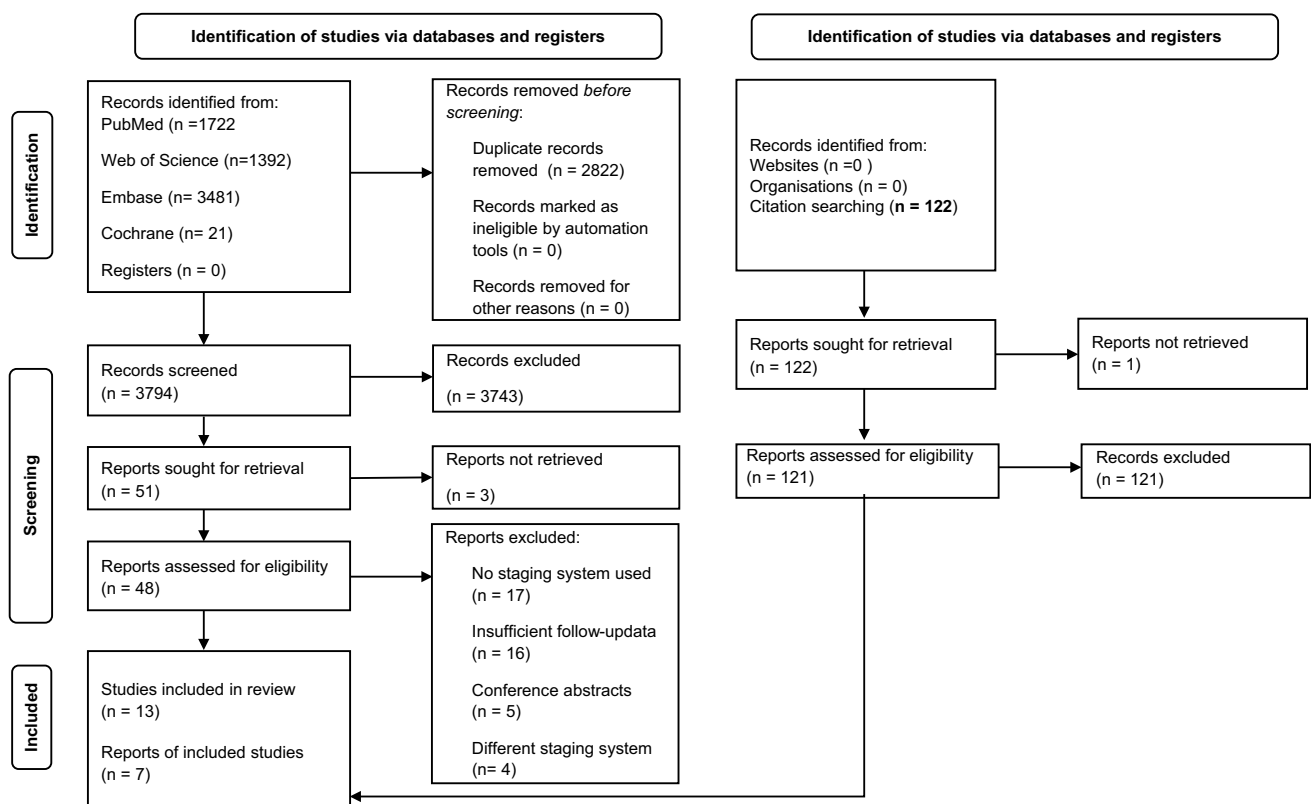


Fig. 1 PRISMA flowchart of the selection process, which started with 6,616 articles and included 13 articles included in the review and 7 included in the meta-analysis section

full-text selection. We have found 13 publications [17–29] that satisfied our criteria, others were excluded because they used no staging system or one different from the one proposed by Potsic et al. [1]. Reference lists of included full texts yielded no further eligible reports.

Results and characteristics of individual studies

In our systematic review, all the included studies (their characteristics are listed in Table 1) were retrospective cohort studies, based on reviewing charts of patients previously treated for congenital cholesteatoma, diagnosed according to the criteria proposed by Levenson et al. [7].

Due to the low incidence rate of congenital cholesteatoma, only one publication [21] included more than 100 patients. The total number of patients included in our review was 633, of whom 216 were female, their ages spanning between six months and 37 years.

A wide range of outcomes was documented apart from our primary and secondary outcomes, such as the incidence of postoperative complications, morphological findings, and the rate of open- and closed-type cholesteatoma.

Risk of bias in studies (Supplementary material, Table 1)

As a result of assessing the risk of bias, all key articles proved to have high risk of bias according to the QUIPS tool [12]. Reasons were insufficient reporting on patients lost to follow-up, not establishing how patients were staged and whether this was done in a standardized way, and failing to define or measure potential confounders.

Results of syntheses

The primary synthesis described in our protocol assessed whether Potsic stage at presentation was predictive of residual disease. The secondary outcome was hearing improvement and additional, not prespecified outcomes were cholesteatoma location and mean age at diagnosis.

Results of statistical synthesis

The forest plot in Fig. 2, which details the results of our meta-analysis, shows the proportion of residual disease in each stage, based on data from 259 patients with a total of 33 residual cases, divided into four stages. Seven reports [17, 18, 20, 22–24, 28] were included in this analysis, where follow-up time of all patients or single patients whose individual data was published within the report exceeded 12 months after surgery.

Results of the statistical analysis showed wide confidence intervals (CI) (CI 0.01–0.33 in stage I; CI 0.09–0.38

in stage II; CI 0.00–0.61 in stage III; CI 0.01–0.81 in stage IV) and high p values (1.00 in stage I; 0.99 in stage II; 1.00 in stage III and 0.28 in stage IV) with I^2 values (0% in stage I–III and 22% in stage IV, overall 0%), suggesting that exact heterogeneity was hard to assess. The intergroup difference was tested with χ^2_3 test ($\chi^2_3 = 3.17$ $p = 0.37$). Thus, differences in the proportions of patients with residual disease in each stage were not shown to be statistically significant.

Results of qualitative analyses

Location of cholesteatoma

Location of cholesteatoma was detailed in ten reports [20, 22–26, 28, 29]. Figure 3 shows our graph summarizing the occurrences of cholesteatoma behind each quadrant of the tympanic membrane, in the attic, and in the mastoid space. In cases where two or more locations were specified, rather than pairing them in separate groups, both were added to their significant cluster.

As a result, we have found that the anterosuperior quadrant was the most common site for cholesteatomas (214 of 563 affected quadrants), followed by the posterosuperior quadrant (163). Less common locations are the posteroinferior quadrant (45), anterior quadrants [20, 25] (not specified) (35), posterior quadrants (not specified) (29), anteroinferior quadrant (29), atticus or epitympanic space [18] (15), mastoid cavity (9), superior quadrants (not specified) (2) and central quadrant [20] (not specified) (1). In 22 cases, multiple [17, 23, 26, 29] (not specified) quadrants were reported.

Hearing improvement

As shown in Table 2, hearing results were reported in nine studies [17–25, 27–29]. All of them used a slightly different approach to assessing hearing improvement, and none of them followed the guidelines of the Committee on Hearing and Equilibrium [30]. Although analyzing hearing improvement was registered as our secondary outcome, we were unable to pool the published results.

One study [29] showed a decreased rate of hearing improvement in more advanced stages. Similarly, in two other reports [18, 27], a significant relationship was shown between stage and postoperative pure tone average (PTA). Although no quantitative analysis was performed, results of a third publication [19] also show that pre- and post-operative hearing results were worse among stage III patients. The remaining two publications either found no significant post-operative hearing improvement [25] or showed no deterioration based on the results available for seven patients [20, 22].

Table 1 Characteristics of included studies. An overview of our key articles' [17–29] main characteristics

	Participants (% of females, age range)	Intervention	Outcomes	Exclusion criteria (in addition to revision surgery and those listed by Levenson et al., 1986)	Follow-up time
Cho et al. 2016	93 CC (31.2% F, 1–17 yrs)	Transcanal myringotomy, tympanoplasty, CWU/CWD mastoidectomy	Age at operation, location, number of patients per year, symptoms, operative procedures, recurrence and complication rate		At least 12 months
Inokuchi et al. 2010	23 CC (48% F, 2–37 yrs)	Transmeatal tympanotomy, atticotomy and scutumplasty without mastoidectomy, CWU/CWD mastoidectomy	Location, symptoms, residual rate, hearing improvement		At least 12 months
Kim et al. 2018	12 CC involving anterior surface of the malleus and tensor tympani tendon (33% F, 2–10 yrs)	TEES, endoscope assisted procedures	Hearing, postoperative complications, residual or recurrent disease	No involvement of the anterior surface of the malleus and tensor tympani tendon, stage IV	3.5–38.0 months
Kobayashii et al. 2015	12 CC (25% F, 1–6 years)	TEES	Hearing improvement, type, size and location of cholesteatoma, complications, and recurrence	Mastoid involvement (stage IV)	3–51 months, mean 23.1 months
Lee et al. 2014	36 CC (36% F, 0.5–6 yrs)	Cholesteatoma removal with or without mastoidectomy	Age at operation, location and type of cholesteatoma, length of hospitalization residual disease, postoperative complications, mean time between initial and second-look surgery	Ossicular involvement and mastoid extension (stage III and IV)	12–56 months
Park et al. 2018	25 CC (24% F, 17 months–9 years)	TEES	Age at operation, location, size and type of cholesteatoma, hearing improvement, residual disease, postoperative complications	Mastoid involvement (stage IV)	Mean 24 months, 12.2–37.3 months
Takagi et al. 2014	71 CC (40.8% F, 1–23 years)	Transcanal or combined transcanal and transmastoid approach, planned two-stage operation, CWD mastoidectomy	symptoms, type and location of cholesteatoma, rate of residual disease		12 months to 6 years, mean period 2.1 years
Jenks et al. 2022	65 CC (29.2% F, 1.2–16 yrs)	TEES	Location, type, surgery characteristics, residual rate, hearing improvement	Stage IV	9–109.2 months
Kim et al. 2019	115 CC (37.4% F, ≤ 15 years)	Transcanal tympanoplasty, tympanomastoidectomy, tympanoplasty with atticotomy	Location, type and symptoms of cholesteatoma, age at diagnosis, residual rate		Min 24 months (mean 55.4 months)

Table 1 (continued)

	Participants (% of females, age range)	Intervention	Outcomes	Exclusion criteria (in addition to revision surgery and those listed by Levenson et al., 1986)	Follow-up time
Park et al. 2009	35 CC (22.9% F, ≤15 years)	Tympanoplasty, epitympanoplasty, CWU/CWD mastoidectomy, ossiculoplasty with PORP placement	CT findings, surgical findings, recurrence rate, hearing assessment		Mean 47 months, 9–128 months
Song et al. 2019	38 CC (47.4% F, 0.8–17.4 years)	Cholesteatoma removal with or without mastoidectomy	Size, type and location of cholesteatoma, rate of residual disease, hearing assessment		mean 30 months, 3–88 months
Stapleton et al. 2012	82 CC (31% F, 0.3–15.3 yrs)	Transcanal tympanoplasty, endaural or postauricular tympanoplasty, CWU tympanomastoidectomy, ossicular reconstruction, second, third and fourth look surgery for 87%	Mean age at diagnosis, location, rate of residual disease and complications, hearing assessment		Mean 4.3 years, 6 months–12 years
Yamatodani et al. 2013	26 CC (42% F, ≤15 years)	Mastoidectomy, myringoplasty, staged tympanoplasty, ossiculoplasty	Type and location of cholesteatoma, rate of residual disease, hearing assessment		10–146 months (median 38 months)
Total	633 CC (33.6% F, 0.5–16 yrs)				

CC congenital cholesteatoma, CWU canal wall up, CWD canal wall down, TEES total endoscopic ear surgery, PORP partial ossicular replacement prosthesis

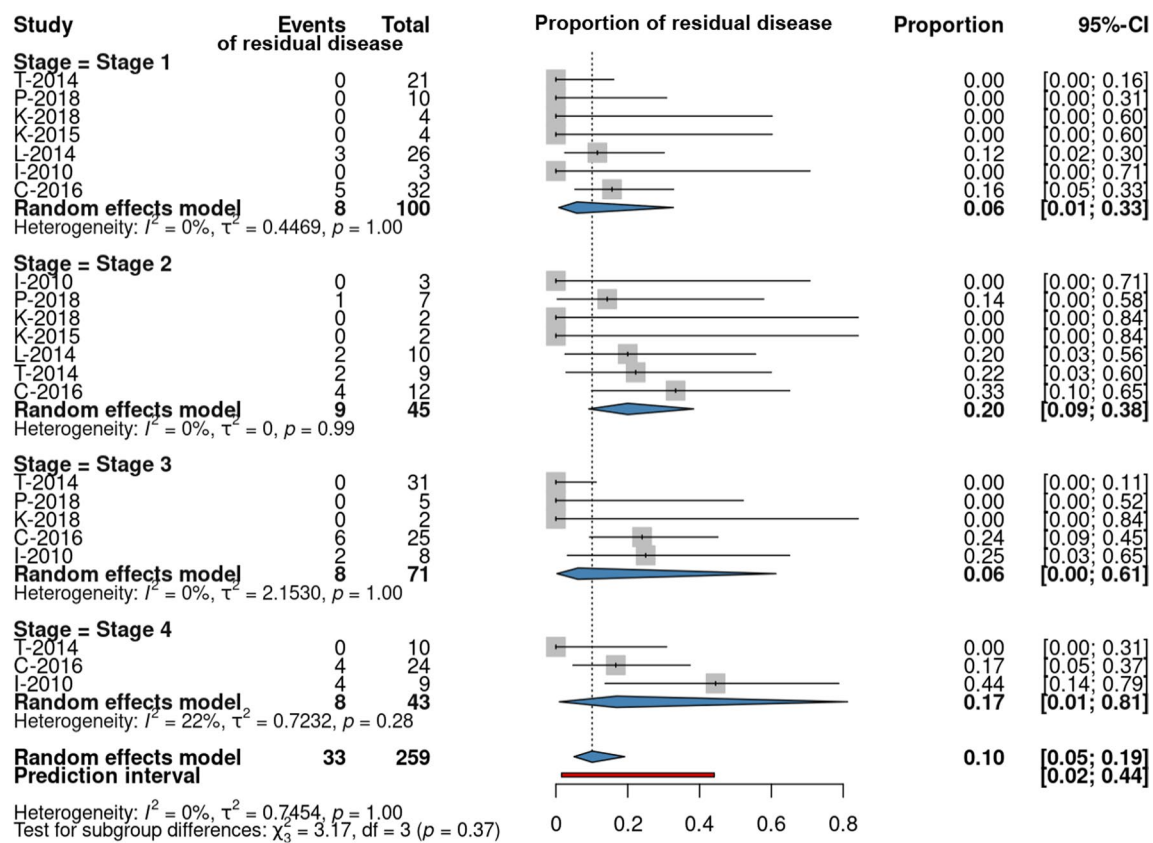


Fig. 2 Forest plot showing the proportion of residual disease from the total number of patients after 1 year in four stages of the Potsic staging system for congenital cholesteatoma

Mean age at staging

Eight studies [17, 19, 20, 22–24, 26, 29] out of our 13 key articles had information on age at diagnosis or surgery. In three reports [19, 22, 23], age had been specified as age at first surgery. Five articles [17, 20, 22–24] had individual patient data, and three [19, 26, 29] had staged means available.

To be able to calculate an approximate mean from these three articles, we have summarized (Fig. 4) the ages of patients by multiplying the mean age by the number of patients in each stage. Thus, the approximate mean age at staging came to be 3.5 years for stage I, 4.3 years for stage II, 7.5 years for stage III, and 9.4 years for stage IV based on data from 129, 53, 90, and 35 patients, respectively. The data exhibits a trend of increasing patient age as the disease becomes more extensive.

Analysis of publication bias

Publication bias was visualized with contour enhanced funnel plots, presented in Fig. 1 of the Supplementary material. No statistical testing was conducted (as less than 10

studies were included) per the recommendations of Harrer et al. [13].

Certainty analysis

The overall level of certainty could not be assessed according to OCEBM 2011 [15] because this tool is not suitable for retrospective cohort studies, which was study design used exclusively in our key articles.

Discussion

To summarize our results, in our meta-analysis of seven reports [17, 18, 20, 22–24, 28] involving 259 patients, we were unable to detect a statistically significant difference in the proportion of residual disease between the four Potsic stages, based on data from patients who were followed for at least 12 months after cholesteatoma removal. Hearing improvement could not be assessed due to varied reporting. Cholesteatomas were most frequently discovered behind the anterosuperior quadrant of the tympanic membrane, and there was a distinct trend of more advanced disease in older

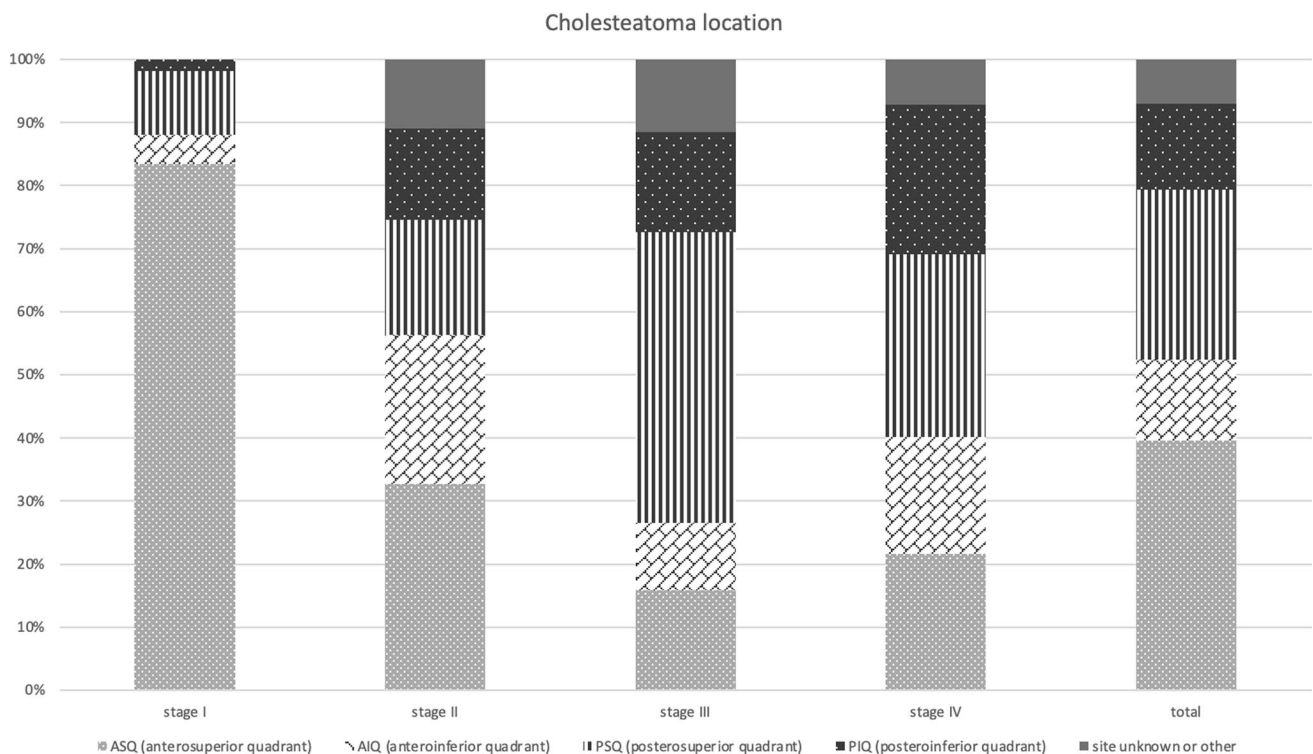


Fig. 3 Bar chart depicting the quadrants of the tympanic membrane cholesteatomas are most commonly visible through in each stage as documented in the key articles 20, 22–26, 28, 29

patients. Both outcomes were consistent with already existing results in the literature.

In their landmark study [1], Potsic and colleagues described some important criteria that an ideal staging system should meet: the categories should be simple and unambiguous with commensurable patient cohort sizes in each stage, and the staging system should also have good predictive value. From the perspective of our patients, the most important of these aspects is outcome prediction. The popularity of this staging system indicates that most of these expectations seem to be met. Although low incidence of this disease means that studies have usually included less than 100 patients, credible confirmation of the stage-based prediction needs much larger sample sizes.

This led us to perform a meta-analysis, collecting all the studies where the reported outcome was connected to the Potsic stage. Additional desired outcomes were to determine an ideal length of follow-up and assess the need for staged surgery and reexploration in early-stage disease. The clinical implication for a reliable staging system is to minimize time spent in the hospital for young children and reduce the number of operations performed on their ears by choosing the proper operation technique as a first procedure, thus optimizing surgical outcomes.

We have found no previous meta-analyses investigating the association between the rate of residual disease and

Potsic stage, but several of our key articles [18, 19, 27] have found an association between advanced-stage cholesteatoma and an increased likelihood of residual disease. One article [26] found no association between stage and residual disease, and another [20] reported that the staging system does not reflect the differences between anteriorly and posteriorly located cholesteatoma.

Several patients from those included in our key articles [23, 24, 28] presented with residual disease after one year, which suggests that a follow-up period longer than 12 months would be desirable. However, in most articles that we found during our search process, some patients were lost to follow-up much sooner. In this analysis we had no choice but to exclude them to provide an optimal level of evidence, which could have been further enhanced, if more data on these patients had been available.

For our secondary outcome of hearing improvement, we planned to conduct a subgroup analysis to compare the stages. Although a guideline has already been published for reporting audiology test results [30], the nine articles [18–20, 22, 24–27, 29] in our analysis that did report on audiological results of all or some studies used different measurements (different frequency thresholds, ABG or PTA based on air conduction, bone conduction or both), which rendered their results unpoolable.

Table 2 Documentation and calculation methods of hearing outcomes in our key articles [17–30]

Article (author, year)	Hearing results	Examined thresholds on audiograms (kHz)	Results reported in the articles	Note
Cho et al. 2016	Not available			
Inokuchi et al. 2010	Staged pre/postoperative PTA for 19/23 patients	0.5, 1, 2	Stage II, III, IV difference not statistically significant; Jonckheere test showed significant relationship between stage and postoperative PTA	Not reported whether results were based on bone/air conduction
Jenks et al. 2022	Staged pre/postoperative PTA, ABG for the majority of patients	0.5, 1, 2, 4	Pre- and post-operative air conduction PTA and ABG were different among Poitic 1–III groups, with worse pre- and post-operative hearing results measured among Poitic stage III cases	
Kim et al. 2018	Unstaged pre/postoperative PTA (air) and PTA (bone) for 8/12 pts	0.5, 1, 2, 4		
Kim et al. 2019	Not available			
Kobayashi et al. 2015	IPD, staged pre/postoperative PTA for 4 patients	0.5, 1, 2	No ear showed any deterioration in hearing acuity, although pure-tone audiometry was performed in seven out of twelve patients	Not reported whether results were based on bone/air conduction
Lee et al. 2014	Not available			
Park et al. 2009	Staged pre/postoperative ABG for 23/35 patients	0.5, 1, 2, 3	In preoperative ABG gap a trend of the increase with advanced disease stage was detected, postoperative statistically significant improvement was not detected	
Park et al. 2018	Pre/postoperative audiogram in 1 case	0.25, 0.5, 1, 2, 4, 8		
Song et al. 2019	Preoperative PTA	Not specified		
Stapleton et al. 2012	Unstaged pre/postoperative PTA for 80/82 patients	0.5, 1, 2		
Takagi et al. 2014	Not available			
Yamatodani et al. 2013	Staged pre/postoperative AC for 14/26 patients	0.5, 1, 2, 3	A trend toward decreased rates of hearing improvement was associated with cholesteatomas of more advanced stage	
Committee on Hearing and Equilibrium Guidelines	Mean, standard deviation and range of postoperative ABG, number of decibels of closure of the ABG (both at least 1 year after treatment), the change in high-tone bone-conduction level in decibels of hearing-loss (6 or more weeks after treatment) for each case	0.5, 1, 2, 3		

PTA pure tone average, ABG air–bone gap, IPD individual patient data, AC air conduction

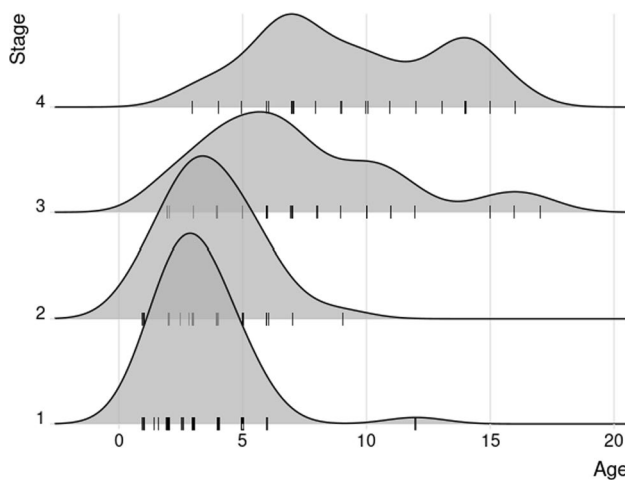


Fig. 4 Mean age (years) at staging for patients diagnosed with congenital cholesteatoma in our key articles

Location of cholesteatoma has been most frequently reported [17, 31–33] to be seen behind the anterosuperior quadrant, however Inokuchi et al. [18] found that patients in East Asia more frequently present with more extensive cholesteatomas involving multiple subregions compared to patients included in other analyses. Our report also found this quadrant to be the one most often affected.

Increase of cholesteatoma size had previously been linked to older age [34], indicating the expansive nature of cholesteatoma. In our analysis, we have also found a connection between advanced disease and older age.

We must highlight that all the included studies had a high risk of bias. As there are no dedicated tools available for reports on staging systems, we have decided to use QUIPS [12] to assess risk of bias, because this tool fit our study design best. However, there were several criteria of QUIPS that the included studies typically failed to meet. In these domains lack of data and deficient reporting resulted in a high risk of bias. Two domains (domain 2 and 4) of the QUIPS tool focuses on whether the reason for patients dropping out of follow-up was listed (together with attempts to collect information from them) and whether the exact duration of follow-up was described in the article. Domain 4 states that a clear definition should be given for the outcomes (in our case incidence of residual disease and extent of hearing improvement), and these are ought to be measured in the same way for all patients. In domain 5, possible confounding factors are an important point, such as different surgical techniques, which have been previously shown to potentially influence the likelihood of cholesteatoma recidivism [35]. In the future, including such data in reports is essential to generate high-level evidence.

Strengths and limitations

Our analysis is the first comprehensive project to summarize the results of congenital cholesteatoma surgery after considerable follow-up (minimum 1 year) and to process them according to the most widely used staging system for this disease. It is also the first to examine the effectiveness of the staging system in predicting outcome, which, according to its authors is a vital feature of a good staging system. During our analysis, we have applied rigorous methodology and followed international guidelines for summarizing previously published data.

Limitations include the retrospective nature of the key articles, which led to heterogeneous surgical techniques, varied measurement of hearing outcomes, and inadequate data on follow-up and attrition. The rarity of congenital cholesteatoma resulted in small patient cohorts and few reports. Other limitations are pooled data in articles (e.g., for mean age at staging we can only calculate estimates) and diverse duration of follow-up periods, which prevented us from including hazard ratios into our forest plot and calculating the exact desirable follow-up duration, wherein residual disease can reasonably be expected.

Implication for practice and research

Should more individual data documenting longer follow-up periods become available, it would be even more informative to calculate hazard ratios for each stage. However, at this time, based on the currently available data in the published literature this was not possible. In the future, more cases with carefully documented, long spanning individual follow-up data (especially in reports with small case numbers) are needed for a proper assessment. Durations of follow-up and the reason for losing patients in the process should also be documented.

In a clinical setting, second-look surgery should not be omitted purely based on stage; however, since the staging system's abilities seem more promising for other outcomes, it is still preferable to stage cholesteatomas using this system.

Conclusion

In our systematic review and meta-analysis, we found that although the staging system published by Potsic et al. theoretically meets the authors' first three criteria for a good staging system, based on data published so far, we cannot confirm its prognostic value. Therefore, prospective, well-designed studies are necessary with rigorously documented follow-up to determine this staging system's true ability to predict occurrence of residual disease.

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Author contributions BK: conceptualization, project administration, data curation, formal analysis, writing-original draft; KS-H: methodology; PH: funding acquisition, methodology; ZM: methodology; AS-W: methodology; PF: data curation, formal analysis; AH: conceptualization; KI: conceptualization, methodology, supervision; writing-review and editing; TH: conceptualization, supervision, writing-review and editing. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

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Data availability The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

Declarations

Conflict of interest The authors have no competing non- or financial interests to declare.

Ethical approval No ethical approval or consent was required for this systematic review with meta-analysis, as all data were already published in peer-reviewed journals.

Patient consent No patients were involved in the present study's design, conduct, or interpretation.

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References

- Potsic WP, Samadi DS, Marsh RR, Wetmore RF (2002) A staging system for congenital cholesteatoma. *Arch Otolaryngol Head Neck Surg* 128:1009–1012. <https://doi.org/10.1001/archotol.128.9.1009>
- Bennett M, Warren F, Jackson GC, Kaylie D (2006) Congenital cholesteatoma: theories, facts, and 53 patients. *Otolaryngol Clin North Am* 39:1081–1094
- Gilberto N, Custódio S, Colaço T, Santos R, Sousa P, Escada P (2020) Middle ear congenital cholesteatoma: systematic review, meta-analysis and insights on its pathogenesis. *Eur Arch Otorhinolaryngol* 277:987–998. <https://doi.org/10.1007/s00405-020-05792-4>
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The prisma 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71. <https://doi.org/10.1136/bmj.n71>
- Higgins JPT, TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (2022) *Cochrane handbook for systematic reviews of interventions* version 6.3 (updated February 2022). Cochrane Database of Systematic Reviews
- Huang X, Lin J, Demner-Fushman D (2006) Evaluation of pico as a knowledge representation for clinical questions. *AMIA Annu Symp Proc* 2006:359–363
- Levenson MJ, Parisier SC, Chute P, Wenig S, Juarbe C (1986) A review of twenty congenital cholesteatomas of the middle ear in children. *Otolaryngol Head Neck Surg* 94:560–567. <https://doi.org/10.1177/01945988609400505>
- Haddaway NR, Grainger MJ, Gray CT (2022) Citationchaser: a tool for transparent and efficient forward and backward citation chasing in systematic searching. *Res Synth Methods*. 13:533–545. <https://doi.org/10.1002/jrsm.1563>
- Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016) Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 5:210. <https://doi.org/10.1186/s13643-016-0384-4>
- McHugh ML (2012) Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)* 22:276–282
- Yung M, Tono T, Olszewska E, Yamamoto Y, Sudhoff H, Sakagami M, Mulder J, Kojima H, İncesulu A, Trabalzini F, Özgürin N (2017) Eaono/jos joint consensus statements on the definitions, classification and staging of middle ear cholesteatoma. *J Int Adv Otol* 13:1–8. <https://doi.org/10.5152/jao.2017.3363>
- Grooten WJA, Tseli E, Ång BO, Boersma K, Stålnacke B-M, Gerdle B, Enthoven P (2019) Elaborating on the assessment of the risk of bias in prognostic studies in pain rehabilitation using quips—aspects of interrater agreement. *Diagn Progn Res* 3:5. <https://doi.org/10.1186/s41512-019-0050-0>
- Harrer M, Cuijpers P, Furukawa Toshi A, Ebert DD (2021) *Doing meta-analysis with r: a hands-on guide*. Chapman & Hall/CRC Press, London, Boca Raton
- Knapp G, Hartung J (2003) Improved tests for a random effects meta-regression with a single covariate. *Stat Med* 22:2693–2710. <https://doi.org/10.1002/sim.1482>
- OCEBM Levels of Evidence Working Group (Jeremy Howick ICJLL, Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson) “The oxford levels of evidence 2”. <https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebml-levels-of-evidence>. Accessed 2023.01.27.
- Jeremy Howick IC, Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, and Hazel Thornton (2011) Explanation of the 2011 oxford centre for evidence-based medicine (ocebml) levels of evidence (background document). <https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebml-levels-of-evidence>. Accessed 2023.02.22.
- Cho HS, Kim HG, Jung DJ, Jang JH, Lee SH, Lee KY (2016) Clinical aspects and surgical outcomes of congenital cholesteatoma in 93 children: Increasing trends of congenital cholesteatoma from 1997 through 2012. *J Audiol Otol* 20:168–173. <https://doi.org/10.7874/jao.2016.20.3.168>
- Inokuchi G, Okuno T, Hata Y, Baba M, Sugiyama D (2010) Congenital cholesteatoma: posterior lesions and the staging system. *Ann Otol Rhinol Laryngol* 119:490–494. <https://doi.org/10.1177/000348941011900711>
- Jenks CM, Purcell PL, Federici G, Villari D, Presutti L, James AL, Hoff SR (2022) Transcanal endoscopic ear surgery for congenital cholesteatoma: a multi-institutional series. *Otolaryngol Head*

- Neck Surg 167:537–544. <https://doi.org/10.1177/01945998211067502>
20. Kim BJ, Kim JH, Park MK, Lee JH, Oh SH, Suh MW (2018) Endoscopic visualization to the anterior surface of the malleus and tensor tympani tendon in congenital cholesteatoma. *Eur Arch Otorhinolaryngol* 275:1069–1075. <https://doi.org/10.1007/s00405-018-4917-4>
 21. Kim H, Yoo SY, Choung YH, Park HY (2019) Is transcanal tympanoplasty an appropriate surgical treatment for congenital middle ear cholesteatoma with ossicular involvement? *Int J Pediatr Otorhinolaryngol* 116:102–106. <https://doi.org/10.1016/j.ijporl.2018.10.030>
 22. Kobayashi T, Gyo K, Komori M, Hyodo M (2015) Efficacy and safety of transcanal endoscopic ear surgery for congenital cholesteatomas: a preliminary report. *Otol Neurotol* 36:1644–1650. <https://doi.org/10.1097/mao.0000000000000857>
 23. Lee SH, Jang JH, Lee D, Lee HR, Lee KY (2014) Surgical outcomes of early congenital cholesteatoma: minimally invasive transcanal approach. *Laryngoscope* 124:755–759. <https://doi.org/10.1002/lary.24313>
 24. Park JH, Ahn J, Moon IJ (2018) Transcanal endoscopic ear surgery for congenital cholesteatoma. *Clin Exp Otorhinolaryngol* 11:233–241. <https://doi.org/10.21053/ceo.2018.00122>
 25. Park KH, Park SN, Chang KH, Jung MK, Yeo SW (2009) Congenital middle ear cholesteatoma in children; retrospective review of 35 cases. *J Korean Med Sci* 24:126–131
 26. Song IS, Han WG, Lim KH, Nam KJ, Yoo MH, Rah YC, Choi J (2019) Clinical characteristics and treatment outcomes of congenital cholesteatoma. *J Int Adv Otol* 15:386–390. <https://doi.org/10.5152/iao.2019.6279>
 27. Stapleton AL, Egloff AM, Yellon RF (2012) Congenital cholesteatoma: Predictors for residual disease and hearing outcomes. *Arch Otolaryngol Head Neck Surg* 138:280–285. <https://doi.org/10.1001/archoto.2011.1422>
 28. Takagi T, Gyo K, Hakuba N, Hyodo J, Hato N (2014) Clinical features, presenting symptoms, and surgical results of congenital cholesteatoma based on Potsic's staging system. *Acta Otolaryngol* 134:462–467. <https://doi.org/10.3109/00016489.2013.875218>
 29. Yamatodani T, Mizuta K, Hosokawa K, Takizawa Y, Sugiyama K, Nakanishi H, Mineta H (2013) Congenital middle ear cholesteatoma: experience from 26 surgical cases. *Ann Otol, Rhinol Laryngol* 122:316–321. <https://doi.org/10.1177/000348941312200505>
 30. Edwin M, Monsell M, Balkany TA, Gates GA, Goldenberg RA, Meyerhoff WL, House JW (1995) Committee on hearing and equilibrium guidelines for the evaluation of results of treatment of conductive hearing loss. American academy of otolaryngology-head and neck surgery foundation, inc. *Otolaryngol Head Neck Surg* 113:186–187. [https://doi.org/10.1016/s0194-5998\(95\)70103-6](https://doi.org/10.1016/s0194-5998(95)70103-6)
 31. Potsic WP, Korman SB, Samadi DS, Wetmore RF (2002) Congenital cholesteatoma: 20 years' experience at the children's hospital of Philadelphia. *Otolaryngol Head Neck Surg* 126:409–414. <https://doi.org/10.1067/mhn.2002.123446>
 32. Nelson JD (1988) Chronic suppurative otitis media. *Pediatr Infect Dis J* 7:446–448. <https://doi.org/10.1097/00006454-198806000-00033>
 33. Nelson M, Roger G, Koltai PJ, Garabedian EN, Triglia JM, Roman S, Castellon RJ, Hammel JP (2002) Congenital cholesteatoma: classification, management, and outcome. *Arch Otolaryngol Head Neck Surg* 128:810–814. <https://doi.org/10.1001/archoto.128.7.810>
 34. Lim HW, Yoon TH, Kang WS (2012) Congenital cholesteatoma: clinical features and growth patterns. *Am J Otolaryngol* 33:538–542. <https://doi.org/10.1016/j.amjoto.2012.01.001>
 35. Illés K, Meznerics FA, Dembrovsky F, Fehérvári P, Bánvölgyi A, Csupor D, Hegyi P, Horváth T (2023) Mastoid obliteration decreases the recurrent and residual disease: Systematic review and meta-analysis. *Laryngoscope* 133:1297–1305. <https://doi.org/10.1002/lary.30413>

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Modeling residual cholesteatoma growth rate: a meta-analysis of individual participant data

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Abstract

Purpose To create a model of residual cholesteatoma growth rate that can be used to estimate optimal timing of follow-up imaging.

Methods Following the recommendations of the PRISMA-IPD guideline and after registering our study protocol on PROSPERO (CRD42023465320), a systematic search was completed in September 2023 and updated in July 2024, conducted in PubMed, Web of Science, Embase, and Cochrane Library. Reference lists of the resulting articles were also searched for potential inclusions. Our search yielded 11,274 articles. Studies with patients of any age and sex diagnosed with residual cholesteatoma were included if data on cholesteatoma size at follow-up were available, collected from imaging results or through second-stage surgery. For statistical analysis, a Monte Carlo simulation approach was applied, and a baseline random-intercept mixed-effects model was fitted.

Results We included 11 articles reporting individual data from 163 patients. All but one of these articles proved to be high risk of bias. Our simulation models suggest that 95% of cholesteatomas reach or grow past the size of 3 millimetres (threshold for imaging) after 28–35 months and 95% of reach or grow past the size of 5 millimetres (threshold for intraoperative identification) after 47–58 months.

Conclusion Analyzing previously published data suggests that residual cholesteatoma may only be radiologically detectable on non-EPI DWI MRI after 28–35 months postoperatively in 95% of patients, indicating delayed follow-up for average risk patients compared to current clinical practice. However, this simulation model, based on retrospective data, aims to uncover growth patterns rather than posing as a new guideline.

Keywords Cholesteatoma · Residual · Growth rate · DWI-MRI

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Introduction

Although many advances were made in cholesteatoma surgery, the risk of residual disease may still be as high as 40% [1–4]. Thus, follow-up after surgery is indispensable. The traditional way of monitoring residual disease used to be second-look surgery performed 1 year after the first procedure [5, 6] even in cases without apparent signs of cholesteatoma during otomicroscopic examination. The emergence of non-echoplanar diffusion weighted magnetic resonance imaging (non-EPI DWI MRI) techniques has changed the obvious need for surgical surveillance, as this imaging modality shows high sensitivity and specificity for cholesteatoma [7, 8]. It has been proven to be more cost-effective compared to the planned second-look surgery [9], however, there is still no established guideline for the optimal timing of radiological examinations [10].

There are different aspects that should be considered when timing the follow-up targeted imaging or the second-stage surgery. If follow-up imaging is performed too early, residual cholesteatoma might go unnoticed due to its small size [11, 12]. If imaging is delayed, residual disease holds the risk of complications or may grow to an extensive size requiring a more radical approach for removal, which may negatively affect postoperative quality of life [13]. Knowing the growth rate of residual cholesteatoma could help determine the ideal time point to detect cholesteatomas in most patients without risking the development of extensive disease in the meantime.

In this meta-analysis of individual participant data, we aimed to summarize all measurements available in the literature on residual cholesteatoma growth and to create a simulation model to estimate the optimal time for follow-up [14].

Methods

This growth and residual cholesteatoma detectability model with systematic review was based on the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) guideline [15] and the Cochrane Handbook [16]. The study protocol has been registered on PROSPERO (CRD42023465320) and was fully adhered to except for one adjustment with the exclusion criteria, as our search yielded only one eligible article containing congenital cholesteatoma growth data. As their different etiopathogenesis may also be associated with disparate growth dynamics from acquired cholesteatomas, we ultimately decided to exclude congenital cholesteatomas from our study.

Inclusion and exclusion criteria

Patients of any age and sex diagnosed with cholesteatoma were included, if data on cholesteatoma growth were available, collected from imaging results or through direct visualization in the operating room. Although our primary goal was to include both acquired and congenital cholesteatoma, the latter was excluded after the selection process for the reasons indicated above. Published prospective or retrospective cohort studies and observational studies written in English were included, whereas reviews, conference abstracts, case reports, guidelines and animal studies were excluded. We also excluded studies where residual cholesteatoma was detected within one month after surgery, because the calculation of growth rate would be extremely distorted with such a short follow-up time. (Fig. 1.)

Information sources and search strategy

The first systematic search was conducted on September 20, 2023, and updated on July 12, 2024 (during the data selection process, we became aware of new studies that were published containing data that might be useful for our analysis) in PubMed, Web of Science, Embase, and Cochrane Library using the search key below, with no filters:

Cholesteatoma AND (growth or follow* or follow-up or recurrence or MRI).

References included in the eligible studies were also scanned using CitationChaser [17]. Corresponding authors of further records that did not contain individual participant data on cholesteatoma size or time interval between surgery and scan were contacted via email. (Fig. 1)

Selection process

We used a citation manager program (EndNote 20, Clarivate Analytics, Philadelphia, PA, USA) for automatic and manual duplicate removal, then title, abstract and, full text selection was performed by two reviewers (BK and JK) working independently, using Rayyan [18]. After each selection step, disagreements were resolved by a third reviewer and inter-rater reliability was assessed using Cohen's kappa [19].

Data collection process

Data from the eligible articles (name of the first author, year of publication, basic demographic characteristics (percentage of females, age, number of patients), age at surgery, cholesteatoma type, (if recurrent, time since last surgery), method of size measurement or imaging modality, size, if surgery technique available and location of cholesteatoma) was entered into a predefined Excel worksheet (Microsoft

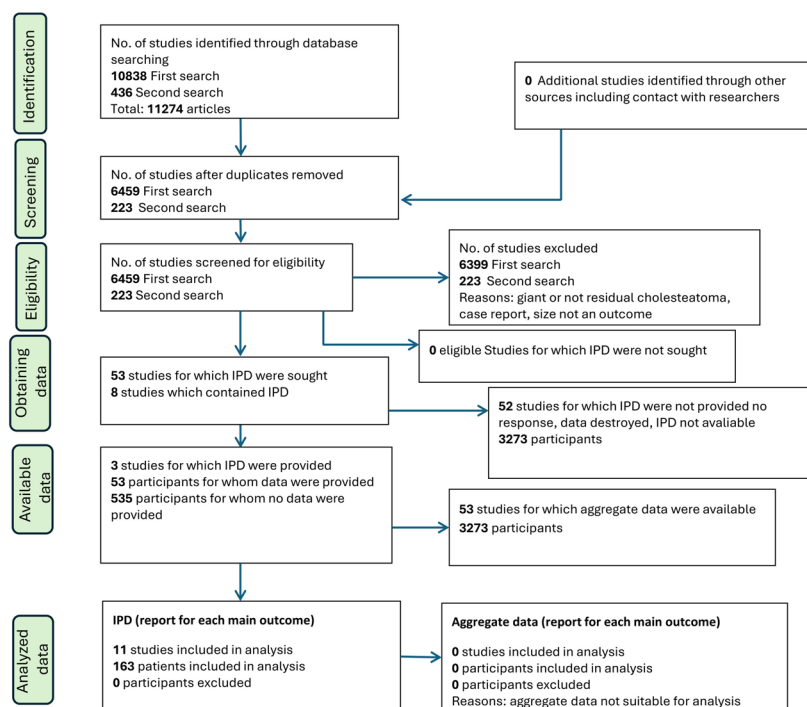


Fig. 1 PRISMA-IPD flowchart of study selection process. IPD: individual participant data, No: number

Corporation, Redmond, Washington, United States). Authors of articles that contained aggregate data on cholesteatoma growth were contacted, and if individual participant data were still available, we asked for anonymized data including patient age, sex, type of surgery, time elapsed between surgery and imaging, as well as cholesteatoma size. Through datasharing requests, we received combined, anonymized individual participant data (IPD) (time between surgery and imaging, cholesteatoma size) for 52 cholesteatomas from 3 articles [11, 20, 21] by the same working group at the Department of Paediatric Otolaryngology, Université Paris Cité. (Table 1.) Radiological and non-radiological methods of measurements were summarized in Online Resource 2 and Online Resource 3.

Data items

Our main outcome was cholesteatoma growth rate. To calculate the growth rate, we included two types of studies. The first comprised purely non-EPI DWI MRI-based reports in which exact size measurements were available for the same residual cholesteatoma at two different time points. Patients in this group were followed, but not operated for different reasons, such as pregnancy or the SARS-CoV-2 pandemic. We termed these datapoints “direct measurements”. The second type of measurements was included in studies where, after a primary surgery, only one set of size data was available

from follow-up MRI imaging or second stage. In these cases, we assumed that the initial size of the residual mass during primary surgery was below the visually detectable range; we estimated it to be zero to one millimeters in these cases, but the true size of the residuals remains unknown. These were named “indirect measurements”. (Fig. 2) In order to validate the joint calculation of the growth rate based on the direct and indirect measurements, we statistically compared the two approaches and performed further analyses to determine whether patient sex, age, and the type of surgery significantly influenced growth rate. We chose 3 mm and 5 mm thresholds to estimate the earliest time of high sensitivity and specificity imaging, and feasible intraoperative identification.

Study risk of bias assessment

The two data reviewers assessed the risk of bias using the JBI critical Appraisal for Case Series [22] and have visualized the results using the Risk-of-bias VISualization web application [23]. Disagreements were resolved through discussion.

Level of evidence

Level of evidence was ranked using the OCEBM 2011 Levels of Evidence Table [24] assisted by the OCEBM Background document [25].

Table 1 Study characteristics. OCEBM: Oxford Centre for Evidence Based Medicine, F: female, CWU BOT: canal wall up with bony obliteration technique, non-EPI DWI MRI: non-echoplanar diffusion-weighted magnetic resonance imaging, mo: month, mm²: square millimeters, * = from these studies we have received combined, anonymized growth data for 52 cases (52 datapoints, all indirect)

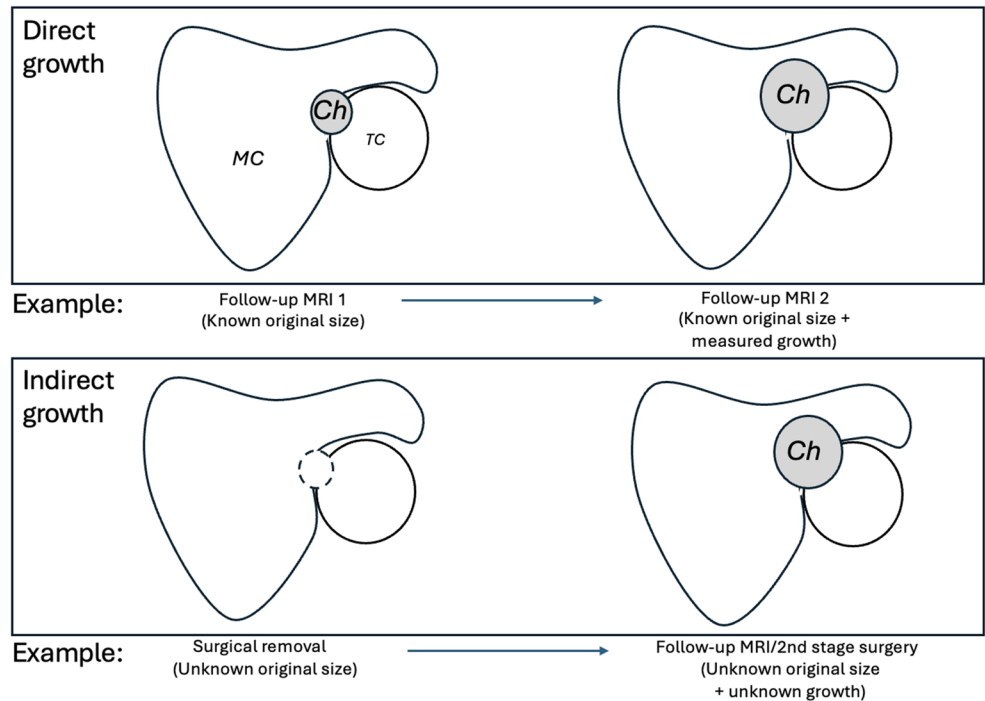
First author, year of publication (Country)	Study method (OCEBM rate of evidence)	No. of cases (female %, age, data on previous operations)	No. of cases with growth data (no. of datapoints, indirect/direct)	Measurement method	Follow-up length	Mean growth rate
Baoudouin et al., 2023 (France) [20]	Retrospective study (4)	140 (NA, 9.2±3.7 years, various techniques)	*	Non-EPI DWI MRI	3.2±2.2 years	Not calculated
Daoudi et al., 2023 (France) [11]	Retrospective study (4)	224 (30% F, 2–18 years)	*	Non-EPI DWI MRI	27±24 months	Not calculated
Delrue et al., 2019 (Belgium) [43]	Retrospective clinical record study (4)	48 (50% F, 14–84 years, post subtotal petrosectomy)	10 (10, 10/0)	EPI and non-EPI DW MRI, long and short axis diameter in coronal view	0.5–13 years (mean 3.9)	0.54 mm ² / month
De Foer et al., 2008 (Netherlands) [44]	Prospective and blinded study (3)	32 (31% F, 7–71 years, post CWU mastoidectomy)	2 (2, 2/0)	Intraoperative findings	11.2–40.3 months (mean 25.2)	Not calculated
Gristwood et al., 1976 (Australia) [45]	Prospective cohort study (3)	141 (50% F, 6–83 years, various techniques)	23 (29, 24/5)	Intraoperative findings	At most 6 years	epitympanic: doubles diameter every 10 mo, mastoid: doubles diameter every 25 mo
Hellingman et al., 2019 (The Netherlands) [46]	Retrospective case series (4)	10 (70%F, 12–72 years, post subtotal petrosectomy)	10 (62, 13/49)	MRI (not specified)	8–186 months (mean 59)	25.6mm ³ /month
Lecler et al., 2015 (France) [47]	Prospective monocentric consecutive study (3)	22 (9%F, 4–18 years)	7 (10, 10/0)	Non-EPI DWI and contrast enhanced MRI	At least 12 months	Not calculated
Pai et al., 2019 (United Kingdom) [48]	Retrospective case review (4)	12 (NA, 4–66 years, various techniques)	34 (34, 34/0)	Non-EPI DWI MRI	3.0–42.8 (Mean 8.1 years, median 6.1)	4 mm/year (median 2, range 0–18)
Simon et al., 2024 (France) [21]	Retrospective observational study (4)	223 (30%, 8.4±4.3 years, various techniques)	*	Non-EPI DWI MRI	95 months±26.2 (range 60–186)	Not calculated
Smith et al., 2020 (United Kingdom) [49]	Retrospective longitudinal study	17 (41%F, 10–72 years)	17 (38, 17/21)	Non-EPI DWI MRI	33 months (range 6–91)	0,6 mm/year (-0,2–19.9 mm / year)
van der Toom et al., 2022 (Belgium) [6]	Retrospective case review	271 (39% F, post CWU BOT with mastoid obliteration)	8 (11, 8/3)	Non-EPI DWI MRI	60 months (IQR 56–62)	1,8 mm/8 months

Statistical methods

Individual participant data were obtained from retrospective and prospective studies reporting cholesteatoma size at one or more time points. Two forms of measurements were available: direct measurements, where lesion size was recorded at two separate clinical encounters, and indirect measurements, where only follow-up size was documented. In the latter case, the clinically established assumption that cholesteatomas originate from a radiologically inapparent state of 0 mm, 0.33 mm, 0.66 mm, and 1 mm was applied to estimate

growth over the observed interval, consistent with prior descriptions of early lesion morphology and radiological detectability [26–28]. Because the two measurement types represent different forms of information and may introduce systematic differences, measurement type (direct vs. indirect) was included as a fixed effect in all models, and an additional sensitivity analysis restricted to directly measured cases was performed to assess robustness, acknowledging the substantially reduced sample size. A separate simulation was also run based exclusively on radiological measurements, based on the results of the risk of bias analysis.

Fig. 2 Demonstrating the distinction between indirect and direct growth data. For direct growth data, we have an exact measurement of the initial size, whereas for indirect datapoints we can make assumptions. MC: mastoid cavity, TC: tympanic cavity, Ch: cholesteatoma



Lesion size measurements were extracted in three formats: two-dimensional values, from which the larger dimension was used as the effective diameter; area measurements, from which the diameter of an equivalent circle was derived; and volume measurements, from which the diameter of an equivalent sphere was computed, following established morphometric principles [28]. Monthly growth rates were calculated by dividing the change in diameter by the elapsed time in months. Because growth rates are strictly positive and typically right-skewed, the values were log-transformed to stabilize variance and improve normality, in line with standard recommendations for modeling log-normal biological processes [29, 30]. Exponentiated fixed-effect coefficients from the resulting models therefore represent multiplicative changes in the geometric mean monthly growth rate.

Linear mixed-effects models were fitted using restricted maximum likelihood estimation, with patient-specific random intercepts nested within studies to account for both within- and between-study heterogeneity [31–33]. Model fitting relied on the lme4 package, which implements well-established numerical approaches for estimating hierarchical models [34]. Covariates included sex, age at surgery, measurement type, and surgical technique, modelled separately when dictated by differences in variable availability. Confidence intervals for fixed-effect estimates were obtained using profile likelihood, a recommended approach for mixed models [34, 35]. Model assumptions

were evaluated through inspection of residual distributions and fitted-residual relationships, and model fit was summarised using marginal and conditional R^2 values computed according to the method of Nakagawa and Schielzeth [36], as implemented in the MuMIn package [37].

To estimate the time required for cholesteatomas to reach clinically relevant sizes, a Monte Carlo simulation study was conducted. An intercept-only mixed-effects model was fitted to the log-transformed growth rates to characterise the underlying distribution of lesion expansion. The fixed-effect estimate, its standard error, and the residual variance were used to define a log-normal data-generating process, drawing on established principles of parametric bootstrapping and Monte Carlo simulation [38–40]. For each target diameter (3 mm and 5 mm), 10,000 independent Monte Carlo draws were generated by sampling log-growth rates from a normal distribution centred on the fixed-effect estimate with variance equal to the sum of its squared standard error and the residual variance. These simulated values were exponentiated and converted into expected times to reach the specified diameter through deterministic transformation. This procedure yields a distribution of plausible growth trajectories rather than replicating a specific study design, and the resulting distributions were summarised using empirical quantiles and density-based visualisations.

All analyses were conducted in R (version 4.4.2; R Core Team 2024) using the lme4 [34], lmerTest [41], and sjPlot [42] packages.

Results

A total of 11 articles were included, encompassing 1272 patients with growth data available for 163 of them [6, 11, 20, 21, 43–49]. During all study selection steps, Cohen's kappa was higher than 0.9. 62 (38%) were male, 32 (19,6%) female, and data on sex were not provided for 69 (42,3%) of them. Mean age was 28,3 years (range: 4–72 years). In total, 248 data points were collected from 170 indirect and 78 direct measurements. (Table 1.)

Biological predictors of growth

The model, including sex and age at surgery, showed that growth rate was slightly higher in males compared to females, with an estimated 19% increase in monthly diameter growth (95% CI: 0% to 42%, $p=0.054$). Age at surgery was not a statistically significant predictor of growth rate (1% decrease per year; 95% CI: -3% to +1%, $p=0.18$). The marginal R^2 was 0.017, and the conditional R^2 was 0.31,

indicating that most of the variability was explained by random effects. Further analysis of age at diagnosis of residual disease was not possible due to a lack of data. (Fig. 3)

Growth type

In a separate model evaluating growth type, directly measured growth was associated with a significant, 25% lower growth rate compared to indirect measurements (95% CI: 6% to 47%, $p=0.01$). This model had a marginal R^2 of 0.029 and a conditional R^2 of 0.28. (Fig. 3) When changing the starting point of indirectly measured growth to 1 mm, there was no significant difference between the two methods (95% CI: 6% to 47%, $p=0.191$). This model had a marginal R^2 of 0.035 and a conditional R^2 of 0.59. (Fig. 4). Simulations with the initial size of indirect cholesteatomas set to 0.33 mm and 0.66 mm were also carried out (Online Resource Figs. 2, 3, 4 and 5.), and also with excluding non-radiologically measured datapoints (Online Resource Fig. 6–7.).

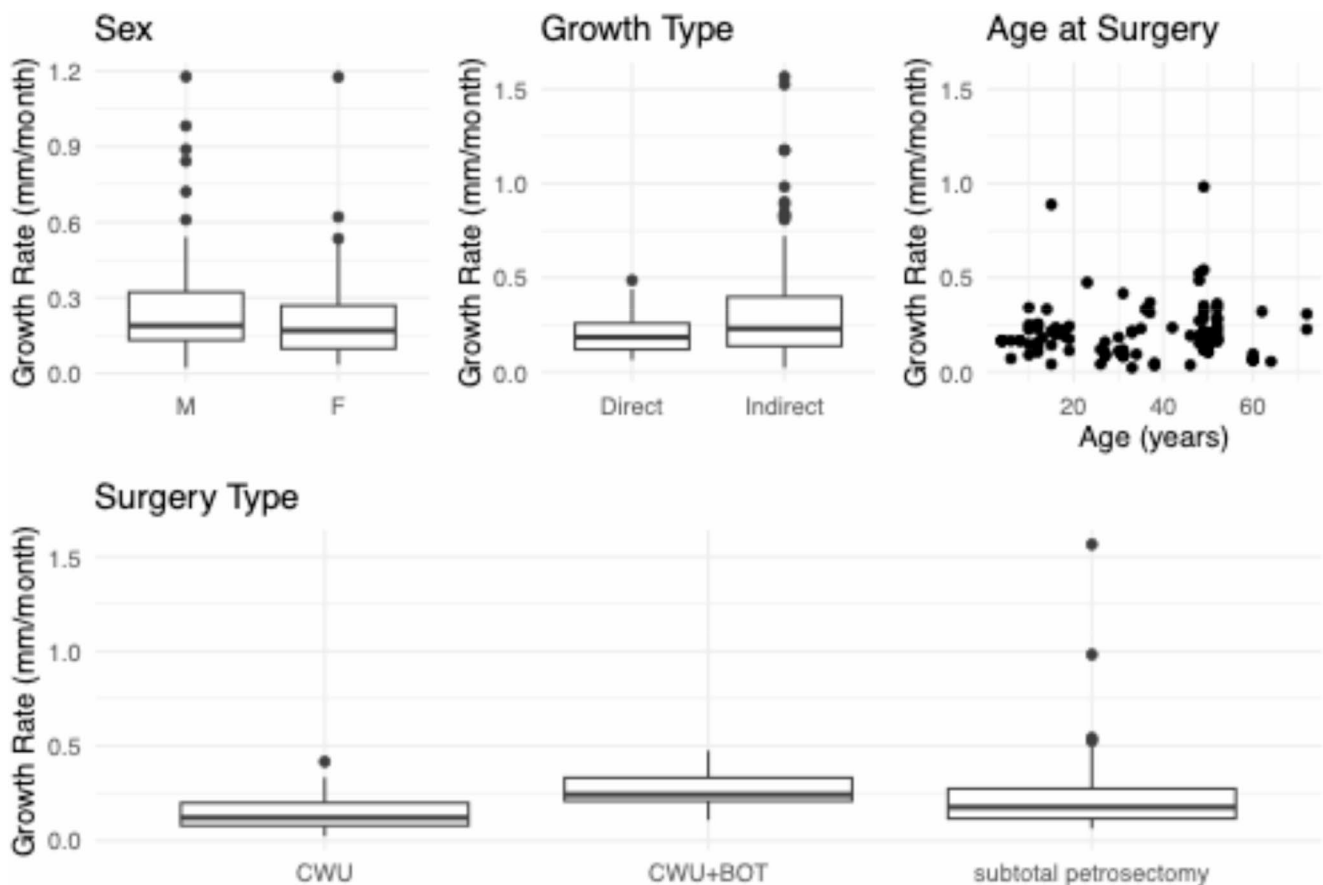


Fig. 3 Summarization of observed relationships with the initial size of indirect cholesteatomas set to 0 mm: top row includes sex, growth type, and age; bottom row shows effects of surgical type. mm: mil-

limetre, M: male, F: female, CWU: canal wall up, CWU+BOT: canal wall up with bony obliteration

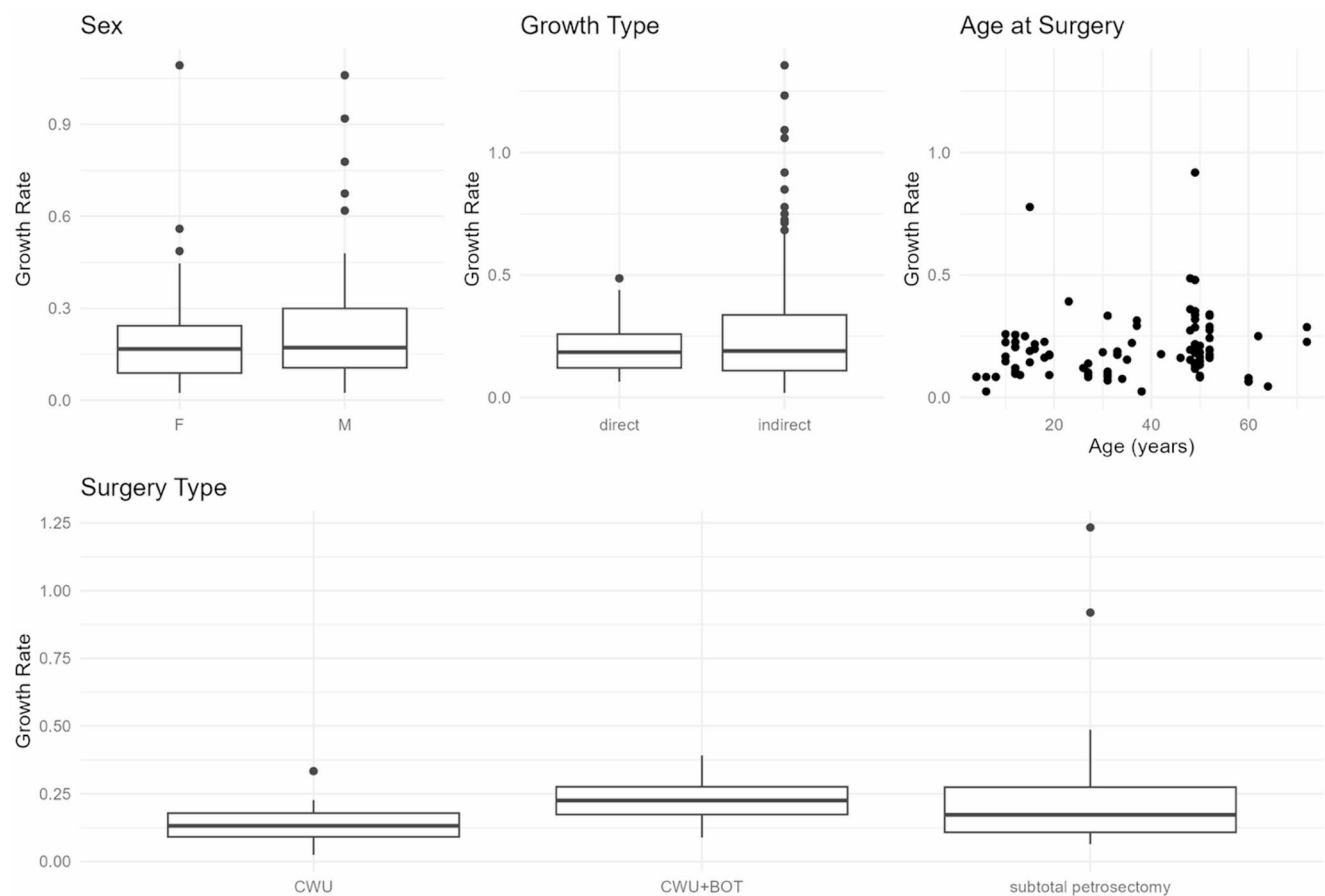


Fig. 4 Summarization of observed relationships with the initial size of indirect cholesteatomas set to 1 mm: top row includes sex, growth type, and age; bottom row shows effects of surgical type. mm: mil-

limetre, M: male, F: female, CWU: canal wall up, CWU+BOT: canal wall up with bony obliteration

Surgical technique

Patients who underwent canal-wall-up surgery with bony obliteration technique (CWU+BOT) had a nonsignificant, 20% higher growth rate compared to CWU alone (95% CI: -7% to +54%, $p=0.14$). Patients with subtotal petrosectomy (STP) had a significantly, 36% higher growth rate compared to CWU (95% CI: 6% to 75%, $p=0.01$). Marginal R^2 was 0.031, and conditional R^2 was 0.29. (Fig. 3)

Simulation study

Using the baseline model with indirectly measured cholesteatomas presumed to be 0 mm as a starting point, we generated simulated growth durations to estimate the time required for cholesteatomas to reach radiological and clinical thresholds (3 mm and 5 mm). For a 3-mm target, 95% of simulated cases reached this size within 28 months. For a 5-mm target, 95% reached this size within 47 months. (Fig. 5) With a starting size of 1 mm for indirectly measured cholesteatomas, the time passed until the earliest radiological

detection (3 mm) increases to 35, and to 58 months for surgical detection (5 mm). (Fig. 6) When excluding non-radiological measurements from direct cases, a 3 mm threshold was found at 27 months and 5 mm at 46 months for 95% of patients (Online Resource Fig. 6–7).

Risk of bias assessment

As a result of the risk of bias analysis using the JBI tool for case series, all but one of our selected articles proved to be high risk of bias, most often due to heterogeneity of measurement protocols and lack of data on disease demographics. (Online Resource 1.)

Discussion

In this review article, we introduce a growth simulation and residual disease detectability model based on cholesteatoma sizes measured during imaging or second-look procedures. These results may support future recommendations for the

Fig. 5 Ridge density plot of simulated time (months) required to reach 3 mm and 5 mm cholesteatoma growth targets, with the initial size of indirect cholesteatomas set to 0 mm. The figure shows the distribution of the likelihood of cholesteatomas reaching a size of 3 or 5 millimetres by a specific timepoint. Dashed red lines indicate 95th percentiles for each target

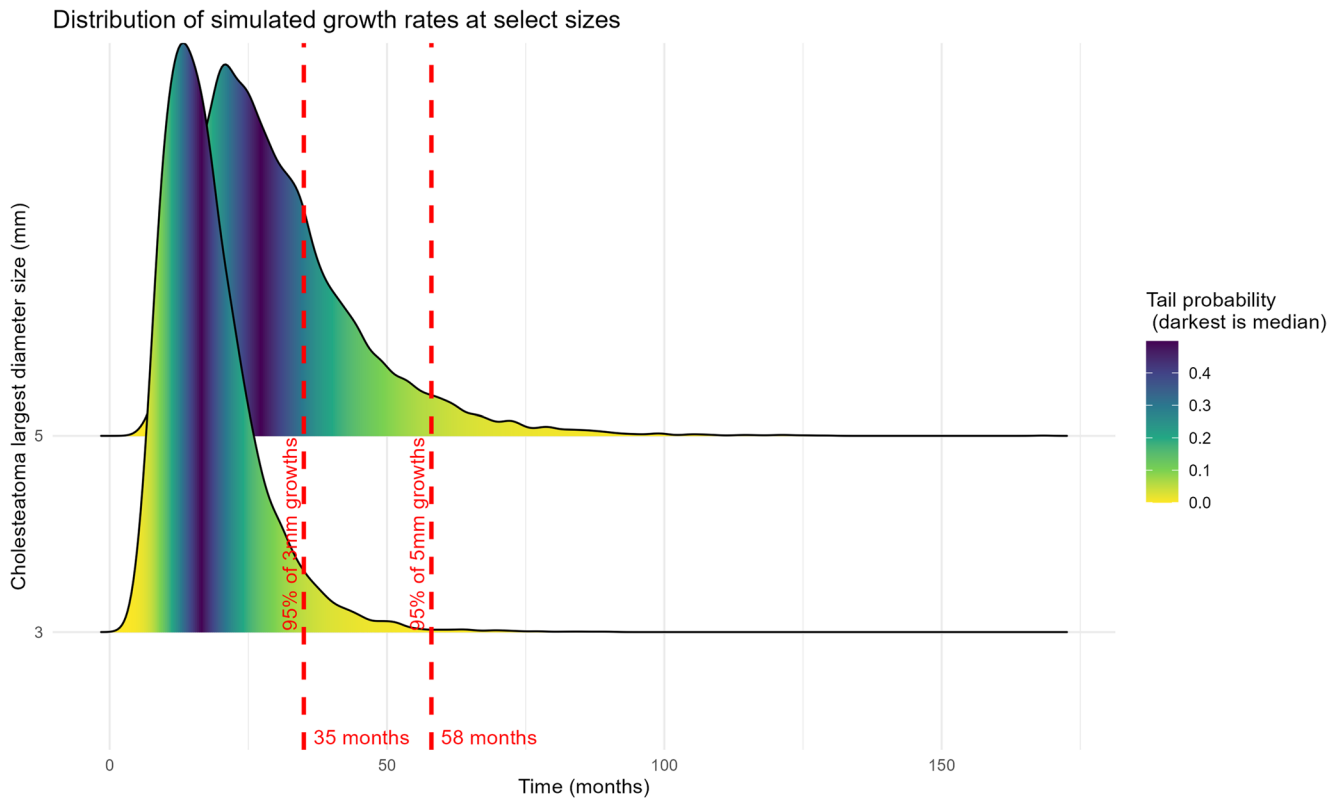
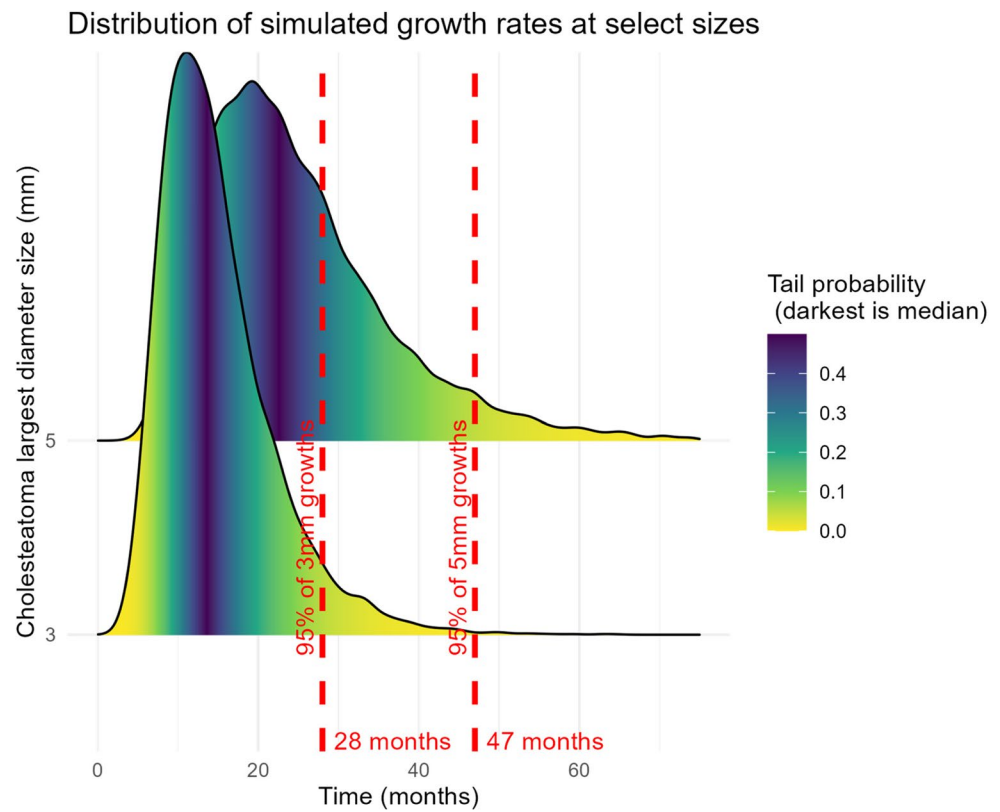


Fig. 6 Ridge density plot of simulated time (months) required to reach 3 mm and 5 mm cholesteatoma growth targets, with the initial size of indirect cholesteatomas set to 1 mm. The figure shows the distribution

of the likelihood of cholesteatomas to reach a size of 3 or 5 millimetres by a specific timepoint. Dashed red lines indicate 95th percentiles for each target

optimal time of follow-up MRIs, for which to our knowledge no widely accepted protocol exists yet. Recent large-scale studies regarding long-term cholesteatoma follow-up showed that a surprisingly high percentage of residual cases were only discovered several years after surgery, and prematurely performed follow-up imaging holds the risk of yielding false negative results [6, 11, 12, 21]. Our growth model which was created using all the available data including previous reports seems to be in accordance with this, since we found that 95% of cholesteatomas measuring 3 mm in diameter can be detected at 28–35 months postoperatively, while 5 mm diameter residual disease becomes visible at 47–58 months after the surgery in 95% of the patients. Although targeted MRI imaging was found to be able to detect residual cholesteatoma as small as 3 mm [50, 51], we also analyzed a 5-mm diameter as a threshold value. This size compares without relevant clinical consequences to 3 mm, but it further reduces the risk of false negative examinations [52, 53], also considering that surgical techniques such as cartilage or cortical bone columella may affect specificity [54, 55]. Following the traditional statistical approach [56], we defined the detection threshold as 95% of the patients with residual cholesteatoma with the aforementioned sizes.

Considering the results of this model, the optimal, cost-effective screening for residual cholesteatoma should be performed no earlier than 2 years in average-risk patients after the first or previous surgery. In contrast to this suggestion, there are many cases of residual disease detected as early as a few months after removal [57]. Some patients have a high risk of developing residual disease [58, 59], and they should be subjected to consistent follow-up, including early MRIs. As more data are needed for a comprehensive risk stratification system for recidivism, surgeons should individually plan follow-up for patients based on intraoperative findings. Another recurring argument against delayed follow-up is to avoid developing complications. However, it was shown during the SARS-CoV-2 pandemic that increased waiting periods for cholesteatoma surgery did not lead to higher rates of major complications [60].

Our model was based on two different measurement methods of growth found in the literature. In one group 2 or more size measurements of the same cholesteatoma were performed at two or more different timepoints. By subtracting the earlier measurement from the latter, we could calculate the exact initial size of residual growth (direct measurement). In the other group we had a single datapoint, collected from imaging results or second-look procedures following primary surgery, where we could only estimate that the size of remaining squamous tissue was close to zero, relying on the judgement of the surgeon (indirect measurement). To lessen the biasing effect of our presumption that indirectly measured cholesteatomas' size was close to zero,

we also ran the simulation with a starting size of 0.33 mm, 0.66 mm, and 1 mm. When comparing these methods, we found that cholesteatomas measured indirectly seemed to grow faster when a starting size of 0 was assumed, and had a wider range of values. As the starting size was increased through 0.33 mm and 0.66 mm and 1 mm, the difference in growth speed faded without a clinically significant change in detectability thresholds.

Although these indirect measurements are technically less precise than direct radiological follow up of the same cholesteatoma using MRI scans, it is of paramount importance to take these results into consideration, as indirect growth rate may better correspond to the typical clinical course of cholesteatoma cases in real life, where patients with cholesteatoma are getting operated on, then followed up, and when a residual or recurrent disease is detected during imaging, a revision surgery is performed. For us, the effect of different starting points in indirect growth sizes indicates that presuming an intraoperative residual cholesteatoma size closer to 1 mm might be more realistic.

Most cholesteatomas in this analysis were measured radiologically, apart from 5 cases of direct measurements, extracted from a study conducted considerably earlier [45]. To account for the heterogeneity caused by this, we also ran an analysis excluding these cases (Online Resource Fig. 6–7), which yielded results close to the original model (3 mm threshold at 27 months, 5 mm threshold at 46 months).

When analyzing basic demographic features, we found a slightly faster growth rate in males; however, age at surgery was not found to be a prognostic factor for growth rate. This latter finding was consistent with the results of a recent large retrospective cohort study, in which residual disease did not appear earlier in children than in adults [12]. Although pediatric cholesteatoma is traditionally thought to be more aggressive, this perception is mainly based on the primary extension upon diagnosis, the extended bony erosion, and observed biochemical properties compared to adults [10, 61, 62] rather than the speed of residual disease expansion.

We also examined whether the space in which residual cholesteatomas develop affects the rate of growth, which is closely related to the type of surgery. Theoretically, there may be a difference between an aerated mastoid space, a post-bony-oblation mastoid bowl, and a cavity filled with autologous fat after subtotal petrosectomy [63]. Kemps et al. in a recent retrospective comparative study established that residual diseases were found earlier in the bony obliterated group compared to subtotal petrosectomy, although it was not indicated whether this difference was significant [64]. We performed a multivariate analysis comparing cholesteatoma growth rate in patients after tympanomastoidectomy with and without bony obliteration of the mastoid cavity, and in patients who had previously undergone subtotal

petrosectomy. The results showed no difference between the groups. It should be noted that the number of cases was relatively low, with asymmetric distribution between the groups, the type of growth measurement was inhomogeneous, and the type of surgery was not randomized.

Several other aspects of residual cholesteatoma growth that would be of interest for further studies which our working group was unable to explore due to data scarcity. For example, it would be important to know whether there is a correlation between growth rate and the localization of the residual cholesteatoma (epitympanum, mesotympanum and mastoid cavity), presence of foreign material in the middle ear cavity such as prostheses or silicone sheets, and age at diagnosis of residual disease.

Strengths

To our knowledge, this is the most comprehensive synthesis of the available data in the literature on the growth rate of residual cholesteatoma based exclusively on IPD. The main results of our study are based on reproducible and objective measurements obtained with non-EPI DWI MRI, the contemporary imaging modality for cholesteatoma follow-up and a simulation model based on the pooled data to estimate the growth rate across a large cohort.

Limitations

Data were gathered from studies with a high risk of bias conducted under varying conditions, particularly with respect to surgery type, modality of follow-up, its timing, and the method of cholesteatoma size measurement. MRI protocols varied significantly, even within study populations, and most measurements were collected retrospectively, after diverse procedures. Little information was available on the initial extent of cholesteatomas, indications for certain types of procedures, and confounding factors. Cholesteatoma growth was simulated using an idealized shape; however, due to the complex anatomy of the middle ear, actual growth patterns are likely to be more intricate, which may have led to deviations in our results.

Conclusion

Our simulation model based on individual participant data indicates that a 3 mm residual disease may first be radiologically detected 28–35 months postoperatively in 95% of patients, and a 5 mm residue might first be discovered at 47–58 months during surgery. Consequently, contrasting current clinical practice, delayed follow-up imaging in average-risk patients might reduce the rate of false negative

screening results and increase cost-effectiveness. Rather than a new guideline defining an exact growth rate, our model, based on retrospective and heterogeneous data, aims to show patterns in cholesteatoma growth. This study is mainly intended to support future recommendations for ideal timing of follow-up imaging or second-look surgeries based on large-scale projects with less heterogeneity, individual participant data, and risk factor analysis for residual cholesteatoma growth.

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Data Availability The datasets used in this study can be found in the full-text articles included in the individual patient analysis, except for the data kindly provided by the working group at Université Paris Cité.

Declarations

Ethical approval and consent No ethical approval or consent was required for this individual patient analysis, as all data were either already published in peer-reviewed journals or anonymized. No patients were involved in the design, conduct, or interpretation of the present study.

Conflict of interest The authors have no competing non-financial or financial interests to declare.

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References

1. Harris A, Mettias B, Lesser T (2016) Pooled analysis of the evidence for open cavity, combined approach and reconstruction of the mastoid cavity in primary cholesteatoma surgery. *J Laryngology Otology* 130:235–241
2. van der Toom HF, van der Schroeff MP, Pauw RJ (2018) Single-stage mastoid obliteration in cholesteatoma surgery and recurrent and residual disease rates: a systematic review. *JAMA Otolaryngology–Head Neck Surg* 144:440–446
3. Britze A, Møller M, Ovesen T (2017) Incidence, 10-year recidivism rate and prognostic factors for cholesteatoma. *J Laryngology Otology* 131:319–328

4. Kerckhoffs KG, Kommer MB, van Strien TH, Visscher SJ, Bruijnzeel H, Smit AL, Grolman W (2016) The disease recurrence rate after the canal wall up or canal wall down technique in adults. *Laryngoscope* 126:980–987
5. Touska P, Connor SE (2025) ESR essentials: Imaging of middle ear cholesteatoma—practice recommendations by the European Society of Head and Neck Radiology. *Eur Radiol* 35:2053–2064
6. van der Toom HF, van Dinther JJ, Zarowski A, Baazil AH, De Foer B, Bernaerts A, Casselman JW, Offeciers E (2022) Radiological follow-up after the bony obliteration tympanoplasty in detecting residual cholesteatoma: towards an optimal postoperative MRI imaging protocol. *Otology Neurotology* 43:e79–e87
7. Muzaffar J, Metcalfe C, Colley S, Coulson C (2017) Diffusion-weighted magnetic resonance imaging for residual and recurrent cholesteatoma: a systematic review and meta-analysis. *Clin Otolaryngol* 42:536–543
8. Bazzi K, Wong E, Jufas N, Patel N (2019) Diffusion-weighted magnetic resonance imaging in the detection of residual and recurrent cholesteatoma in children: a systematic review and meta-analysis. *Int J Pediatr Otorhinolaryngol* 118:90–96
9. Patel TA, Etttyreddy A, Cheng T, Smith K, Sridharan SS, McCall AA (2024) Cost-effectiveness of diffusion weighted MRI versus planned second-look surgery for cholesteatoma. *Ann Otol Rhinol Laryngol* 133:665–671
10. Molinari G, Reale M, Albero A, Russo FY, Di Lullo AM, Gaffuri M, Ralli M, Turri-Zanoni M, Simon F, Anschuetz L (2025) Follow-up strategies in pediatric cholesteatoma: a systematic review. *Eur Arch Otorhinolaryngol* 282:11–22
11. Daoudi H, Levy R, Baudouin R, Couloigner V, Leboulanger N, Garabédian EN, Belhous K, Boddaert N, Denoyelle F, Simon F (2024) Performance of non-epi DW MRI for pediatric cholesteatoma follow-up. *Otolaryngology–Head Neck Surg* 170:221–229
12. Eggink MC, de Wolf MJ, Ebbens FA, de Win MM, Dijkers FG, van Spronsen E (2025) MRI-DWI detection of residual cholesteatoma: Moving toward an optimum follow-up scheme. *Eur Arch Otorhinolaryngol* 282:659–668
13. Yilala MH, Fancello G, Sanna M (2024) Management of petrous bone cholesteatoma: The Gruppo Otorologico experience. *Eur Arch Otorhinolaryngol* 281:5211–5224
14. Hegyi P, Erőss B, Izbéki F, Párniczky A, Szentesi A (2021) Accelerating the translational medicine cycle: The Academia Europaea pilot. *Nat Med* 27:1317–1319
15. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF (2015) Preferred reporting items for a systematic review and meta-analysis of individual participant data: The PRISMA-IPD statement. *JAMA* 313:1657–1665
16. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J (2019) Updated guidance for trusted systematic reviews: a new edition of the Cochrane handbook for systematic reviews of interventions. *The Cochrane database of systematic reviews* 2019:ED000142, Wiley Blackwell, no. 1002 (2019), p.3–655
17. Haddaway NR, Grainger MJ, Gray CT (2022) CitationChaser: A tool for transparent and efficient forward and backward citation chasing in systematic searching. *Res synthesis methods* 13:533–545
18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016) Rayyan—a web and mobile app for systematic reviews. *Syst reviews* 5:210
19. Cohen J (1960) A coefficient of agreement for nominal scales. *Educ Psychol Meas* 20:37–46
20. Baudouin R, Simon F, Levy R, Breton S, Alciato L, Talab E, Leboulanger N, Couloigner V, Garabédian EN, Denoyelle F (2023) Early magnetic resonance imaging to diagnose residual cholesteatoma in children and benefit of radiological review. *Otolaryngol Head Neck Surg*. <https://doi.org/10.1002/ohn.392>
21. Simon F, Remangeon F, Loundon N, Leboulanger N, Couloigner V, Garabédian N, Denoyelle F (2024) Pediatric cholesteatoma follow-up: Residual and recurrence in 239 cases with over 5-year hindsight. *Laryngoscope* 134:4789–4798
22. Munn Z, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A, Stephenson M, Aromataris E (2020) Methodological quality of case series studies: An introduction to the JBI critical appraisal tool. *JBI Evid synthesis* 18:2127–2133
23. McGuinness LA, Higgins JP (2021) Risk-of-bias visualization (robvis): An R package and shiny web app for visualizing risk-of-bias assessments. *Res synthesis methods* 12:55–61
24. OCEBM Levels of Evidence Working Group (Jeremy, Howick ICJLL, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, Moschetti I, Phillips B, Hazel Thornton, Olive Goddard and Mary Hodgkinson) The Oxford levels of evidence 2. Accessed 2025.01.27. *BMJ*, 2008. 336(7650): p. 924–6 <https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebmllevels-of-evidence>
25. Jeremy Howick IC, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, Moschetti I, Phillips B, Thornton H (2011) Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence (background document). <https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebmllevels-of-evidence>. Accessed 2023.02.22
26. Vercruysse JP, De Foer B, Somers T, Casselman J, Offeciers E (2009) Magnetic resonance imaging of cholesteatoma: An update. *B-ENT* 5:233–240
27. Williams M, Ayache D (2006) Imagerie des otites chroniques de l'adulte. *Journal de radiologie* 87:1743–1755
28. Weibel C (1979) Nilpotence and k-theory. *J Algebra* 61:298–307
29. Bland JM, Altman DG (1996) Transformations, means, and confidence intervals. *BMJ: Br Med J* 312:1079
30. Limpert E, Stahel WA, Abbt M (2001) Log-normal distributions across the sciences: Keys and clues: On the charms of statistics, and how mechanical models resembling gambling machines offer a link to a handy way to characterize log-normal distributions, which can provide deeper insight into variability and probability—normal or log-normal: That is the question. *Bioscience* 51:341–352
31. Laird NM, Ware JH (1982) Random-effects models for longitudinal data. *Biometrics* 963–974
32. Pinheiro JC, Bates DM (2000) Mixed-effects models in S and S-PLUS. Springer
33. Gelman A, Hill J (2007) Data analysis using regression and multilevel/hierarchical models. Cambridge University Press
34. Bates D, Mächler M, Bolker B, Walker S (2015) Fitting linear mixed-effects models using lme4. *J Stat Softw* 67:1–48
35. Venzon D, Moolgavkar S (1988) A method for computing profile-likelihood-based confidence intervals. *J Roy Stat Soc: Ser C (Appl Stat)* 37:87–94
36. Nakagawa S, Schielzeth H (2013) A general and simple method for obtaining R² from generalized linear mixed-effects models. *Methods Ecol Evol* 4:133–142
37. Bartoń K (2023) Mumin: Multi-model inference. R package version 1.47. 5. 2023. In
38. Efron B, Tibshirani RJ (1994) An introduction to the bootstrap. Chapman and Hall/CRC
39. Davison A, Hinkley D (1997) Bootstrap methods and their application, Cambridge Univ., Cambridge University Press
40. Robert CP, Casella G, Casella G (1999) Monte Carlo statistical methods. Springer
41. Kuznetsova A, Brockhoff PB, Christensen RH (2017) LmerTest package: Tests in linear mixed effects models. *J Stat Softw* 82:1–26
42. Lüdtke D (2021) Sjplot-data visualization for statistics in social science. Zenodo
43. Delrue S, De Foer B, van Dinther J, Zarowski A, Bernaerts A, Vanspauwen R, Casselman JW, Offeciers E, Somers T (2019) The value of diffusion-weighted MRI in the long-term follow-up after subtotal petrosectomy for extensive cholesteatoma and chronic

- suppurative otitis media. *Otol Neurotol* 40:e25–e31. <https://doi.org/10.1097/mao.0000000000002049>
44. De Foer B, Vercruysse J-P, Bernaerts A, Deckers F, Pouillon M, Somers T, Casselman J, Offeciers E (2008) Detection of postoperative residual cholesteatoma with non-echo-planar diffusion-weighted magnetic resonance imaging. *Otolaryngol* 29:513–517
 45. Gristwood R, Venables W (1976) Growth rate and recurrence of residual epidermoid cholesteatoma after tympanoplasty. *Clin Otolaryngol Allied Sci* 1:169–182
 46. Hellingman CA, Logher JL, Kammeijer Q, Waterval JJ, Ebbens FA, van Spronsen E (2019) Measuring growth of residual cholesteatoma in subtotal petrosectomy. *Acta Otolaryngol* 139:415–420
 47. Lecler A, Lenoir M, Peron J, Denoyelle F, Garabedian EN, Pointe HD, Nevoux J (2015) Magnetic resonance imaging at one year for detection of postoperative residual cholesteatoma in children: Is it too early? *Int J Pediatr Otorhinolaryngol* 79:1268–1274. <https://doi.org/10.1016/j.ijporl.2015.05.028>
 48. Pai I, Crossley E, Lancer H, Dudau C, Connor S (2019) Growth and late detection of post-operative cholesteatoma on long term follow-up with diffusion weighted magnetic resonance imaging (dwi mri): A retrospective analysis from a single uk centre. *Otolaryngol Neurotol* 40:638–644
 49. Smith WK, Naidu L, Subrahmanyam HK (2020) The use of serial non epi dwi mri scans to determine the growth of cholesteatoma. *Bengal J Otolaryngol Head Neck Surg* 28:215–220
 50. Jindal M, Riskalla A, Jiang D, Connor S, O'Connor AF (2011) A systematic review of diffusion-weighted magnetic resonance imaging in the assessment of postoperative cholesteatoma. *Otolaryngol Neurotol* 32:1243–1249
 51. Li PM, Linos E, Gurgel RK, Fischbein NJ, Blevins NH (2013) Evaluating the utility of non-echo-planar diffusion-weighted imaging in the preoperative evaluation of cholesteatoma: A meta-analysis. *Laryngoscope* 123:1247–1250
 52. Lingam RK, Bassett P (2017) A meta-analysis on the diagnostic performance of non-echoplanar diffusion-weighted imaging in detecting middle ear cholesteatoma: 10 years on. *Otolaryngol Neurotol* 38:521–528
 53. Geoffroy A, Guesmi M, Nebbia JF, Leloutre B, Bailleux S, Maschi C (2013) Mri for the diagnosis of recurrent middle ear cholesteatoma in children—can we optimize the technique? Preliminary study. *Pediatr Radiol* 43:464–473
 54. Kálmán J, Horváth T, Liktó B, Dános K, Tamás L, Gődény M, Polony G (2021) Limitations of non-echo planar diffusion weighted magnetic resonance imaging (non-epi mri) in cholesteatoma surveillance after ossicular chain reconstruction. A prospective study. *Auris Nasus Larynx* 48:630–635
 55. Walters H, Lee-Warder L, Mentias Y, Arullendran P (2023) Cartilage grafts mimicking cholesteatoma recurrence on diffusion-weighted magnetic resonance imaging: A case series. *J Laryngology Otolaryngol* 137:938–941
 56. Hazra A (2017) Using the confidence interval confidently. *J Thorac disease* 9:4125
 57. Covelli E, Margani V, Filippi C, Elfarag HH, Volpini L, Romano A, Bozzao A, Barbara M (2022) Proposal of a magnetic resonance imaging follow-up protocol after cholesteatoma surgery: A prospective study. *Acta Otolaryngol* 142:484–490
 58. Volgger V, Lindeskog G, Krause E, Schrötmair F (2020) Identificação de fatores de risco para colesteatoma residual em crianças e adultos: Um estudo retrospectivo de 110 casos de cirurgia revisionais. *Braz J Otorhinolaryngol* 86:201–208
 59. Roger G, Denoyelle T, Chauvin P, Schlegel-Stuhl N, Garabedian E-N (1997) Predictive risk factors of residual cholesteatoma in children: A study of 256 cases. *Otolaryngol Neurotol* 18:550–558
 60. Hussain MH, Mair M, Mahmood S, Sakagiannis G, Rojoa DM, Raheman FJ, Irvine E, Rea P (2021) Delays in surgery for cholesteatoma due to covid-19: Is there an impact on rates of recidivism and major complications? *Eur Arch Otorhinolaryngol* 278:3291–3297
 61. Kuo C-L, Shiao A-S, Yung M, Sakagami M, Sudhoff H, Wang C-H, Hsu C-H, Lien C-F (2015) Updates and knowledge gaps in cholesteatoma research. *Biomed Res Int* 2015:854024
 62. Jackson R, Addison A, Prinsley P (2018) Cholesteatoma in children and adults: Are there really any differences? *J Laryngology Otolaryngol* 132:575–578
 63. HINOHIRA Y, KIYOFUMI G, YANAGIHARA N, BREDBERG G, ALSTERBORG E (1998) Effects of mastoid cavity obliteration on the growth of experimentally produced residual cholesteatoma. *Acta Otolaryngol* 118:101–104
 64. Kemps G, Geven L, Kunst H, Mylanus E, Mulder J, Lanting C, Pennings R (2024) Surgical treatment for troublesome mastoid cavities: Canal wall reconstruction with bony obliteration versus subtotal petrosectomy. *Otolaryngol Neurotol* 45:273–280

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