Otalgia as a Predictor of Cholesteatoma Formation in Chronic Suppurative Otitis Media

Evidence-based Case Report

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ABSTRACT

Cholesteatoma has the potential for fatal complications; however, many remain undetected until advanced stages. Otalgia is suggested as an indicator of an impending intratemporal or intracranial complication and is commonly presented before episodes of characteristic foul-smelling, purulent discharge. This study aims to find whether otalgia has a prognostic value for cholesteatoma in adults with chronic suppurative otitis media. Literature searches using Pubmed, Cochrane, and ScienceDirect were done from March 12-16, 2022. Two articles were selected and appraised using the center of evidence-based medicine Oxford tool for prognostic study. Both studies retrospectively found no statistically significant characteristics or clinical findings, including otalgia on first hospital admission that might distinguish between chronic suppurative otitis media with and without cholesteatoma. Even though all studies have good validity, applicability, and precise prognostic estimates, considerable discrepancies between the two studies exist; therefore, clinical interpretation remains questionable. Otalgia does not have a significant prognostic value for cholesteatoma risk in adults with chronic suppurative otitis media.

Keywords: Cholesteatoma, chronic suppurative otitis media, otalgia.

ABSTRAK

Kolesteatoma berpotensi menyebabkan komplikasi fatal, namun banyak kasus tidak terdeteksi hingga stadium lanjut. Otalgia diusulkan dapat menjadi indikator komplikasi intratemporal atau intrakranial; biasanya muncul sebelum episode keluarnya cairan bernanah berbau busuk. Pencarian literatur menggunakan Pubmed, Cochrane, dan ScienceDirect telah dilakukan dari 12 hingga 16 Maret 2022. Dua artikel dipilih dan dinilai menggunakan alat *Oxford center of evidence-based medicine* untuk studi prognostik. Kedua penelitian retrospektif tidak menemukan karakteristik pasien atau temuan presentasi klinis yang signifikan secara statistik, termasuk otalgia, yang mungkin memandu perbedaan antara otitis media supuratif kronik dengan atau tanpa kolesteatoma saat pertama kali masuk rumah sakit. Meskipun semua penelitian memiliki validitas dan penerapan yang baik, serta perkiraan prognostik yang tepat, terdapat perbedaan besar antara kedua studi tersebut, sehingga interpretasi klinisnya masih dipertanyakan. Otalgia tidak memiliki peran prognostik yang signifikan untuk risiko kolesteatoma pada dewasa dengan otitis media supuratif kronis. **Fabiola Cathleen. Otalgia sebagai Prediktor Kolesteatoma pada Otitis Media Supuratif Kronik: Laporan Berbasis Bukti.**

Kata Kunci: Kolesteatoma, otitis media supuratif kronik, otalgia.

INTRODUCTION

Background

Cholesteatoma is a well-demarcated, noncancerous cyst of keratinizing squamous epithelium in the temporal bone. The term is a misnomer since the lesion neither contains cholesterol nor is neoplastic in nature. It can be classified into two types: congenital type, which forms before birth without a history of chronic middle ear disease or previous otologic procedures, and acquired type, which usually occurs as a result of chronic suppurative otitis media.[1] Approximately 70%-96% of cholesteatoma are acquired.[2] The incidence of acquired cholesteatoma ranges from three to fifteen cases per 100.000 children and 9–12.6 cases per 100.000 adults annually.[3]

It results from the enzymatic activity of the cholesteatoma matrix in an environment of chronic infection. Pathogenesis primarily focuses on four theories: invagination, migration, metaplasia, and hyperplasia, either as an independent process or a complex hybrid of all four.[4] Recent studies also found a link between its pathogenesis and genomic alterations: upregulation of epidermal growth factor receptor (EGFR) and transforming growth factor alpha (TGF-α).[5] Its locally invasive nature allows the destruction of middle ear structures and has the potential to cause fatal complications without effective

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nonsurgical therapies.

However, cholesteatoma often progresses and remains undetected until intra- or extracranial complications manifest in advanced stages, such as meningitis and brain abscesses.[6] Aquino, *et al,* found that about 66.5% of acquired cholesteatoma cases have otorrhea,[7] usually described as recurrent, foul-smelling, scant, and purulent discharge with or without hearing loss. Otalgia, headache, vomiting, and fever are reported to be nontypical presentations of cholesteatoma,[1] but Castle, *et al,* found that otalgia may indicate impending intratemporal or intracranial complications and is commonly present prior to episodes of purulent discharge.[7] As an earlier diagnosis is needed, this study aims to find whether the presence of otalgia can predict cholesteatoma formation in adult patients with chronic suppurative otitis media.

Case Illustration

A 22-year-old female presented with right otorrhea for two months before presenting to the hospital, which was characterized as purulent, yellowish, persistent, and odorless. The symptom was preceded by intermittent otalgia (VAS 3) and a sense of fullness in the ear. Hearing loss, tinnitus, spinning sensations, nausea, and vomiting were all denied. One month ago, her otalgia worsened and radiated to the back of her right ear and right side of the head (VAS 5), causing sleep disturbances. She also began to be aware of a slight hearing loss. The patient was then referred to Dr. Cipto Mangunkusumo Hospital and treated with an eardrop containing active ingredients per 5 mL: polymyxin B sulfate 50,000 IU, neomycin sulfate 25 mg, fludrocortisone acetate 5 mg, lidocaine HCl 200 mg, and oral ofloxacin 200 mg twice a day. She felt no symptom improvement.

The patient also admittedly experienced repeated sneezing, nasal pruritus, airflow obstruction, and mostly clear nasal discharge weeks before the symptom appeared, without cough or fever. Similar intermittent episodes have been reported since two years ago, notably on exposure to dust, but they did not interfere with her sleep, work, or daily activities. The patient has never sought medical care for these complaints.

She was mildly ill with a blood pressure of 96/72 mmHg, a pulse rate of 92 x/min, a respiratory rate of 18 x/min, and a body temperature of 36.1°C. There was retro-auricular tenderness and scanty yellowish, odorless mucopurulent discharge on the canal of her right ear. The right tympanic membrane lost its light reflex with poorly marginated perforation partially covered by granulation tissue. Her face, nose, throat, and cranial nerve examinations were all within normal limits. Supporting examinations have not been done.

Clinical Question

Does otalgia in chronic suppurative otitis media in adult patients have a predictive role for cholesteatoma formation?

METHODS

Search Strategy

Three online databases, including Pubmed, Cochrane, and Science Direct, were sought from March 12th to 16th 2022, using the following terms as medical subject headings or keywords: "cholesteatoma", "chronic suppurative otitis media", and "symptom", with their related terms or synonyms. The search strategy is summarized in **Table 2**. An additional manual search of similar article suggestions and bibliographies provided in selected articles was also performed.

Eligibility Criteria

Studies were eligible for inclusion if they were relevant to the PICO of this study, written in Bahasa Indonesia or English, and were cohort studies or systematic reviews of cohort studies. The study selection was limited to a systematic review of cohort studies or cohort studies, as they are the two best study designs for prognosis studies. Studies were excluded if they were not reviewed, published, or publicized earlier than year 2000 and if the full text is unretrievable.

Article Selection

The study selection process follows the preferred reporting items for systematic review and meta-analyses (PRISMA) statements' flow diagram.[9] All retrieved records were filed in a Microsoft Excel worksheet to enable immediate manual removal of duplicates.

Table 1. PICO formulation.

Patient/Problem (P)	Indicator (I)	Comparison (C)	Outcome (O)
Patients with chronic suppurative otitis media	Otalgia	Without otalgia	Cholesteatoma
Clinical Question	Prognostic		
Study Design	Cohort, systematic review of cohort studies		

Table 2. Literature searching strategy.

Database	Search Strategy	Hits
Pubmed	(((((cholesteatoma, middle ear[MeSH Terms]) NOT (children[Title/Abstract])) NOT (pediatric[Title/Abstract])) NOT (congenital[Title/Abstract])) OR ((suppurative otitis media[MeSH Terms]) OR (chronic suppurative otitis media[Title/Abstract]))) AND (((((((symptom[Title/Abstract]) OR (sign[Title/Abstract])) OR (clinical manifestation[Title/Abstract])) OR (feature[Title/Abstract])) OR (presentation[Title/Abstract])) OR (profile[Title/Abstract])) OR (indicator[Title/Abstract])) OR (predictor[Title/Abstract]))	120
Cochrane	((cholesteatoma):ti,ab,kw OR ("chronic suppurative otitis media"):ti,ab,kw) AND ((predictor):ti,ab,kw OR (clinical manifestation):ti,ab,kw OR (symptom):ti,ab,kw OR (feature):ti,ab,kw OR (indicator):ti,ab,kw)	6
ScienceDirect	(cholesteatoma -children -recurrence -congenital -pediatric OR 'chronic suppurative otitis media') AND (presentation OR feature OR symptom OR 'clinical manifestation')	83
Total Hits		209

The remaining studies will be screened based on their titles and abstracts following the inclusion and exclusion criteria of this EBCR. After screening, the process continued with a full-text eligibility assessment, which is also based on the inclusion criteria. The remaining studies will be included in this EBCR; data is then extracted and collected in a formulated form, which includes study details (title, author, publication year, study design, setting, population, sample size, and outcome) and participants' details (samples' mean age).

Critical Appraisal Method

The quality of each included study is evaluated using the critical appraisal tool for prognosis studies in English from the centre of evidence-based medicine (CEBM) of the University of Oxford.[10] Three domains - validity, importance, and applicability of study - were assessed.

RESULTS

Results of Article Searching and Selection

A database search resulted in 209 total records: 120, 6, and 83 from PubMed, Cochrane, and Science Direct, respectively. Twelve additional records were identified manually from similar article suggestions (n = 4) and bibliographies from other studies not identified in electronic searches (n = 8), resulting in a total of 221 records retrieved. Duplicates (n = 1) are immediately removed, leaving 220 records to be screened. Further exclusion was done to 204 studies, as they are irrelevant to the PICO of this report (n = 202), or written in languages other than Bahasa and English (n = 2), resulting in 16 studies being assessed for eligibility. Five studies have incompatible study designs; one study was written in German; seven studies do not correlate with the PICO of this study; and the full text of one study cannot be retrieved. With further exclusion of those records (n = 14), two studies were included in the qualitative synthesis. Figure presents the summary of article selection following the four-phased PRISMA Statements' flow diagram. Table 3 illustrates the characteristics of the two studies located in the USA and Ireland, with a total of 144 participants included in this EBCR. All studies used retrospective cohorts.

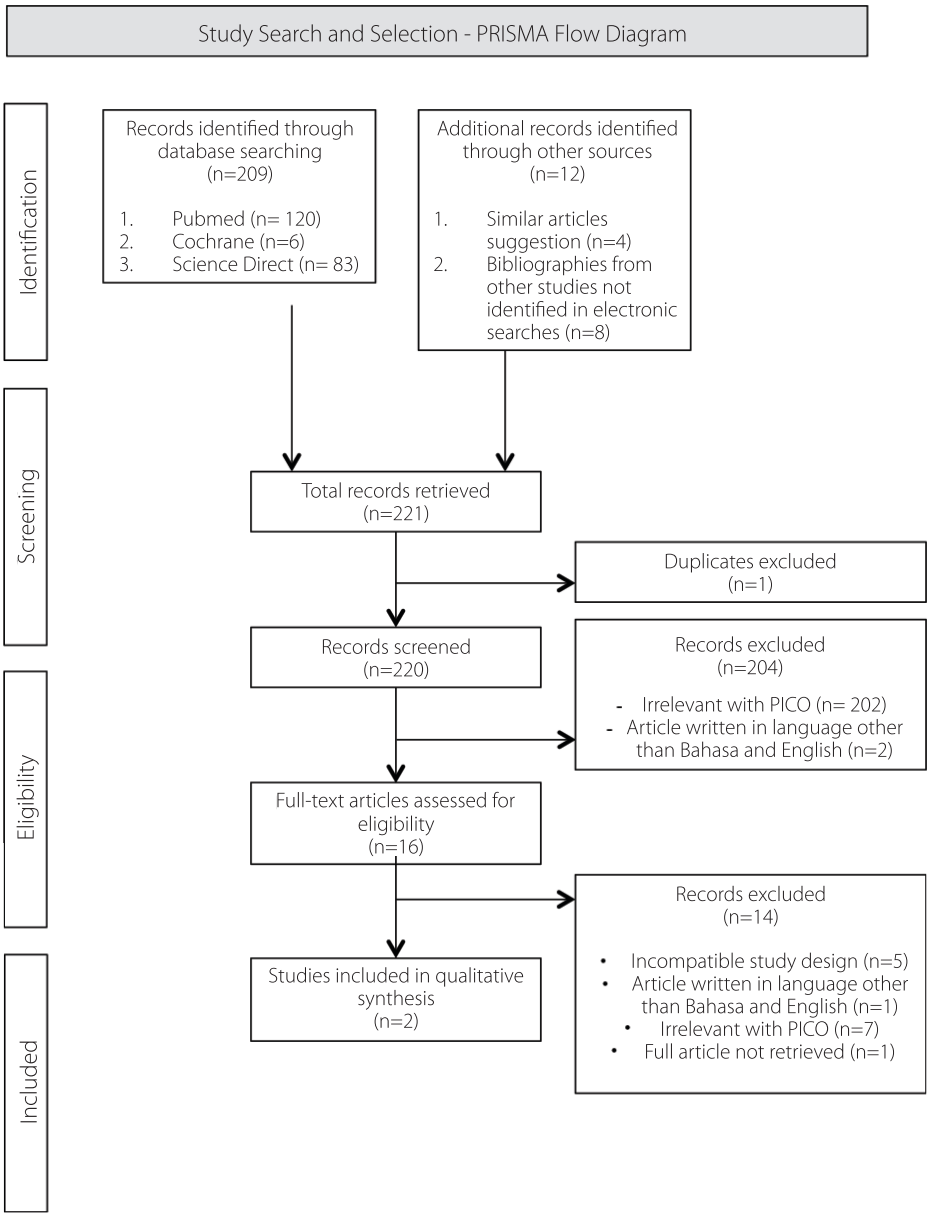

Figure. Article selection using PRISMA statement's flow diagram.

Result

The summary of the critical appraisal result is shown in Table 4, while the complete critical appraisal result can be found in **Appendix 1**. All studies were valid. The blinding method in both studies was unclear but still considered acceptable since the cholesteatoma diagnosis was confirmed surgically and all data was recorded from legitimate medical records. As for the importance aspect, all studies have precise prognostic estimates due to a narrow 95% confidence interval. The results from both studies can be applied to the patient in this report.

DISCUSSION

Two retrospective cohort studies by Clark JH, *et al,*[11] and Sheahan P, *et al,*[12] analyzed otalgia as a presenting symptom of chronic suppurative otitis media on first ENT hospital admission to predict cholesteatoma formation. Both studies found no statistically significant patient characteristics or clinical findings, including otalgia, that might distinguish chronic suppurative otitis media with or without cholesteatoma.[11,12] Small study population in each study should be a limitation to the statistical power to demonstrate significant results.

Even though the validity and applicability of both studies are acknowledged, the clinical pertinence of their prognostic estimates remains questionable because of the significant discrepancies in prevalence in those studies, which is 67% in Clark JH, *et al,* compared to 25% in Sheahan P, *et al,* This could be overlooked by the seemingly precise


Table 3. Study characteristics.

	Clark JH, *et al.* 2016.[11]	Sheahan P, *et al.* 2001.[12]
Title	Secondary acquired cholesteatoma: presentation and tympanoplasty outcomes	Clinical features of newly presenting cases of chronic otitis media
Study Design	Retrospective cohort, age-matched	Retrospective cohort
Study Setting	Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins Hospital, Baltimore, Maryland, USA	ENT Department of Waterford Regional Hospital, Ireland
Study Population	All hospital admissions and outpatient visits associated with the procedure code for tympanoplasty or tympanomastoidectomy	All new cases of chronic otitis media presented to the ENT unit
Diagnosis of Cholesteatoma	Confirmation at surgery	Confirmation at surgery
Sample Size	82	64
Mean Sample Age	30.9±6.2 years old in the cholesteatoma group and 30.6±6.2 years old in the noncholesteatoma group	34 years old in all groups and 27 years old in the cholesteatoma group
Outcome	RR = 1.49, p = 0.157	RR = 1.11, p >0.05

Table 4. Summary of critical appraisal.

	Clark JH, *et al.* 2016.[11]	Sheahan P, *et al.* 2001.[12]
Validity		
A representative sample of patients assembled at a common point	Unclear	Yes
Long and complete follow-up	Yes	Yes
Blinding	Unclear	Unclear
Prognostic factor adjustment	Yes	Yes
Importance		
How likely are the outcomes over time?	otalgia as presenting symptoms in 15 patients; 10 had cholesteatoma on examination	otalgia as presenting symptoms in 24 patients reporting, 6 had cholesteatoma on examination
Prognostic estimates	p= 67% SE=1.8% 95%CI= 63.47%–70.53%	p= 25% SE=1.5% 95%CI= 22.06%–27.94%
Applicability		

confidence interval if those studies are reviewed separately (63.47%–70.53% from Clark JH, *et al,* and 22.06%–27.94% from Sheahan P, *et al).* This near-three-fold difference may also result from the fact that Clark JH, *et al,* recruited patients from tertiary care academic centers that may have more advanced disease with poorer prognoses, in this case, cholesteatoma, compared to Sheahan P, *et al,* who engaged with the general population. Different study locations and racial factors in both studies should not affect epidemiological disparity, as Caucasians mostly inhabit both countries. Caucasians are known to have the highest cholesteatoma prevalence compared to other races, which may explain the high cholesteatoma prevalence in both studies included.[13] The true worldwide or country-based prevalence is difficult to estimate; it is reported to be 26% in South Korea and 0.08% in Saudi Arabia.[14,15]

This study concludes that otalgia does not have a significant prognostic role in cholesteatoma formation in patients with chronic suppurative otitis media. This finding supports previous articles emphasizing the difficulty of cholesteatoma early detection due to its insidious or subtle symptoms.[1,16] The current approximation of cholesteatoma formation lies in the presence of retroauricular abscess or fistulae, granulation tissue or polyp on the ear canal, marginal or attic perforation, foul-smelling discharge, or cholesteatoma depiction on mastoid imaging; however, none of these provide much clinical relevance.[17] About a third of cholesteatoma patients did not even report any history of otorrhea.[12]

The strength of this report includes adequate time for cohort follow-up and the similar population in both studies. The limitation is that there are only two included studies with a limited participant size.

CONCLUSION AND RECOMMENDATION

Conclusion

This EBCR concluded that otalgia does not have a significant prognostic role in cholesteatoma detection in patients with chronic suppurative otitis media.

Recommendation

Cholesteatoma should be suspected in all patients with chronic suppurative otitis media, regardless of their symptoms. Developing other approaches to earlier detection of cholesteatoma is needed, one that is less invasive, more cost-effective, and as effective as time-tested surgical options.

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APPENDIX

Appendix 1. Full critical appraisal result of Clark JH, *et al,* 2016.

Validity		
Questions	**Yes/No/ Unclear**	**Comments**
Was the defined representative sample of patients assembled at a common (usually early) point in the course of their disease?	Unclear	All patients' clinical characteristics were taken as their presenting symptoms from their first hospital admission reports in medical records. However, patients were recruited from tertiary care and academic centers
Was patient follow-up sufficiently long and complete?	Yes	All patients were followed from their first symptom appearance to hospital admission
Were outcome criteria either objective or applied in a 'blind' fashion?	Unclear	Cholesteatoma diagnosis was done by operation and published criteria for secondary acquired cholesteatoma, but there is no mention of blinding
If subgroups with different prognoses are identified, did adjustment for important prognostic factors take place?	Yes	There is no subgroup with a different prognosis identified; therefore, no adjustment is necessary
Importance		
Questions		**Comments**
Outcomes over time		Fifteen patients reported otalgia as presenting symptoms; 10 had cholesteatoma on examination
Precision of prognostic estimates		p = 10/15 = 67% SE = √{0,67x(1-0,67)/15} = 0.018 = 1.8% 95%CI = 67% +- 1.96x1.8% = 63.47%–70.53%
Applicability		


Questions	Yes/No/ Unclear	Comments
Similarity of the study patients to clinical illustrations	Yes	The mean sample age of cholesteatoma group (30.9±6.2 years old) of the study resembles patient's age (22 years old). The patient is also a newly presented case of chronic suppurative otitis media

Appendix 2. Full critical appraisal result of Sheahan P, *et al,* 2001.

Validity		
Questions	**Yes/No/ Unclear**	**Comments**
Was the defined representative sample of patients assembled at a common (usually early) point in the course of their disease?	Yes	All patients' clinical characteristics were taken as their presenting symptoms from their first hospital admission reports in medical records. Patients were recruited from the only ENT unit in the South-Eastern Health Board region in Ireland, with a population of 400.000. Most of the population will, therefore, have received treatment for ENT disease in this unit, with all of their records readily accessible.
Was patient follow-up sufficiently long and complete?	Yes	All patients were followed from their first symptom appearance to hospital admission.
Were outcome criteria either objective or applied in a 'blind' fashion?	Unclear	The examination was done objectively by audiometric assessment and an operating microscope; however, there is no mention of blinding.
If subgroups with different prognoses are identified, did adjustment for important prognostic factors take place?	Yes	There is no subgroup with a different prognosis identified; therefore, no adjustment is necessary.
Importance		
Questions		**Comments**
Outcomes over time		From 24 patients reporting otalgia as presenting symptoms, 6 had cholesteatoma on examination.
Precision of prognostic estimates		p= 6/24 = 25% SE = √{0,25x(1-0,25)/24} = 0,015 = 1.5% 95%CI = 25% +- 1.96x1.5% = 22.06%–27.94%
Applicability		
Questions	**Yes/No/ Unclear**	**Comments**
Similarity of the study patients to clinical illustrations	Yes	The mean sample age of cholesteatoma group (27 years old) of the study matches patient's age (22 years old). The patient is also a newly presented case of chronic suppurative otitis media.