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A Life Dedicated to Science, Education, and the Homeland: In Memory of Prof. Dr. Şinasi Yalçın (1955-2025)

Original Investigations

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Türk Otorinolarengoloji Arşivi

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Obituary

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A Life Dedicated to Science, Education, and the Homeland: In Memory of Prof. Dr. Şinasi Yalçın (1955-2025)

İrfan Kaygusuz, Turgut Karlıdağ

Fırat University Faculty of Medicine, Department of Otorhinolaryngology, Elazığ, Türkiye

Prof. Dr. Şinasi Yalçın

Prof. Dr. Şinasi Yalçın, MD, known as the "Teacher of Teachers," passed away on May 1, 2025, at the age of 70 in his beloved hometown of Elazığ. On the first anniversary of his passing, we commemorate him with deep respect for both the invaluable contributions he made to the Faculty of Medicine at Fırat University and the enduring legacy he left to the Turkish Otorhinolaryngology (ENT) community.

Early Years and a Life Devoted to Education: Şinasi Yalçın was born on January 15, 1955, in Elazığ. He began his education in his hometown and, in 1972, enrolled at Middle East Technical University to study Engineering. However, his passion for medicine led him to transfer to the Kayseri Gevher Nesibe Faculty of Medicine in 1974. He completed his medical education in 1980 at Dokuz Eylül University Faculty of Medicine, graduating third in his class. He completed his residency training in 1986 at 19 Mayıs University. Although he was exempt from compulsory service due to his academic excellence, he chose to serve his hometown by joining Fırat University in Elazığ.

A Story of Achievement at Fırat University: Appointed as an assistant professor in 1986 at the Department of Otorhinolaryngology of Fırat University, Dr. Yalçın transformed a clinic with limited resources into an internationally accredited center for education and research over a period of 35 years. To modernize the clinic, he mobilized local resources in Elazığ and personally contributed to acquiring numerous facilities, from surgical instruments to advanced technological equipment.

He was promoted to full professor in 1995 and held several key administrative positions, including serving on the senate, as deputy chief physician, and as head of department. Over the course of his 42-year professional career, he trained thousands of medical students and 52 ENT specialists, leaving an indelible mark on medical education and the ENT community. He also made substantial contributions to the scientific literature through more than 300 publications, presentations, and book chapters.

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Leadership in the Turkish ENT Community and Regional Development: Prof. Dr. Şinasi Yalçın's vision extended beyond his own institution. Believing that collaboration among Anatolian clinics would foster collective advancement, he helped establish the Fırat-Dicle Basin ENT and Head and Neck Surgery Association in 1998. This association set a precedent for other regional societies in Türkiye and contributed to the development of the national organizational structure (Figure 1).

Between 2010 and 2012, he served as the 10th President of the Turkish Otorhinolaryngology and Head and Neck Surgery Society and as the Chairman of the 32nd National Congress of Otorhinolaryngology and Head and Neck Surgery. He also emphasized the importance of cadaveric dissection in residency training and founded the Prof. Dr. Şinasi Yalçın Microsurgery and Dissection Laboratory, a pioneering initiative in Türkiye (Figures 2-4).

"The Agha of Elazığ": Known among his colleagues as "The Agha of Elazığ," Dr. Yalçın has won the hearts of many with his hospitality and fatherly demeanor. He has always encouraged his students to practice empathy, and by saying, "Never leave patients helpless in the emergency room," has personally embodied the most fundamental principle of medical ethics.

Figure 1. The symposium of the Fırat-Dicle Basin ENT and Head and Neck Surgery Association, 2000

Figure 2. The Prof. Dr. Şinasi Yalçın Microsurgery and Dissection Laboratory, Professor Şinasi Yalçın, with his colleagues, 2016

Figure 3. Temporal Bone Dissection Course, 2017

Figure 4. Advisory board of the Turkish Society of Otorhinolaryngology and Head and Neck Surgery, 2018

Even during the most challenging periods of his illness, he remained devoted to science, continuing to attend symposia, often with respiratory support, and to share his professional experience. His happy family life with his wife Nevin, his companion of 52 years, along with their two sons and three grandchildren, was a major source of strength behind his academic achievements (Figures 5 and 6).

Figure 5. 5th National Medical Students' Congress, 2018

Figure 6. Monthly scientific meeting of the Fırat-Dicle Basin ENT and Head and Neck Surgery Association, 2021

Prof. Dr. Şinasi Yalçın was not only a surgeon and academic but also a true role model for his students, distinguished by his discipline, generosity, and unwavering commitment to his principles. His scientific legacy and ethical values will continue to live on through the many physicians he trained. Since May 1, 2025, every first of May has carried a profound sense of sorrow for us.

May he rest in peace.

Original Investigation

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Evaluation of Extended Indications for Cochlear Implantation Beyond Conventional Criteria

Mehmet Murat Günay[1], Sibel Alicura Tokgöz[1], İlker Akyıldız[1], Serap Er[2], Dilara Söylemez[2], Murad Mutlu[1], Muharrem Dağlı[1]

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Abstract

Objective: This study evaluated the indications for cochlear implant (CI) that extend beyond the current criteria of the Health Implementation Communiqué (HIC) of the Turkish Social Security Institution.

Methods: A retrospective review was performed on 27 patients who underwent CI, even though they did not meet the HIC criteria. All cases were approved by the Scientific Advisory Board on Auditory Implants of the Ministry of Health. Demographic, clinical, and audiological data, including pre- and post-operative pure-tone averages (PTA) and speech discrimination scores (SDS), were analyzed.

Results: The cohort included 15 females and 12 males, with a median age of 17 years. Etiologies comprised congenital hearing loss (n=14), idiopathic sudden sensorineural hearing loss (n=3), post-meningitic hearing loss (n=2), Menière's disease (n=1), and other acquired causes. Exclusion from the HIC criteria was mainly due to age restrictions for bilateral CI, audiological thresholds outside defined limits, single-sided deafness, SDS above 30%, or a gap of more than four years between chronological and language age. Audiological outcomes from 22 patients revealed a median PTA with the CI alone of 35 dB hearing level and a median SDS of 58%, with significant improvement compared to baseline ($p<0.001$). While most patients demonstrated substantial benefit, 14.8% (cases 6, 17, 21, 25) exhibited poor performance (SDS <30%). Case analyses underscored the impact of etiology and duration of auditory deprivation on outcomes.

Conclusion: CI beyond conventional reimbursement criteria can provide meaningful functional gains. Individualized, evidence-based, multidisciplinary evaluation supports broader access to hearing rehabilitation and is consistent with global trends in personalized auditory care.

Keywords: Cochlear implant, hearing loss, single-sided deafness, social security, reimbursement incentive, cochlear implant candidacy, insurance coverage

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Introduction

Hearing loss profoundly affects communication, cognition, and quality of life (1). Cochlear implants (CI) improve outcomes, yet global utilization remains below 15%, with inequities in access (2). Initially restricted to post-lingually deafened adults with profound hearing loss [>100 dB hearing level (HL)], CI candidacy has expanded to children, bilateral implantation, residual hearing, and single-sided deafness (SSD) (3,4). While guidelines

generally align in this direction, reimbursement and socioeconomic factors vary considerably across countries (4-7). Demonstrating the benefits in patients excluded from coverage is essential to expand healthcare and reduce inequities.

In Türkiye, candidacy and reimbursement for CI are regulated by the Health Implementation Communiqué (HIC) of the Turkish Social Security Institution (SSI), which defines explicit audiological and clinical thresholds for eligibility. According to the latest update in 2024, CI is reimbursed for patients with bilateral severe-to-profound sensorineural hearing loss (SNHL) with no benefit from binaural hearing aids (8). From an audiometric standpoint, CI eligibility in children older than two years and in adults requires either a bilateral four-frequency pure-tone average (4PTA) of ≥80 dB HL or a better-ear 4PTA of ≥70 dB HL combined with a worse-ear 4PTA of ≥90 dB HL, accompanied by speech discrimination scores (SDS) below 30% when measurable. For children aged two years or younger, bilateral SNHL of ≥90 dB HL constitutes the audiological threshold for candidacy. Additionally, candidates are expected to have an expressive and/or receptive language age that does not differ by more than four years from their chronological age. In individuals older than four years, the SSI does not reimburse simultaneous or sequential bilateral CI unless the hearing loss is meningitis-related or accompanied by bilateral blindness (8).

While the HIC criteria provide standardized guidelines for reimbursement, they restrict CI to a narrow subset of patients and exclude several groups who may still derive substantial benefits. Among those potentially benefiting are individuals with SSD, candidates for tinnitus suppression, and those considered for bilateral CI beyond the regulatory age limits (9-15). In addition, there exists a "gray zone" of patients who fall at the margins of audiological criteria, such as those with borderline SDS, or discrepancies between chronological age and language age. Although these patients may not strictly meet the regulatory thresholds, they often represent a group in whom CI can provide meaningful functional and developmental gains.

In many high-volume CI centers, clinical decision-making increasingly extends beyond these conventional boundaries, guided by evidence-based, individualized assessments and multidisciplinary team discussions involving otolaryngologists, audiologists, and speech-language pathologists (15). In Türkiye, patients who do not meet the formal HIC criteria but are anticipated to benefit from auditory implantation are individually evaluated by the Scientific Advisory Board on Auditory Implants (SABAI), which assesses candidacy based on current evidence, patient-specific factors, and expected functional outcomes.

The presented study aims to evaluate whether patients excluded from national reimbursement criteria, yet approved through individualized scientific board evaluation, can achieve clinically meaningful audiological benefit consistent with internationally expanding candidacy standards. Examining these indications is essential to bridge the gap between regulatory frameworks and evidence-based practices highlighted in contemporary literature.

Methods

Study Design and Ethical Approval

This retrospective study was carried out in the Department of Otorhinolaryngology at the University of Health Sciences Türkiye, Ankara Etlik City Hospital, a tertiary referral center performing more than 80 CIs annually. Ethical approval was obtained from the University of Health Sciences Türkiye, Ankara Etlik City Hospital Scientific Research Ethics Committee (approval no: AEŞH-BADEK-2025-0269, date: 30.04.2025). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from adult participants and from the legal guardians of pediatric patients.

Patient Selection

Medical records of patients evaluated for CI between November 2022 and December 2024 were retrospectively reviewed. The study included 27 patients who did not meet the current HIC reimbursement criteria but were considered suitable candidates by the institutional CI board and subsequently approved by the SABAI of the Ministry of Health.

Exclusion criteria were:

- Patients who met the standard HIC criteria for CI
- Patients evaluated by SABAI but not approved for CI
- Cases in which an alternative auditory implant (e.g., auditory brainstem implant or bone-anchored hearing aids) was recommended.

Data Collection

Demographic, clinical, and audiological data were retrospectively retrieved from the institutional electronic medical records. The extracted variables included:

- Age, sex, and occupation
- Etiology of hearing loss
- Duration of auditory deprivation, side, and degree of hearing loss
- Preoperative unaided 4PTA (500, 1000, 2000, and 4000 Hz), SDS, and auditory brainstem response (ABR) findings

• Preoperative assessment of language and speech development

• Intraoperative electrophysiological responses [neural response telemetry (NRT) measurements]

• Postoperative audiological performance during follow-up assessments.

All patients underwent standard audiological evaluations both preoperatively and postoperatively. Hearing and speech performance were assessed at a minimum of 6 months postoperatively using age-appropriate measures.

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as mean±standard deviation or as median with interquartile range (IQR) and minimum-maximum values, depending on distribution. Improvement in paired SDS values (postoperative minus preoperative) was assessed using the Wilcoxon signed-rank test.

Results

A total of 27 patients comprised the study cohort, including 15 females and 12 males, with a median age of 17 years (IQR: 6-43; range: 2-61). Etiologies of hearing loss included congenital SNHL (n=14), idiopathic sudden SNHL (ISSNHL, n=3), chronic otitis media (n=1), post-meningitic hearing loss (n=2), progressive SNHL (n=1), Menière's disease (n=1), and other acquired conditions such as head trauma, labyrinthitis, and otosclerosis surgery (Table 1).

Criteria leading to exclusion from HIC reimbursement:

• Bilateral CI candidates older than four years (n=10),

• Audiological thresholds outside the defined limits (n=5),

• SSD (n=5),

• SDS greater than 30% (n=4),

• Gap between chronological and language age exceeding four years (n=3) (Table 1).

Table 1. Demographic, etiological, and audiological characteristics of cochlear implant candidates outside HIC eligibility criteria

Case	Age (years)	Sex	Etiology	Side of hearing loss	Duration of auditory deprivation	PTA-AC (dB), PTA-BC (dB), SDS (%), or ABR results	Reason for HIC criteria non-compliance
Case 1	34	M	ISSNHL	Right	6 months	R: 109/72/12 L: 35/35/92	Outside the defined audiological threshold levels
Case 2	<2	F	Congenital	Bilateral	6 months	R: 100 dB, ABR wave V(+) L: 85 dB, ABR wave V(+)	Outside the defined audiological threshold levels
Case 3	51	F	Chronic otitis media	Bilateral	10 years	R: 99/68/16 L: 85/49/52	Outside the defined SDS levels
Case 4	43	M	Head trauma	Left	5 months	R: 6/6/100 L: 120/76/0	Single-sided deafness
Case 5	61	F	Progressive SNHL	Bilateral	10 years	R: 100/56/36 L: 85/52/76	Outside the defined SDS levels
Case 6	30	F	Microvascular decompression surgery for trigeminal neuralgia	Right	24 months	R: 117/77/0 L: 9/9/100	Single-sided deafness
Case 7	5	F	Congenital	Bilateral	5 years (left CI+)	R: 100 dB, ABR wave V(-) L: 85 dB, ABR wave V(-)	Bilateral CI after age 4 (right ear)
Case 8	45	M	ISSNHL	Left	6 months	R: 21/21/96 L: 114/73/20	Single-sided deafness
Case 9	7	M	Congenital	Bilateral	7 years (right CI+)	R: 116/73/0 L: 99/73/0	Bilateral CI after age 4 (left ear)/ language-chronological age gap >4 years
Case 10	24	F	Post-meningitic SNHL	Bilateral	22 years (right CI+)	R: 118/78/0 L: 113/78/0	Bilateral CI after age 4 (left ear)

Table 1. continued

Case	Age (years)	Sex	Etiology	Side of hearing loss	Duration of auditory deprivation	PTA-AC (dB), PTA-BC (dB), SDS (%), or ABR results	Reason for HIC criteria non-compliance
Case 11	<2	M	Congenital	Bilateral	2 years	R: 70 dB, ABR wave V(+) L: 100 dB, ABR wave V(-)	Outside the defined audiological threshold levels
Case 12	36	F	Post-AOM labyrinthitis	Bilateral	4 months	R: 120/71/0 L: 119/71/0	Bilateral CI after age 4 (simultaneously)
Case 13	7	M	Congenital	Bilateral	7 years (right CI+)	R: 100 dB, ABR wave V(-) L: 100 dB, ABR wave V(-)	Bilateral CI after age 4 (left ear)
Case 14	11	F	Post-meningitic left-ear SNHL, progressive right-ear SNHL	Bilateral	3 years (left CI+)	R: 110/73/0 L: 118/73/0	Bilateral CI after age 4 (right ear)
Case 15	9	F	Congenital	Bilateral	2 years	R: 111/71/0 L: 116/71/0	Language-chronological age gap >4 years (expressive language age: 2 years 3 months)
Case 16	6	F	Congenital	Bilateral	6 years	R: 111/73/0 L: 108/73/0	Language-chronological age gap >4 years (expressive language age: 1 year 3 months)
Case 17	5.5	M	Congenital	Bilateral	5 years	R: 113/77/0 L: 115/77/0	Language-chronological age gap >4 years (expressive language age: 1 year)
Case 18	5	F	Congenital	Bilateral	5 years (left CI+)	R: 100 dB, ABR wave V(-) L: 100 dB, ABR wave V(-)	Bilateral CI after age 4 (right ear)
Case 19	45	M	Menière's disease	Bilateral	2 years	R: 99/73/0 L: 48/42/76	Outside the defined audiological threshold levels
Case 20	51	F	Otosclerosis surgery	Left	18 months	R: 36/18/92 L: 120/70/0	Outside the defined audiological threshold levels
Case 21	8	F	Congenital	Right	8 years	R: 104/77/0 L: 7/7/100	Single-sided deafness
Case 22	17	F	Congenital	Bilateral	17 years (right CI+)	R: 120/72/0 L: 105/72/0	Bilateral CI after age 4 (left ear)
Case 23	51	F	Otosclerosis surgery (bilateral)	Bilateral	18 months	R: 103/45/28 L: 90/45/76	Outside the defined SDS levels
Case 24	18	M	Congenital	Bilateral	18 years	R: 91/72/8 L: 79/68/52	Outside the defined SDS levels
Case 25	12	F	Congenital	Right	11 years	R: 10/7/100 L: 120/77/0	Single-sided deafness
Case 26	34	F	ISSNHL (left at 17, right at 26)	Bilateral	Left 10 years (CI+ 7 years ago), right 8 years	R: 88/72/0 L: 103/72/0	Bilateral CI after age 4 (right ear)
Case 27	6	F	Congenital	Bilateral	1 year (right CI+)	R: 119/77/0 L: 109/77/0	Bilateral CI after age 4 (left ear)

PTA: Pure-tone average, AC: Air conduction, BC: Bone conduction, SDS: Speech discrimination score, ABR: Auditory brainstem response, HIC: Health Implementation Communiqué, SNHL: Sensorineural hearing loss, ISSNHL: Idiopathic sudden SNHL, CI: Cochlear implantation, M: Male, F: Female, R: Right, L: Left, AOM: Acute otitis media

The median duration of auditory deprivation among all patients was 60 months (IQR: 18-120). CI was performed in 15 patients in the right ear, 10 patients in the left ear, and two patients underwent simultaneous bilateral implantation. Intraoperative NRT was successfully obtained from all electrodes in 23 patients, whereas in one patient no response was recorded from any electrode (0/22; case 6). Intraoperative NRT responses and postoperative audiological outcomes are summarized in Table 2.

Preoperative mean 4PTA-air conduction in the ear selected for CI was 105.3±12.2 dB HL, and median 4PTA-bone conduction was 73.0 dB HL (IQR: 68-77), with a preoperative median SDS of 0% (IQR: 0-8). Audiological outcomes from 22 patients, evaluated at ≥6 months post-implantation (range, 6-24 months; mean: 14 months), revealed a median 4PTA with CI alone of 35 dB HL (IQR: 28-46). Postoperative median SDS of the implanted ear was 58% (IQR: 37-70). The median difference between paired SDS values (calculated as postoperative minus preoperative) was 50% ($p<0.001$, Wilcoxon signed-rank test). Overall, the cohort demonstrated substantial benefit from CI, although a subgroup exhibited limited outcomes. At present, there is no universally accepted definition of poor CI performance. In our study, poor performance was defined as a 12 month postoperative SDS in quiet of <30%, in accordance with Carlson (16). Overall, 14.8% of patients in our cohort—three pediatric cases (17, 21 and 25) and one adult case (6)—demonstrated suboptimal CI outcomes.

The adult case (case 6), a 30-year-old female with a history of microvascular decompression for trigeminal neuralgia, was diagnosed with SSD. Despite radiological evidence of nerve integrity and a positive promontory stimulation test (PST) preoperatively, postoperative assessments revealed no benefit, and the device was explanted 6 months after implantation. Two pediatric cases involved SSD with long durations of auditory deprivation (7 and 8 years). Although intraoperative NRT responses were present, both failed to achieve functional auditory benefit postoperatively. The third pediatric case (case 17), a 5.5-year-old male immigrant with congenital bilateral profound SNHL, had been using bilateral hearing aids for three years. Despite positive intraoperative NRT responses from all electrodes and a postoperative 4PTA of 35 dB HL at 1 year, his SDS remained 0%, with no observable listening behaviors.

Table 2. Intraoperative NRT responses and pre- and postoperative audiological outcomes

Criteria leading to exclusion from HIC reimbursement	Case	Intraoperative NRT responses	Preoperative SDS in the ear selected for CI (%)	Postoperative SDS with CI (%)	Postoperative PTA (dB HL) with CI
Single-sided deafness	Case 4	12/12	0	48	34
	Case 6	**0/22**	**0**	**0**	**94**
	Case 8	12/12	20	60	25
	Case 21	**12/12**	**0**	**0**	**77**
	Case 25	**11/12**	**0**	**28**	**67**
Bilateral CI candidates older than four years	Case 7	22/22	N/A	40	45
	Case 9	22/22	0	40	58
	Case 10	22/22	0	56	35
	Case 12	22/22	0	92	30
	Case 13	12/12	0	64	10
	Case 18	12/12	N/A	52	35
	Case 22	22/22	0	52	29
	Case 26	22/22	0	80	25
	Case 27	22/22	0	88	52
Outside the defined audiological threshold levels	Case 1	22/22	12	68	25
	Case 2	12/12	N/A	60	25
	Case 11	22/22	N/A	44	40
	Case 19	12/12	0	68	35
SDS >30% in the contralateral ear	Case 3	12/12	16	40	32
	Case 23	10/12	28	76	45
	Case 24	22/22	8	64	30
Gap between chronological and language age exceeding four years	**Case 17**	**12/12**	**0**	**0**	**35**

HIC: Health Implementation Communiqué, NRT: Neural response telemetry, PTA: Pure-tone average, CI: Cochlear implant, SDS: Speech discrimination score, N/A: SDS test was not applicable due to the patient's age, bold values indicate patients with poor performance (SDS <30%), HL: Hearing level

Discussion

Growing evidence in recent literature indicates that patients beyond conventional indications may also achieve meaningful auditory and communicative benefits from CI (6,10-16). However, in Türkiye, many candidates fall outside of the current HIC criteria, while in other regions insurance restrictions continue to limit access. By contrast, countries such as Australia, Germany, and Italy provide comprehensive reimbursement, whereas Medicaid patients in the United States remain less likely to receive bilateral implants (4,17,18). These disparities underscore the importance of considering candidacy and coverage together. The presented study therefore evaluated extended indications and discussed their clinical rationale within the framework of current regulatory criteria.

CI for patients with SSD has been performed worldwide for several years. Randomized controlled trials and multicenter studies demonstrated that CI in patients with SSD significantly improves speech perception in noise, sound localization, and speech intelligibility (10,11,19). In our cohort, five patients underwent CI for SSD, comprising three adults and two children (aged 8 and 12 years). Notably, three of the four cases without functional auditory benefit belonged to this subgroup. In case 6, prior surgical trauma to the cochlear nerve likely contributed to poor outcomes. Successful CI requires sufficient cochlear nerve health, and anatomical integrity alone does not guarantee effective stimulation (20). Moreover, the utility of PST remains controversial, as positive responses do not ensure good CI performance, while negative responses do not necessarily exclude benefit (21). Of the adult patients, the other two presented with post-lingual SSD secondary to ISSNHL, and both achieved excellent postoperative outcomes. In accordance with current recommendations, these patients initially underwent standard treatment for ISSNHL, and CI was performed only after a minimum three-month waiting period following salvage therapy (19).

Duration of deafness is a strong predictor of CI outcomes in bilateral deafness, with early intervention linked to better results. In SSD, some studies report benefits even after long SSD durations, while others—especially in congenital SSD—show limited improvement (22,23). The metaanalysis by Benchetrit et al. (24) on CI outcomes in children with SSD showed that most children (79.6%) experienced improved speech perception in noise after CI, whereas 16.7% showed no improvement, attributed to prolonged durations of deafness (>4-7 years). In our cohort, two patients with congenital SSD likewise failed to benefit, likely due to extended auditory deprivation (7 and 8 years). The limited sample size precluded statistical analyses on the association between duration of deafness and CI outcomes. Nevertheless, these findings highlight the importance of considering auditory deprivation duration when selecting congenital SSD candidates for CI.

Bilateral CI yields superior outcomes compared with unilateral use by restoring binaural summation, squelch, and head shadow effects, thereby improving listening comfort (25). According to the current HIC, bilateral CI is reimbursed primarily for children younger than four years with bilateral severe to profound SNHL. In our cohort, 10 patients who had previously received a unilateral CI underwent contralateral implantation. Of these, seven were younger than 18 years (median age 7), while three were adults. Despite wide variability in duration of deafness (four months to 22 years), all patients achieved satisfactory outcomes in terms of 4PTA and SDS with the newly implanted ear. In the pediatric group, this may be explained by the fact that all patients used hearing aids preoperatively in their impaired ear, which may have helped mitigate the effects of deprivation. Adult patients, despite not having contralateral amplification, also achieved favorable outcomes. Although data on sound localization, speech perception in noise, and quality of life were not available—representing a limitation of this study—growing evidence increasingly supports bilateral implantation not only in young children but also in older pediatric and adult populations, demonstrating long-term auditory, cognitive, and quality of life benefits (25). Van de Heyning et al. (4) examined CI candidacy criteria across 17 countries; all centers performed bilateral CI in children, and fourteen centers reported performing bilateral implantation in adults. Expanding candidacy criteria for bilateral implantation beyond current HIC restrictions would better align national policy with international recommendations.

Current HIC regulations define strict audiological thresholds for CI, primarily based on PTA and SDS. In clinical practice, however, borderline cases are frequently encountered that do not fully meet these numerical limits yet clearly exhibit functional hearing disability. For instance, one patient fulfilled the PTA criteria but demonstrated marked interaural asymmetry in SDS (36% vs. 76%). In another case, a two-year-old child presented with profound SNHL in one ear (L: 100 dB, ABR wave V–) and severe loss in the contralateral ear (R: 70 dB, ABR wave V+), technically outside the defined thresholds. In our cohort, CI was performed in five patients whose audiological thresholds were outside the previously defined HIC criteria and in four patients with SDS greater than 30%. All of these patients demonstrated clinically meaningful improvements in CI performance.

Candidacy has gradually expanded to include patients with greater residual acoustic hearing and higher aided speech recognition scores. However, recent data from the United States indicate that excessively stringent insurance and medicare requirements often delay implantation until binaural sentence scores deteriorate, resulting in

unnecessarily prolonged auditory deprivation in the poorer ear and worse postoperative outcomes (14). Zwolan et al. (26) conducted an analysis using audiometric data to predict adult CI candidacy, and the 60/60 guideline—defined as a PTA of ≥60 dB HL in the better ear and an unaided monosyllabic word score of ≤60%—yielded a sensitivity of 96%. In countries using monosyllabic scores in quiet (e.g., Austria, Belgium, Canada, Germany, Japan), candidacy thresholds for CI are typically set at ≤50%, while India and Switzerland apply ≤40% (4). In Türkiye, HIC criteria are more restrictive, requiring ≤30% SDS. Collectively, these findings underscore the need to revise candidacy and coverage criteria to prevent avoidable delays in implantation (14).

We also included an exceptional subgroup of patients outside the HIC language age criterion. Although technically outside the reimbursement criteria, borderline cases exist, for example, when the gap slightly exceeds four years (e.g., 4.5 years) or language age is just below the threshold (e.g., 3 years 9 months). Consistent with clinical evidence, CI may be justified when auditory verbal potential and rehabilitation progress are evident. This individualized approach, balancing neurodevelopmental potential and prognosis, reflects the ethical principle of maximizing benefit while minimizing unnecessary intervention. Literature supports this view, showing that carefully selected borderline candidates may achieve favorable outcomes when auditory verbal indicators are present, whereas results remain poor in cases of profound and prolonged deprivation (14,27). However, among the three patients in this subgroup, one did not benefit from CI. This patient, a 5.5-year-old immigrant with an expressive language age of one year, was unable to receive postoperative audiological rehabilitation in his native language, which may have contributed to the lack of benefit. In summary, we advocate flexible, evidence-based interpretation of candidacy criteria, particularly in borderline cases, to ensure timely auditory access and prevent further deprivation.

According to the HIC the lower age limit for CI is 12 months. Although our cohort did not include patients implanted before 12 months of age, several studies in literature have reported favorable outcomes in these expanding indication groups (28). CI has also been explored as a therapeutic option for severe, treatment-resistant tinnitus through mechanisms of auditory stimulation and cortical reorganization (13). These emerging indications, although not yet standard within the current HIC framework, merit consideration in future policy and clinical decision-making. Further national data and prospective evaluations are warranted before these indications can be integrated into routine clinical practice. The results of this study support the need to revise the current HIC criteria. Since these patients did not meet the existing criteria, CI would not have been possible without individual assessment and referral through SABAI. However, due to the small sample size and the heterogeneity of indication subgroups, these findings cannot be generalized. Nevertheless, we believe that each clinic should report its own outcomes and publish case experiences to strengthen the broader evidence base.

Study Limitations

This study has several limitations that should be acknowledged. First, its retrospective design and relatively small sample size may restrict the generalizability of the findings. Second, audiological outcomes were assessed at a minimum of six months, which may not fully capture long term performance trajectories. Third, heterogeneity in patient etiologies, age at implantation, and duration of auditory deprivation introduces variability that could influence outcomes. Finally, the absence of a control group meeting standard HIC criteria limit direct comparison between conventional and extended indications. Future prospective, multicenter studies with larger cohorts and longer follow-up are warranted to validate and expand upon these results.

Conclusion

CI is evolving beyond the conventional boundaries defined by the HIC of the SSI. While current criteria provide a framework for access and standardization, they do not fully reflect the diversity of clinical scenarios. Our findings show that patients outside reimbursement indications such as those with SSD, residual hearing, borderline cases, or bilateral implantation in selected adults may still achieve meaningful auditory benefits. Decisions regarding extended indications should be guided by individualized assessment, multidisciplinary consensus, and scientific evidence. Expanding candidacy and revising reimbursement criteria will support more inclusive rehabilitation. Accordingly, further prospective multicenter studies focusing on extended indications are needed to strengthen this approach.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Ankara Etlik City Hospital Scientific Research Ethics Committee local committee (approval no: AEŞH-BADEK-2025-0269, date: 30.04.2025).

Informed Consent: Written informed consent was obtained from adult participants and from the legal guardians of pediatric patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.M.G., S.A.T., İ.A., S.E., D.S., M.M., M.D., Concept: M.M.G., S.A.T., İ.A., S.E., D.S., M.M., M.D., Design: M.M.G., S.A.T., İ.A., S.E., D.S., M.M.,

M.D., Data Collection and/or Processing: M.M.G., S.E., D.S., Analysis or Interpretation: M.M.G., S.A.T., İ.A., Literature Search: M.M.G., M.M., M.D., Writing: M.M.G.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Main Points

- Cochlear implantation beyond conventional reimbursement limits provided substantial functional benefits in most patients.
- Extended indications included single-sided deafness (SSD), borderline audiological thresholds, bilateral cochlear implant (CI) age restrictions, and language-age discrepancies.
- Postoperative outcomes showed significant improvement: mean pure-tone averages 38.2 dB hearing level and median speech discrimination scores (SDS) 54% ($p<0.001$). Poor performance (SDS <30%) occurred in 14.8% of cases, mainly linked to congenital SSD and prolonged auditory deprivation.
- Individualized, evidence-based, multidisciplinary evaluation supports broader CI candidacy, aligning national practice with global trends in personalized auditory care.
- Findings demonstrate the importance of revising reimbursement coverage, as rigid limits fail to reflect clinical realities or contemporary evidence.

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Original Investigation

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Role of Nasal Nitric Oxide in the Diagnosis of Epithelial Remodeling Types of Nasal Polyps

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Abstract

Objective: The aim of this study is to investigate the clinical application value of exhaled nasal nitric oxide (nNO) in the pathological diagnosis and classification of epithelial remodeling in nasal polyps (NP).

Methods: The differences between the nNO levels in patients with NP exhibiting different types of epithelial remodeling and the correlations between nNO and clinical data were retrospectively analyzed. The diagnostic value of nNO in NP was evaluated using receiver operating characteristic curves.

Results: The levels of nNO in the control group were found to be significantly higher than those in the epithelial hyperplasia, goblet cell hyperplasia, and squamous metaplasia groups (p=0.001, p=0.001, p=0.02). Furthermore, the levels were found to be significantly higher in the squamous metaplasia group than those in the epithelial hyperplasia and goblet cell hyperplasia groups (p=0.025, p=0.018). The percentage and count of eosinophils in peripheral blood in the goblet cell hyperplasia group were significantly higher than in the control group (p=0.001). nNO levels were negatively correlated with the ethmoid-to-maxillary computed tomography score ratio (E/M ratio) and Lund-Mackay score (L-M score) in the epithelial hyperplasia group and the goblet cell hyperplasia group (r=-0.518, p<0.05; r=-0.640, p<0.01; r=-0.421, p<0.01; r=-0.599, p<0.001, respectively). Similarly, a negative correlation was identified between nNO levels and the L-M score in the squamous metaplasia group (r=-0.612, p<0.01). nNO levels exhibited moderate diagnostic value in differentiating non-chronic sinusitis patients from epithelial hyperplasia, goblet cell hyperplasia, and squamous metaplasia [area under the curve (AUC) =0.898, p<0.001; AUC=0.882, p<0.001; AUC=0.720, p=0.025, respectively].

Conclusion: nNO has been shown to have significant clinical value in the preliminary pathological diagnosis and prediction of NP lesions with nasal epithelial hyperplasia, goblet cell hyperplasia, and squamous metaplasia.

Keywords: Nasal polyps, sinusitis, nitric oxide, cell differentiation, metaplasia, goblet cells, receiver operating characteristic curve

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Introduction

Chronic sinusitis (CRS) is a common chronic inflammatory disease of the nasal cavity and paranasal sinuses, caused by the interaction of multiple factors, including environmental and host-related factors (1). Nasal polyps (NP) are a type of CRS characterized by inflammation and benign hyperplasia of the mucosa of the nasal cavity and nasal sinuses (2). The respiratory mucosa of the nasal cavity and sinuses is covered by pseudostratified ciliated columnar epithelium, while the anterior nasal cavity is covered by squamous epithelium (3). The airway epithelial barrier, composed of a mucous layer overlying the ciliated epithelium, is important in heating and humidifying the air and maintaining the host's innate immune defense (3). The epithelial tissue in type 2 immune-mediated inflammatory states has been found to exhibit barrier dysfunction, characterized by decreased epithelial cell diversity due to abnormal differentiation of basal cells (4). Therefore, environmental and intrinsic signals enable epithelial basal progenitor cells to proliferate and differentiate into ciliated and goblet cells or undergo squamous metaplasia, thereby rapidly changing the composition and function of the epithelium, which may play an important role in the pathogenesis of CRS (5).

Nitric oxide (NO) is a colorless, odorless gas found in the human body in a variety of cells, including epithelial cells, nerve cells, endothelial cells, and inflammatory cells. Inducible NO synthase (iNOS) produces NO from L-arginine and is mainly expressed in respiratory epithelial cells and immune cells involved in respiratory inflammation. Proinflammatory factors can induce NO production by iNOS. Therefore, NO is an important marker of respiratory inflammation (6). In the upper respiratory tract, nasal NO (nNO) is produced mainly by the mucous membranes of the nasal passages and the sinuses (7). Our team's previous study found that epithelial remodeling in NP predominantly presents as three types: epithelial hyperplasia, goblet cell hyperplasia, and squamous metaplasia (6). Therefore, exploring the differences in nNO levels among different types of epithelial tissue remodeling has important clinical value for predicting epithelial remodeling types and improving the accuracy of CRS diagnosis.

Methods

Patients

CRS patients with NP (CRSwNP) (n=85) who underwent endoscopic nasal surgery were identified in the The Second Qilu Hospital of Shandong University from January 2024 to March 2025. Subjects (n=28) with symptomatic nasal septal deviation requiring septoplasty surgery served as controls. None of the controls had chronic rhinosinusitis with or without NP at computed tomography (CT) examination. CRSwNP diagnosis was made based on history taking, physical examination, nasal endoscopic examination, and CT findings of the sinuses according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (1). The inclusion criteria of the control group were no smoking history, no history of CRS, allergic rhinitis (AR), or asthma; no abnormal nasal secretions, polyps, or other masses, normal blood routine, normal serum immunoglobulin E (IgE) level, and normal lung function. Exclusion criteria: under 18 years of age, presence of cystic fibrosis, ciliary immobility syndrome, aspirin intolerance triad, immunodeficiency disease, severe systemic disease, respiratory infection in the last month, menstruation, or pregnancy. Ethical approval was obtained from the Ethics Committee of the Second Hospital of Shandong University (approval number: KYLL-2018(KJ)P-0025, date: 26.02.2018). The written consent from all subjects was obtained.

Clinical Data

The diagnosis of AR is determined by the Allergic Rhinitis and Its Impact on Asthma and European Academy of Allergy and Clinical Immunology guidelines (clinical symptoms, such as nasal obstruction, rhinorrhea, sneezing, and nasal itching; and objective evidence of allergic sensitization, including serum allergen-specific IgE) (8). The diagnosis of asthma is made according to the results of the pulmonary function relaxation test or by a respiratory doctor. The percentage of eosinophils in peripheral blood and the count of eosinophils were detected using the XN9000 RapidBio blood analyzer. The CT scans were scored according to the Lund-Mackay score system, and the ratio of the total score of both ethmoid sinuses to the total score of the maxillary sinuses (E/M ratio) was calculated (9,10).

The nNO Test

The nNO test was sampled, analyzed, and automatically generated using the breath analyzer Sunvou-CA2122 (Sunvou Medical Electronics, Wuxi, China). After 30 minutes of rest, the patient was placed in a seated position, and the relatively unobstructed nostril was closed with a nasal plug, while the other nostril was kept unobstructed. Then a whistle was placed in the patient's mouth, and the patient was asked to continuously blow after a deep inhalation without breath-holding. The air pump of the instrument was used to aspirate air from the nostril at a constant flow rate of 10 mL/s. The NO gas produced in the nasal cavity and sinuses was collected from the nasal cavity by this airflow. Whistling was used to ensure velum closure and prevent contamination from the lower respiratory tract during nasal sampling. After sampling was completed, the instrument analyzed the sample and automatically generated the results.

Tissue Samples

NP tissue samples were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin for histological analysis. The epithelial cell hyperplasia, goblet cell hyperplasia and squamous metaplasia of NP tissue were evaluated under optical microscope according to the results of hematoxylin and eosin staining. It was defined as normal epithelium or no epithelial hyperplasia when the epithelial surface of NP tissue had no obvious hyperplasia, or the number of epithelial layers was ≤4 (Figure 1). It was defined as epithelial hyperplasia when the epithelial surface of NP tissue was ≥4 (Figure 2). Goblet cell hyperplasia was defined when the number of goblet cell layers on the epithelial surface was ≥2 (Figure 3). Squamous metaplasia was defined when the normal pseudostratified ciliated columnar epithelium disappeared and the ciliated cells and goblet cells on the epithelial surface were completely replaced by squamous cells (Figure 4) (11).

Statistical Analysis

SPSS version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Mean ± standard deviation was used for the descriptive statistics of continuous variables. The independent samples t-test and χ^2 test were used to evaluate differences between groups for variables conforming to a normal distribution, and the Mann-Whitney U test was used for variables not conforming to a normal distribution. Spearman's correlation coefficient was used to analyze the correlation between nNO and clinical data. The predictive value of nNO for CRS was analyzed using the receiver

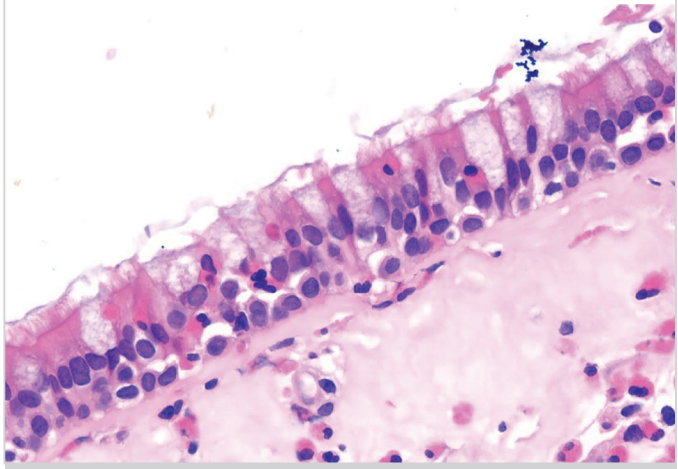

Figure 1. Type of epithelium: normal epithelium (H&E staining ×400)
H&E: Hematoxylin and eosin

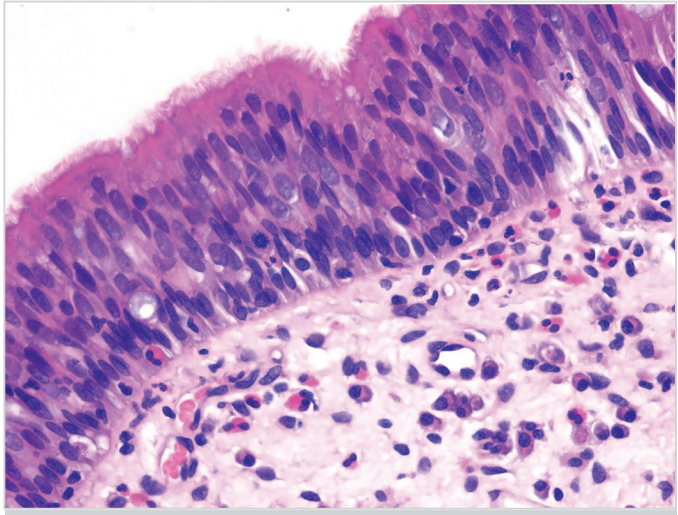

Figure 2. Type of epithelium: epithelial hyperplasia (H&E staining x400)
H&E: Hematoxylin and eosin

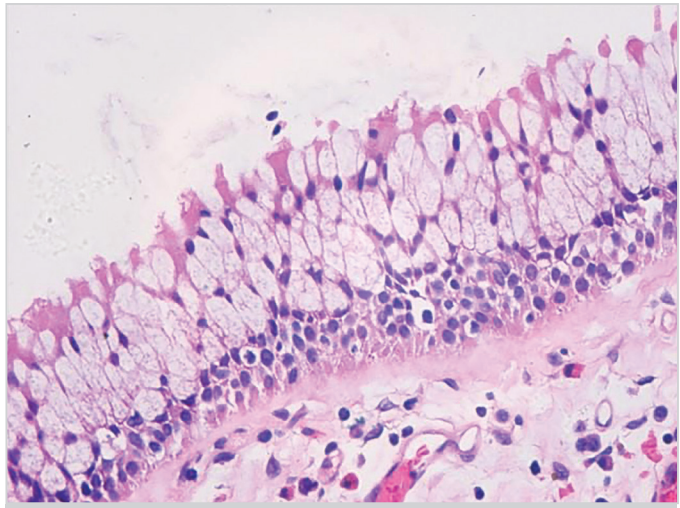

Figure 3. Type of epithelium: goblet cell hyperplasia (H&E staining ×400)
H&E: Hematoxylin and eosin

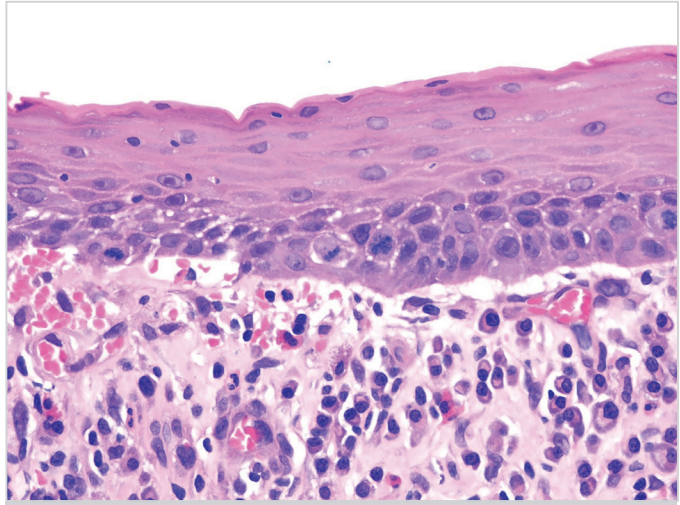

Figure 4. Type of epithelium: squamous metaplasia (H&E staining ×400)
H&E: Hematoxylin and eosin

operating characteristic (ROC) curve. A p-value of <0.05 was considered to indicate statistical significance.

Results

Comparison of Clinical Data

Of the 85 CRSwNP patients, 25 had epithelial hyperplasia, 47 had goblet cell hyperplasia, and 13 had squamous metaplasia based on histological analysis. There was no significant difference in gender among the various groups of patients. The mean age of the epithelial hyperplasia group was significantly higher than that of the control group (p=0.01). The percentage and absolute count of peripheral blood eosinophils in the goblet cell hyperplasia group were significantly higher than those of the control group (p=0.01). In contrast, the nNO level was significantly higher in the control group compared to the epithelial cell hyperplasia, goblet cell hyperplasia, and squamous metaplasia groups (p=0.001, p=0.001, p=0.02). There were no significant differences in terms of gender, smoking history, or body mass index (p>0.05) (Table 1).

nNO Levels in the Group of Epithelial Remodeling Types

The mean nNO levels in the squamous metaplasia group were significantly higher than those in both the epithelial hyperplasia and goblet cell hyperplasia groups (p=0.025, p=0.018). However, there were no significant differences in nNO levels between the epithelial hyperplasia and goblet cell hyperplasia groups (p=0.78) (Figure 5).

Correlations Between nNO Levels and Clinical Data

In the epithelial hyperplasia and goblet cell hyperplasia groups, nNO levels were negatively correlated with both the E/M ratio and the Lund-Mackay score (epithelial hyperplasia: r=-0.518, p<0.05; r=-0.640, p<0.01; goblet cell hyperplasia: r=-0.421, p<0.01; r=-0.599, p<0.001, respectively). In the squamous metaplasia group, nNO levels were negatively correlated with the Lund-Mackay score (r=-0.612, p<0.01), but showed no significant correlation with the E/M ratio (p>0.05). No significant correlations were found between nNO levels and age, body mass index, peripheral blood eosinophil percentage, or eosinophil count in any of the groups (control, epithelial hyperplasia, goblet cell hyperplasia, and squamous metaplasia) (p>0.05) (Table 2).

ROC Curve Analysis

ROC curve analysis demonstrated that nNO had moderate diagnostic performance in distinguishing non-CRS subjects from those with epithelial hyperplasia, goblet cell hyperplasia, or squamous metaplasia [area under the curve (AUC) =0.898, p<0.001; AUC=0.882, p<0.001; and AUC=0.720, p=0.025, respectively] (Figure 6).

Discussion

With the lucubration of the research on the pathogenesis of CRS, more and more attention has been paid to the role of epithelial barrier damage and epithelial tissue remodeling in the pathogenesis of CRS. Tissue remodeling is an abnormal manifestation of tissue injury and has been extensively

Table 1. Comparison of clinical characteristics among the study groups

	Control	Epithelial hyperplasia	Goblet cell hyperplasia	Squamous metaplasia	p-value	p-value	p-value
	(n=28); 1	(n=25); 2	(n=47); 3	(n=13); 4	(1 vs. 2)	(1 vs. 3)	(1 vs. 4)
Male/female	20/8	18/7	34/13	7/6	0.96	0.93	0.27
Smoking, n (%)	7 (25)	9 (36)	14 (29.8)	5 (38.5)	0.38	0.66	0.38
Allergic, n (%)	—	4 (16)	13 (27.7)	5 (38.5)	—	—	—
Asthma, n (%)	—	3 (12)	10 (21.3)	1 (7.7)	—	—	—
Recurrence, n (%)	—	5 (20)	8 (17.0)	1 (7.7)	—	—	—
eCRSwNP, n (%)	—	12 (48)	37 (78.7)	9 (69.2)	—	—	—
Age, years	41.39±13.85	51.48±11.53	46.91±11.02	42.38±13.41	0.01	0.08	0.88
BMI (kg/m^2)	25.08±4.12	25.62±4.00	26.35±2.85	25.22±3.64	0.54	0.23	0.95
EOS percentage, %	2.86±2.84	4.00±3.34	5.10±3.59	4.33±3.99	0.14	0.01	0.60
EOS count (x10^{-9}•L^{-1})	0.17±0.14	0.24±0.19	0.33±0.22	0.28±0.26	0.15	0.00	0.52
E/M ratio	—	1.52±0.92	2.33±1.08	1.42±1.24	—	—	—
Lund-Mackay score	—	13.78±8.12	15.89±5.64	13.23±6.80	—	—	—
nNO (ppb)	428.7±121.2	214.5±114.1	222.0±127.9	331.4±151.8	0.00	0.00	0.02

eCRSwNP: Eosinophilic chronic rhinosinusitis with nasal polyps, BMI: Body mass index, EOS: Blood eosinophil, E/M ratio: Ratio of the computed tomography scores for the ethmoid sinus and maxillary sinus, nNO: Nasal nitric oxide, ppb: Part per billion

studied in lower respiratory diseases, as well as in CRS. Tissue eosinophilia and eosinophilia activation were found to be significantly correlated with CRS remodeling features, associated mucosal injury, and clinical symptoms (12).

In recent years, people have come to realize that NO is not only an environmental pollutant but also a biological medium, playing a significant role in regulating physiological processes such as vascular dilation and cardiovascular systems in both animals and humans (13). As a pro-inflammatory medium NO increases susceptibility to airway hyperreactivity in humans and plays a very complex role in the pathophysiology of airway response (14). At present, FeNO has been widely used in clinical diagnosis and efficacy evaluation, and monitoring of asthma (15). nNO is produced mainly by the mucous membranes of the nasal cavity and the nasal sinuses but the relationship between its level and the mucosal epithelial status of the nasal cavity and nasal sinuses is not clear.

When we grouped the types of polyp epithelial remodeling in CRSwNP patients, we found that nNO levels in the squamous metaplasia group were significantly higher than those in the epithelial hyperplasia and goblet cell hyperplasia groups. Pasto et al. (16) found that NO played a significant role in stimulating ciliary movement in the respiratory tract, and the increase of nNO level in squamous CRSwNP patients could be related to the increased feedback of NO production due to the loss of ciliary structure. Cilia are hair-like organelles composed of microtubules. The nose and sinuses use the connecting complex between the mucociliary clearance system and the epithelial cells as their first line of defense against the environment (17). Li et al. (18) found that cilia structure and function were abnormal in patients with CRSwNP. The injury of motor cilia was accompanied by epithelial hyperplasia and other epithelial cell changes, which may be the cause of chronic mucosal inflammation or infection in patients with CRS (18). Ma et al. (19) reported that compared with the control group, the expression of ciliogenic protein in the sinus epithelium of CRS patients with ciliated deletion was significantly reduced. Overall, epithelial barrier remodeling caused by ciliary dysfunction in CRSwNP patients can cause changes in nNO levels. We can preliminarily determine the remodeling type of epithelial tissue and ciliary changes of CRSwNP by nNO.

ROC curve analysis showed that nNO had moderate predictive value in differentiating non-CRS from epithelial

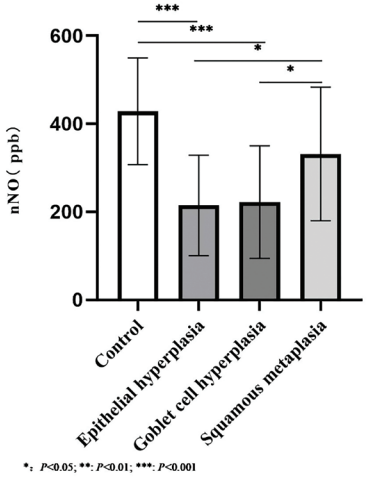

Figure 5. Comparison of nNO among epithelial remodeling groups
nNO: Nasal nitric oxide, ppb: Part per billion

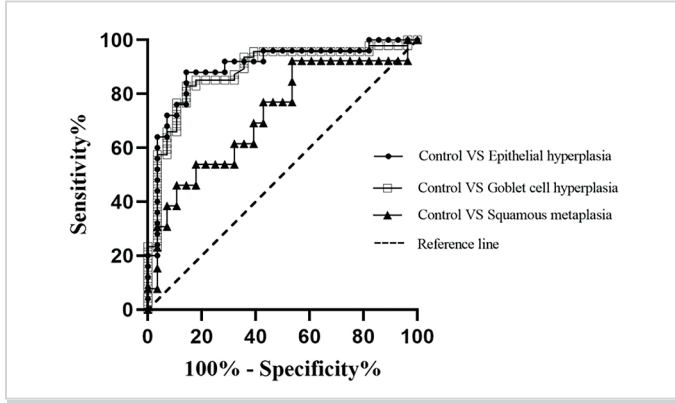

Figure 6. ROC curve of nNO for the diagnosis of epithelial hyperplasia, goblet cell hyperplasia, and squamous metaplasia
ROC: Receiver operating characteristic, nNO: Nasal nitric oxide

Table 2. Correlation of nNO with clinical data in epithelial type group

	Control	Epithelial hyperplasia	Goblet cell hyperplasia	Squamous metaplasia
	r	r	r	r
Age	0.304	-0.127	-0.171	-0.0469
BMI (kg/m^2)	0.170	0.171	-0.177	-0.555
EOS percentage, %	-0.136	0.278	-0.185	0.277
EOS count (x10^{-9}•L^{-1})	-0.157	0.296	-0.161	0.197
E/M ratio	—	-0.518*	-0.421**	-0.344
Lund-Mackay score	—	-0.640**	-0.599***	-0.612*

*: p<0.05, **: p<0.01, ***: p<0.001, BMI: Body mass index, EOS percentage: Blood eosinophil percentage, EOS count: Blood eosinophil count, E/M ratio: Ratio of the computed tomography scores for the ethmoid sinus and maxillary sinus

hyperplasia, goblet cell hyperplasia, and squamous cell metaplasia. Therefore, nNO has certain clinical application value in predicting the epithelial remodeling type of NP. CRS is a heterogeneous disease with multiple inflammatory mechanisms involved and inflammatory progression. The specific histopathological differentiation between CRSwNP and CRSsNP patients is still difficult to clearly identify (20). The histopathological features of CRSwNP are related to the severity of the prognosis, and we need to further explore the relationship between histopathological features of CRSwNP and disease progression.

In recent years, the remodeling of the epithelial barrier has aroused great interest among researchers. The occurrence of tissue remodeling is caused by the joint action of inflammation and related cytokines, regulatory factors, enzymes and other factors, which in turn determine the type of tissue remodeling (21). Studies have attempted to correlate cytokines and other tissue markers with tissue remodeling changes, such as periosteal protein, transforming growth factor-β, and interleukin-13, with basement membrane thickening and fibrosis (22). We can preliminarily predict the type of epithelial tissue remodeling of CRSwNP through the study of nNO, which is of great value for the clinical diagnosis and treatment of CRSwNP. We found that epithelial changes play an increasingly crucial role in the pathogenesis of CRSwNP with the in-depth study of the mechanisms related to epithelial tissue remodeling. However, the related mechanism remains to be further studied.

Study Limitations

Due to the relatively small sample size, the exact reference value of nNO for the accurate diagnosis of CRSwNP needs to be further studied, and our conclusion also needs to be expanded for further verification and in-depth study. It will be necessary in the future to further increase the sample size to eliminate the influence of factors such as age. We did not conduct the nasal patency test, which might have affected the relevant results.

Conclusion

In conclusion, the nNO test has become simple and can be used as a biological marker in the evaluation of nasal inflammatory diseases with the advancement of technology and the implementation of standardization work. As a quantitative, non-invasive, convenient and safe tool, the nNO test has certain clinical application value in predicting the type of epithelial remodeling of NP.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of the Second Hospital of Shandong University (approval number: KYLL-2018(KJ) P-0025, date: 26.02.2018).

Informed Consent: The written consent from all subjects was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.J., L.Z., X.Z., K.Y., L.S., Concept: L.S., Design: X.L., L.S., Data Collection and/or Processing: X.L., H.Z., Analysis or Interpretation: X.L., H.Z., Literature Search: X.L., H.Z., L.S., Writing: X.L., L.S.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Main Points

- The nasal nitric oxide (nNO) levels in control group was significantly higher than that of epithelial hyperplasia, goblet cell hyperplasia and squamous metaplasia groups ($p<0.05$), and squamous metaplasia group was significantly higher than that in epithelial hyperplasia group and goblet cell hyperplasia group ($p<0.05$).
- The percentage and count of eosinophilia in peripheral blood of goblet cell hyperplasia group was significantly higher than that of control group ($p<0.05$).
- The nNO levels was negatively correlated with E/M ratio and Lund-Mackay score in epithelial hyperplasia group and goblet cell hyperplasia group ($r=-0.518$, $p<0.05$; $r=-0.640$, $p<0.01$; $r=-0.421$, $p<0.01$; $r=-0.599$, $p<0.001$), and nNO levels in squamous cell metaplasia group was negatively correlated with Lund-Mackay score ($r=-0.612$, $p<0.01$).
- The nNO levels was moderately valuable in differentiating non-chronic sinusitis from epithelial hyperplasia, goblet cell hyperplasia, and squamous cell metaplasia [area under the curve (AUC) =0.898, $p<0.001$; AUC=0.882, $p<0.001$; AUC=0.720, $p=0.025$].

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Original Investigation

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Long-Term Postoperative Swallowing Findings After Carbon Dioxide Laser Transverse Posterior Cordotomy in Bilateral Vocal Fold Paralysis: A Retrospective Cross-sectional FEES Study

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Abstract

Objective: To describe the frequency and pattern of long-term postoperative swallowing abnormalities detected by flexible endoscopic evaluation of swallowing (FEES) after carbon dioxide (CO_2) laser transverse posterior cordotomy for bilateral vocal fold paralysis (BVFP), and to relate these findings to patient-reported and functional swallowing measures.

Methods: This retrospective, single-center cross-sectional study included 17 adults with BVFP who had previously undergone CO_2 laser transverse posterior cordotomy and were evaluated at a single postoperative time point between January and June 2025. Swallowing safety and efficiency were assessed using FEES with boluses representing International Dysphagia Diet Standardisation Initiative levels 0 (thin liquid; dyed water), level 3 (moderately thick; dyed yogurt), and level 7 (regular; cracker). Airway invasion and pharyngeal residue were graded using the Penetration-Aspiration Scale and Yale Pharyngeal Residue Severity Rating Scale. Functional Oral Intake Scale (FOIS), Functional Outcome Swallowing Scale (FOSS), and Eating Assessment Tool-10 scores were also recorded.

Results: All participants were female (n=17; mean age 60.9±13.3 years) with a mean postoperative follow-up of 70.6±41.6 months. Penetration was common across consistencies; thin-liquid aspiration occurred in one patient. Vallecular and pyriform sinus residue was observed in a subset of patients. Most maintained full or near-full oral intake (FOIS 7, 76.5%) with mild functional limitation (FOSS 1-2, 94.1%).

Conclusion: This descriptive postoperative series contributes objective FEES-based long-term swallowing data after CO_2 laser transverse posterior cordotomy in BVFP. FEES frequently demonstrated penetration and pharyngeal residue despite generally preserved oral intake, but these findings should not be interpreted as a treatment effect because baseline swallowing data were unavailable.

Keywords: Vocal cord paralysis, lasers, deglutition disorders, endoscopy, laryngoscopy

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Introduction

Bilateral vocal fold paralysis (BVFP) is primarily managed as an airway disorder, and carbon dioxide (CO_2) laser transverse posterior cordotomy (TPC) is an established posterior glottic-widening procedure that improves airway patency while preserving acceptable voice quality (1-3). Accordingly, most studies on TPC have focused on respiratory outcomes, decannulation rates, revision surgery, and voice-related outcomes rather than on detailed instrumental findings of swallowing (4-7).

Swallowing deserves separate evaluation in this population because posterior glottic widening may affect laryngeal closure, and BVFP may coexist with impaired laryngopharyngeal sensation secondary to recurrent laryngeal or vagal nerve injury (8,9). Patient-reported symptoms and oral intake may remain satisfactory even when flexible endoscopic evaluation of swallowing (FEES) demonstrates penetration, aspiration, or pharyngeal residue, particularly when abnormalities are mild, compensated, or associated with reduced sensory response (9,10). Therefore, patients may appear functionally stable despite objective swallowing abnormalities.

Several studies have evaluated swallowing, quality of life, and overall outcomes after posterior cordotomy; however, swallowing assessment has generally relied on patient-reported measures, chart review, or functional scales rather than a standardized FEES-based protocol for assessing airway invasion and pharyngeal residue (4-7,10). To our knowledge, no previous study has specifically characterized long-term postoperative swallowing findings after CO_2 laser TPC in patients with BVFP using FEES together with the Penetration-Aspiration Scale (PAS) and Yale Pharyngeal Residue Severity Rating Scale (YPRSRS) across standardized International Dysphagia Diet Standardisation Initiative (IDDSI) consistencies. Accordingly, the present study was designed to address this gap.

Accordingly, the aim of this study was to characterize long-term postoperative swallowing findings in patients with BVFP following CO_2 laser TPC. Specifically, we sought to determine the frequency and pattern of penetration, aspiration, and vallecular or pyriform sinus residue and to relate these objective FEES findings to Eating Assessment Tool-10 (EAT-10), Functional Oral Intake Scale (FOIS), and Functional Outcome Swallowing Scale (FOSS) scores. These findings may help clinicians better understand the spectrum of FEES findings encountered in this postoperative population and provide a basis for future prospective perioperative studies.

Methods

This retrospective cross-sectional study evaluated postoperative swallowing at routine follow-up visits between January and June 2025 in patients who had previously undergone CO_2 laser TPC for BVFP at a tertiary academic center. The study protocol was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University (approval no: 2024/481, date: 14.11.2024). Written informed consent was obtained from all patients.

All patients had undergone unilateral CO_2 laser TPC according to the technique described by Dennis and Kashima (3). Under microlaryngoscopy, the posterior portion of one true vocal fold and approximately 3-4 mm of the adjacent false vocal fold were excised with the CO_2 laser. At follow-up, all patients had tracheostomy-independent respiration and exercise tolerance sufficient for daily activities.

The interval between cordotomy and FEES (mean postoperative follow-up duration) was 70.6±41.6 months.

Seventeen patients met the inclusion criteria: prior laser cordotomy for BVFP, absence of head and neck cancer, and ability to complete study procedures. Patients were excluded if they were <18 years old, pregnant, had undergone laryngeal surgery other than the index CO_2 laser TPC before the FEES assessment, had received head and neck radiotherapy, had structural abnormalities of the oropharynx or larynx, or had swallowing impairment related to neurological disease.

FEES was performed in the outpatient setting by a single examiner (first author) using a flexible video laryngoscope (3.7 mm; Karl Storz, Tuttlingen, Germany). No topical anesthetic was used. Boluses corresponding to IDDSI level 0 (thin liquid; blue-dyed water), IDDSI level 3 (moderately thick; blue-dyed yogurt), and IDDSI level 7 (regular; cracker) were administered (11). All examinations were digitally recorded for offline scoring.

Methylene blue was added in small amounts to the water and yogurt to enhance contrast with the mucosa during FEES (12,13). The procedure was performed by the same examiner in all patients to maintain procedural consistency. The recorded videos were subsequently reviewed independently by two otolaryngologists experienced in FEES.

Swallowing safety was graded using the 8-point PAS (14). Swallowing efficiency was graded using the YPRSRS for the vallecula and pyriform sinuses (15). Functional oral intake was assessed using the FOIS and the FOSS (16,17). Subjective dysphagia was assessed using the EAT-10, which was completed by the participants without investigator assistance or interpretation (18,19).

For interpretation, PAS scores of 1 indicate no airway invasion, scores of 2-5 indicate penetration (material entering the laryngeal vestibule above the vocal folds), and scores of 6-8 indicate aspiration (material passing below the vocal folds) (14). The YPRSRS grades residue severity separately for the vallecula and pyriform sinuses, ranging from 1 (none)

to 4 (severe) (20). An EAT-10 score of ≥3 was considered indicative of clinically meaningful dysphagia symptoms (19).

Statistical Analysis

Two otolaryngologists experienced in FEES independently scored the anonymized video recordings offline and were blinded to each other's ratings and to questionnaire results. Interrater agreement was evaluated using weighted kappa statistics. Discrepant scores were resolved by consensus for descriptive reporting (21).

Descriptive statistics are reported as mean±standard deviation and median (minimum-maximum), as appropriate. Given the lack of preoperative data and a control group, results are presented primarily descriptively. Although these analyses do not directly estimate the effect of cordotomy, exploratory one-sample comparisons were performed to provide secondary clinical context. Analyses were conducted using RStudio software (22). Statistical significance was set at $p<0.05$.

Results

All results represent a single-time-point postoperative descriptive assessment. Participant characteristics are summarized in Table 1. The cohort comprised 17 females with a mean age of 60.9±13.3 years and a mean body mass index of 29.7±4.2 kg/m². Mean postoperative follow-up time was 70.6±41.6 months. BVFP etiology was thyroidectomy in 16 patients (94.1%) and idiopathic in 1 patient (5.9%). All thyroidectomy-related cases had undergone total thyroidectomy; surgical indications were thyroid neoplasia, including papillary thyroid carcinoma in 14 patients and follicular thyroid carcinoma in 2 patients. Age ranged from 24 to 83 years, postoperative follow-up ranged from 12 to 132 months, and body mass index ranged from 20.9 to 38.2 kg/m² (Table 1). In the reviewed operative and pathological records, none of the thyroid carcinoma patients had documented cervical lymph node metastasis or had undergone therapeutic lateral neck dissection or prophylactic or therapeutic central neck dissection.

Patient-reported dysphagia was generally mild (EAT-10 mean 3.24±4.21; median 3), although 9 patients (52.9%) had an EAT-10 score ≥3. Most participants reported full oral intake without restriction (FOIS 7, 76.5%), and functional swallowing limitation was mild (FOSS 1-2, 94.1%) (Table 2; Figure 1).

Penetration (PAS 2-5) occurred in eight patients (47.1%) with thin liquid, seven patients (41.2%) with moderately thick consistency, and six patients (35.3%) with regular consistency. Thin-liquid aspiration (PAS 6-8) was observed in one patient (5.9%) (Supplementary Video), whereas no aspiration was observed with moderately thick or regular consistencies. Median PAS scores were 2 for thin liquid and 1 for both moderately thick and regular consistencies (Table 2).

Pharyngeal residue was present in both the vallecula and pyriform sinuses. Residue graded as YPRSRS ≥2 occurred in the vallecula in ten patients (58.8%) with thin liquid, seven patients (41.2%) with moderately thick consistency, and seven patients (41.2%) with regular consistency. Corresponding pyriform sinus residue occurred in ten (58.8%), seven (41.2%), and five (29.4%) patients, respectively.

Median residue scores were 2 for thin liquid in both the vallecula and pyriform sinuses and 1 for both moderately thick and regular consistencies (Table 2).

The main descriptive pattern was preserved functional oral intake despite frequent penetration and pharyngeal residue detected by FEES. When dichotomized, PAS >1 occurred in 52.9% of patients for thin liquid, 41.2% for moderately thick consistency, and 35.3% for regular consistency. YPRSRS >1 was most common with thin liquid (vallecula 58.8%, pyriform

Table 1. Patient demographics and clinical features

Characteristics		Mean (±SD)	Median (min-max)
Sex (F/M)		17/0	
Age (mean±SD)		60.9 (±13.3)	62 (24-83)
BMI (kg/m²) (mean±SD)		29.7 (±4.2)	30.3 (20.9-38.2)
Etiology of the BVFP	Thyroidectomy	16	
	Idiopathic	1	
Type of thyroidectomy	Total thyroidectomy	16	
Indication for thyroidectomy	Papillary carcinoma	14	
	Follicular carcinoma	2	
Lymph node metastasis		0	
Neck dissection		0	
Postoperative follow-up time (month)		70.6 (±41.6)	72 (12-132)

SD: Standard deviation, F: Female, M: Male, BMI: Body mass index, BVFP: Bilateral vocal fold paralysis, min: Minimum, max: Maximum

52.9%). Figure 1 summarizes the distributions of EAT-10, FOIS, and FOSS scores, whereas Figure 2 summarizes the highest PAS and YPRSRS scores. Representative FEES images illustrating penetration and post-swallow vallecular and pyriform sinus residue are presented in Figures 3-5.

Interrater agreement for FEES-based scales was substantial to almost perfect across consistencies, with weighted kappa values shown in Table 3.

Table 2. Swallowing evaluation outcomes

	Reference value	Mean±SD	Median (min-max)	Test statistics*	p
EAT-10	3	3.24±4.21	3 (0-18)	95	0.193
PAS regular	1	1.53±0.87	1 (1-3)	15.0	**0.024**
PAS moderately thick	1	1.76±1.03	1 (1-4)	28.0	**0.010**
PAS thin-liquid	1	2.18±1.43	2 (1-6)	45.0	**0.004**
YPRSRS-V regular	1	1.47±0.87	1 (1-4)	15.0	**0.027**
YPRSRS-V moderately thick	1	1.76±1.15	1 (1-4)	28.0	**0.010**
YPRSRS-V thin-liquid	1	1.82±0.95	2 (1-3)	45.0	**0.004**
YPRSRS-PS regular	1	1.41±0.71	1 (1-3)	15.0	**0.027**
YPRSRS-PS moderately thick	1	1.65±0.93	1 (1-3)	28.0	**0.010**
YPRSRS-PS thin-liquid	1	1.76±0.83	2 (1-3)	45.0	**0.004**
FOSS	0	1.35± 0.61	1 (1-3)	153	**<0.001**
FOIS	7	6.76±0.44	7 (6-7)	0	**0.036**

*:Wilcoxon signed rank test. The bold prints in the p column indicate that there is a significant difference when compared with the reference values in the literature. SD: Standard deviation, min: Minimum, max: Maximum, EAT-10: Eating Assessment Tool-10, PAS: Penetration-Aspiration Scale, YPRSRS-V: The Yale Pharyngeal Residue Severity Rating Scale for Vallecula, YPRSRS-PS: The Yale Pharyngeal Residue Severity Rating Scale for Pyriform Sinus, FOSS: Functional Outcome Swallowing Scale, FOIS: Functional Oral Intake Scale

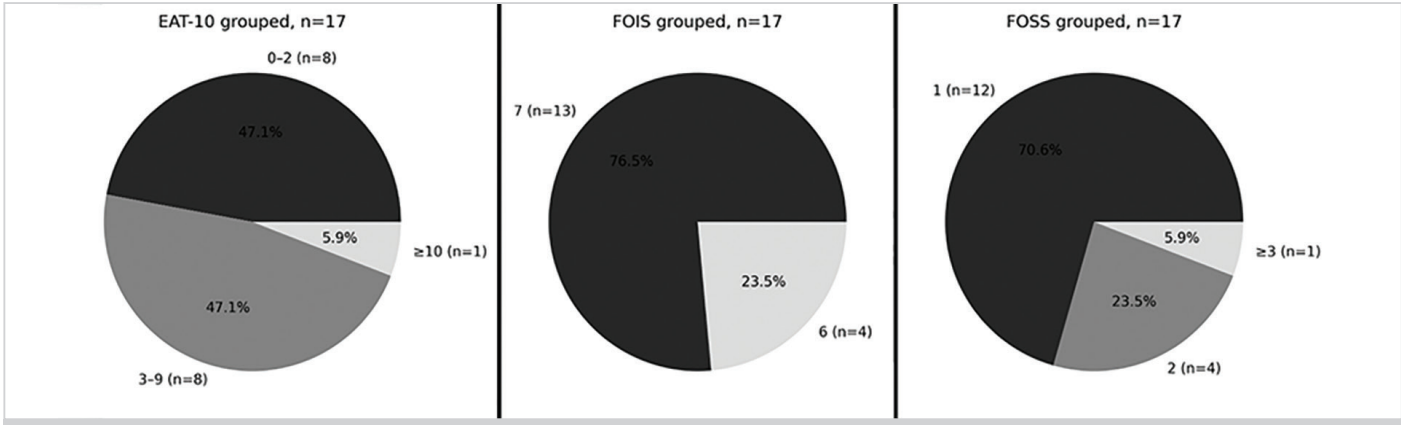

Figure 1. Distribution of EAT-10, FOIS, and FOSS grouped scores among the study cohort
EAT-10: Eating Assessment Tool-10, FOIS: Functional Oral Intake Scale, FOSS: Functional Outcome Swallowing Scale

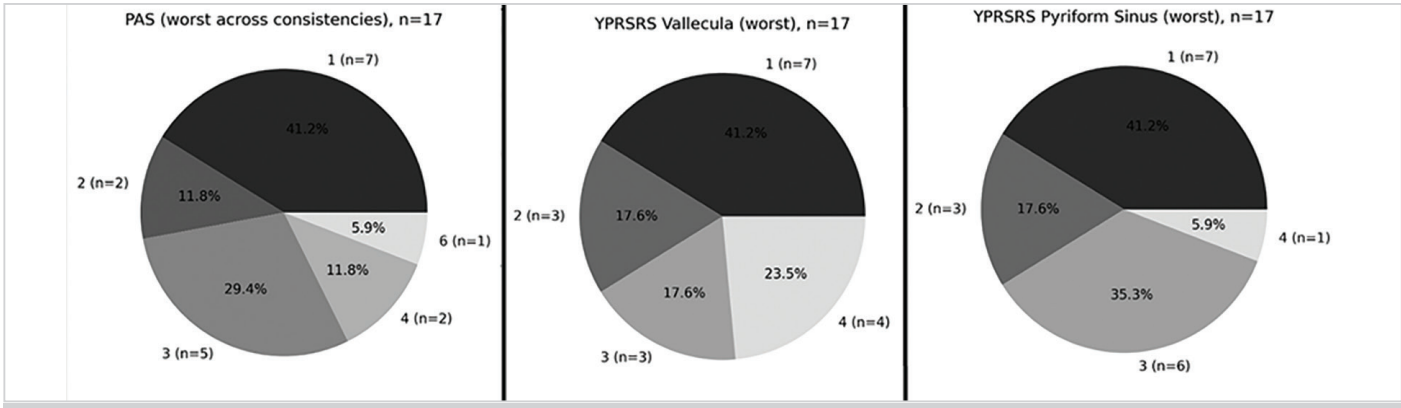

Figure 2. Distribution of worst PAS and YPRSRS scores across assessed consistencies
PAS: Penetration-Aspiration Scale, YPRSRS: Yale Pharyngeal Residue Severity Rating Scale

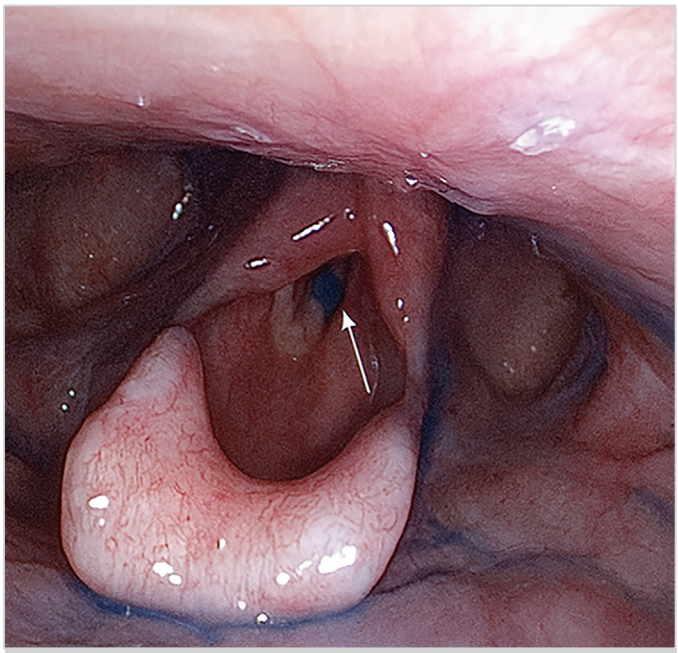

Figure 3. FEES image demonstrating penetration of blue-dyed IDDSI level 3 bolus into the laryngeal vestibule (arrow) after transverse posterior cordotomy
FEES: Flexible endoscopic evaluation of swallowing, IDDSI: International Dysphagia Diet Standardisation Initiative

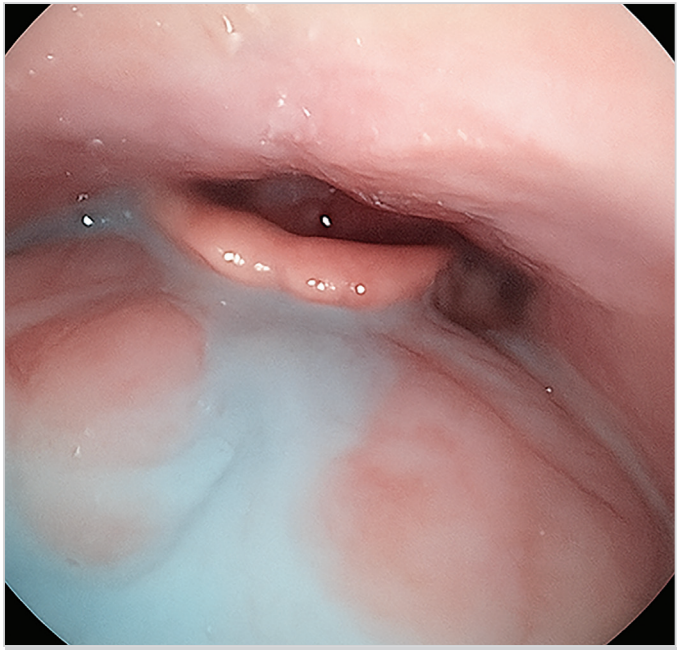

Figure 4. FEES image demonstrating post-swallow pharyngeal residue (blue-dyed bolus) in the vallecula
FEES: Flexible endoscopic evaluation of swallowing

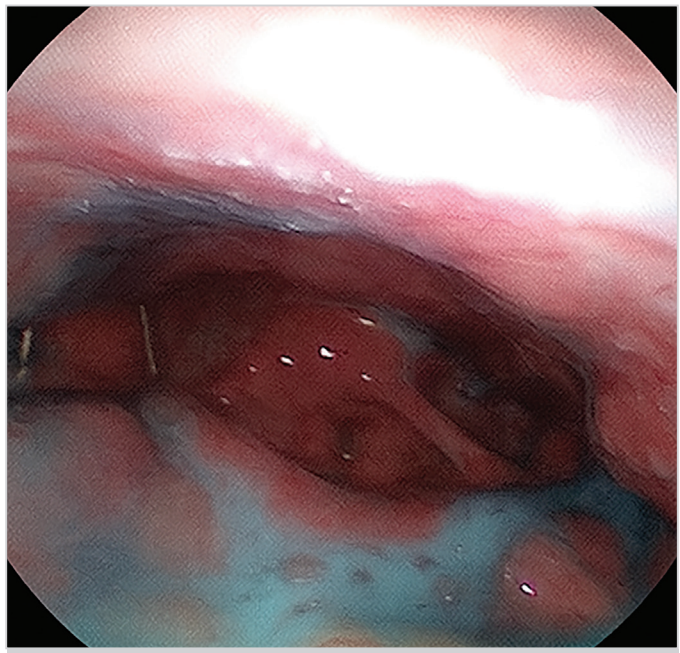

Figure 5. FEES image demonstrating post-swallow pharyngeal residue (blue-dyed bolus) in the hypopharynx/pyriform sinus region
FEES: Flexible endoscopic evaluation of swallowing

Table 3. Interrater reliability results

Parameter	Weighted Kappa
PAS regular	0.92
PAS moderately thick	0.83
PAS thin-liquid	0.86
YPRSRS-V regular	0.91
YPRSRS-V moderately thick	0.85
YPRSRS-V thin-liquid	0.79
YPRSRS-PS regular	0.89
YPRSRS-PS moderately thick	0.85
YPRSRS-PS thin-liquid	0.86

PAS: Penetration-Aspiration Scale, YPRSRS-V: The Yale Pharyngeal Residue Severity Rating Scale for Vallecula, YPRSRS-PS: The Yale Pharyngeal Residue Severity Rating Scale for Pyriform Sinus

Discussion

This study describes long-term postoperative swallowing findings after CO_2 laser TPC in BVFP using objective FEES-based measures. Most patients maintained full or near-full oral intake and had only mild functional limitation, but penetration and pharyngeal residue were frequent on FEES. This discordance suggests that patient-reported and functional measures alone may not fully capture postoperative swallowing findings. Because preoperative FEES data and a control group were unavailable, these observations should be interpreted as a descriptive postoperative profile rather than as evidence that cordotomy caused the swallowing abnormalities.

These findings should be viewed in the context of the existing TPC literature. Previous studies have mainly evaluated airway patency, decannulation or revision rates,

aerodynamic parameters, voice outcomes, or quality of life (4-7). Swallowing-specific evidence remains limited. Conklin et al. (10) examined perceived dysphagia after unilateral cordotomy and reported limited patient-reported change. In contrast, the present study adds an instrumental perspective by applying PAS and YPRSRS scoring to FEES recordings, showing that objective penetration and residue can coexist with preserved oral intake. This supports the selective use of instrumental swallowing assessment in postoperative BVFP patients, especially when symptoms or risk factors are present.

The possible pathomechanism of penetration in these patients is multifactorial. A persistent posterior glottic gap may reduce complete glottic closure during swallowing, while underlying recurrent laryngeal or vagal nerve injury may also impair laryngopharyngeal sensation and the cough response. Thin liquids may enter the laryngeal vestibule more easily because of rapid bolus flow, whereas residue may reflect reduced pharyngeal clearance, impaired pharyngolaryngeal coordination, age-related muscle weakness, or ineffective clearing swallows. Residue in the vallecula or pyriform sinuses may subsequently spill into the laryngeal vestibule after swallowing and contribute to penetration (8,23).

Patients with EAT-10 scores ≥3 or more pronounced penetration may represent a heterogeneous subgroup rather than a single mechanism. Possible contributors include individual differences in laryngopharyngeal sensation, age-related swallowing reserve, reflux or other comorbid factors, bolus flow characteristics, and compensatory swallowing behavior. Because of the small sample size, the present study could not identify predictors of higher EAT-10 scores or penetration; therefore, these findings should be interpreted descriptively.

Although this study cannot determine which surgical factors reduce postoperative penetration, the findings reinforce the importance of preserving airway-protective structures while achieving adequate airway widening. In practice, cordotomy should be limited to the minimum posterior glottic enlargement necessary for breathing, with careful avoidance of unnecessary anterior extension, excessive contralateral vocal fold injury, or excessive supraglottic or arytenoid tissue removal. A precise unilateral and, when appropriate, staged approach may help balance airway gain with preservation of glottic closure during swallowing, consistent with the principle of limited posterior glottic enlargement described for TPC (3).

In the present dataset, airway invasion was observed most often with thin liquids, whereas aspiration was rare and occurred only with thin liquids. This pattern is compatible with the known effect of bolus viscosity on swallowing safety and efficiency. Moderately thick boluses may slow bolus flow and reduce aspiration risk, but increased viscosity can also increase pharyngeal coating and residue when clearance is impaired (23). Thus, diet recommendations should be individualized according to instrumental findings rather than automatically recommending thickened liquids for all patients.

Management of patients with penetration should also be individualized. In patients with preserved oral intake, no recurrent pulmonary events, and penetration without aspiration, immediate major diet restriction may not be necessary. Instead, counseling on small sips, slower intake, avoidance of large-volume thin liquids, repeated swallows, throat clearing, and referral to a speech-language pathologist for compensatory strategies may be appropriate. Diet modification or thickening should be reserved for selected patients after instrumental assessment, especially because thickened boluses may increase residue (23).

FEES with sensory testing (FEESST) may have a role in future studies because it can assess laryngopharyngeal sensation and the laryngeal adductor reflex in addition to bolus flow. This may help distinguish penetration or aspiration related primarily to structural glottic insufficiency from abnormalities related to impaired sensation and silent airway invasion. Tabaee et al. (9) demonstrated that reduced laryngopharyngeal sensation in vocal fold immobility was associated with penetration and aspiration, supporting the relevance of sensory assessment in this population.

From a clinical perspective, these observations may support selective postoperative swallowing screening in BVFP patients after cordotomy, especially in those with cough during liquid intake, recurrent chest infections, weight loss, advanced age, or comorbidities that may affect sensation and airway-protective reflexes. Because dysphagia in this age group can also reflect age-related sarcopenia, polypharmacy, reflux, or neurologic disease, endoscopic abnormalities should be interpreted in their clinical context rather than attributed to cordotomy alone (24-27).

The strengths of this study include long postoperative follow-up, the use of validated FEES-based scales (PAS and YPRSRS), standardized IDDSI consistencies, integration of functional (FOIS, FOSS) and symptom-based (EAT-10) measures, and blinded independent rating with substantial-to-almost-perfect interrater agreement. These features provide a more objective and clinically interpretable description of postoperative swallowing than symptom reports alone.

Study Limitations

Limitations include the retrospective cross-sectional design, small sample size, and all-female cohort, which limit generalizability. Most importantly, preoperative instrumental swallowing assessment and a control group were unavailable; therefore, the present data cannot determine whether FEES

abnormalities were pre-existing, related to BVFP itself, caused by cordotomy, or influenced by age and comorbid conditions. The bolus protocol was limited to representative IDDSI consistencies. Future prospective studies with baseline and postoperative FEES or FEESST are needed to clarify trajectories, mechanisms, and risk factors.

Conclusion

In this descriptive long-term postoperative series, patients with BVFP who underwent CO_2 laser TPC generally maintained functional oral intake, although FEES frequently demonstrated penetration and pharyngeal residue, with rare thin-liquid aspiration. The main contribution of this study is to provide an objective FEES-based description of postoperative swallowing patterns in a population previously characterized mainly by airway, voice, and subjective swallowing outcomes. Because preoperative swallowing data and a control group were unavailable, these findings should not be directly interpreted as an effect of cordotomy surgery. Prospective studies using preoperative and postoperative FEES or FEESST are needed.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University (approval no: 2024/481, date: 14.11.2024).

Informed Consent: Written informed consent was obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.D., O.Ç., M.A., M.B.Ö., Ö.Ç., E.T., Ö.K., S.Ç.K., Concept: E.D., O.Ç., M.A., M.B.Ö., Ö.Ç., E.T., Ö.K., S.Ç.K., Design: E.D., O.Ç., M.A., M.B.Ö., Ö.Ç., E.T., Ö.K., S.Ç.K., Data Collection and/or Processing: E.D., O.Ç., M.A., M.B.Ö., Ö.Ç., E.T., Ö.K., S.Ç.K., Analysis or Interpretation: E.D., O.Ç., M.A., M.B.Ö., Ö.Ç., E.T., Ö.K., S.Ç.K., Literature Search: E.D., O.Ç., M.A., M.B.Ö., Ö.Ç., E.T., Ö.K., S.Ç.K., Writing: E.D., O.Ç., M.A., M.B.Ö., Ö.Ç., E.T., Ö.K., S.Ç.K.

Conflict of Interest: Özgür Kemal Prof. MD is associate editor in Turkish Archives of Otorhinolaryngology. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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Main Points

- This study describes long-term postoperative flexible endoscopic evaluation of swallowing (FEES) findings after carbon dioxide laser transverse posterior cordotomy in patients with bilateral vocal fold paralysis.
- FEES frequently demonstrated penetration and pharyngeal residue, although most patients maintained full or near-full oral intake.
- The study adds objective Penetration-Aspiration Scale- and Yale Pharyngeal Residue Severity Rating Scale-based swallowing data to a literature that has mainly emphasized airway, voice, and patient-reported outcomes.
- Because preoperative FEES data and a control group were unavailable, prospective perioperative FEES or FEES with sensory testing studies are needed.

Supplementary Video: Representative flexible endoscopic evaluation of swallowing examination demonstrating penetration and pharyngeal residue after posterior transverse laser cordotomy for bilateral vocal fold paralysis

Video 1 Link: https://youtu.be/sZPNBCFMI7I

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Original Investigation

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Photogrammetric Comparison of Septal Extension Grafts and Columellar Strut Grafts Reinforced with Septocolumellar Sutures

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Abstract

Objective: To compare the effects of septal extension (SE) grafts and columellar strut (CS) grafts reinforced with septocolumellar sutures on nasal tip projection, rotation, and patient-reported outcomes in primary rhinoplasty using standardized photogrammetric analysis.

Methods: This retrospective cohort study included 60 patients who underwent primary rhinoplasty between 2019 and 2024 (30 SE and 30 CS grafts reinforced with septocolumellar sutures). Nasal tip projection, rotation, and anthropometric parameters were assessed using Rhinobase software. Functional and esthetic outcomes were evaluated using the Nasal Obstruction Symptom Evaluation Questionnaire (NOSE) and Facial Aesthetic Quality of Life Questionnaire (FACE-Q).

Results: The mean age was 27.8 years, and 70% of the participants were female. The mean postoperative follow-up was 9.5±2.7 months. Although baseline nasal length and tip projection were lower in the SE group, both techniques produced comparable postoperative improvements in nasal tip projection, rotation, and nasal length. Postoperative FACE-Q and NOSE scores were also similar between groups, despite lower preoperative FACE-Q scores in the SE group (p=0.003).

Conclusion: CS grafts reinforced with septocolumellar sutures achieved functional and esthetic outcomes comparable to SE grafts. These findings suggest that septocolumellar suturing may compensate for the structural advantages traditionally attributed to SE grafts in primary rhinoplasty.

Keywords: Rhinoplasty, photogrammetry, nasal septum, nasal cartilages, treatment outcome, patient satisfaction

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Introduction

Achieving optimal nasal tip projection (TP) and rotation is a key determinant of rhinoplasty success. Nasal tip stability results from the combined effects of several anatomical and technical factors, such as soft tissue characteristics, including thickness and elasticity, the configuration and rigidity of the alar cartilages, the integrity of intercrural ligamentous structures, domal suture techniques, and the selective use of grafts aimed at establishing a balanced relationship between the medial crura and the infralobular region (1,2).

Anderson (3) first described the biomechanical behavior of the nasal tip through the concept of the nasal tip complex, later termed the tripod theory. According to this model,

variations in nasal TP and rotation arise from alterations in the relative length and orientation of the medial and lateral crura. In this three-legged support system, the lateral crura act as paired stabilizing components, whereas the medial crura together form the central supporting element.

A wide range of grafting methods has been proposed to maintain or enhance nasal tip support during rhinoplasty. Among these techniques, septal extension (SE) and columellar strut (CS) grafts are the most commonly utilized. The SE graft is secured to the caudal septum and directed toward the anterior septal angle, creating a stable framework for positioning the medial crura and reconstructed domal segments (4). Conversely, the CS graft is placed within a pocket between the medial crura and extended toward the anterior nasal spine, where it provides structural support while allowing a greater degree of flexibility compared with SE grafts (5).

Both grafting methods are designed to improve nasal tip stability and allow modification of projection, medial crural alignment, and columellar show, although their biomechanical behavior and long-term effects may differ (6). Therefore, this study aims to directly compare CS grafts reinforced with septocolumellar sutures with SE grafts by quantitatively evaluating their effects on nasal tip protrusion and rotation using standardized photogrammetric analysis.

Methods

Study Design and Participants

This study was designed as a retrospective cohort analysis and included 60 patients who underwent primary open rhinoplasty at a tertiary referral center between 2019 and 2024. Of these, 30 patients were treated using SE grafts (Group 1), while the remaining 30 patients received CS grafts (Group 2).

To maintain surgical uniformity, the study population was limited to patients on whom all operative steps were performed in an identical manner, except for the technique used for nasal tip support. Patients with a history of prior nasal or maxillofacial surgical interventions were excluded.

Patients with revision rhinoplasty or severe tip deformities requiring advanced structural lateral crural reconstruction were also excluded to maintain surgical homogeneity. As this was a retrospective study, nasal skin thickness was assessed clinically and considered during surgical planning; however, no formal stratification according to skin thickness was performed.

Data Collection

Demographic data (age, sex, follow-up time) were recorded. Esthetic satisfaction was assessed using the Facial Aesthetic Quality of Life Questionnaire (FACE-Q) Nose Satisfaction Scale (10 items), and functional outcomes were evaluated with the Turkish version of the Nasal Obstruction Symptom Evaluation (NOSE) questionnaire (7,8). Both instruments were administered preoperatively and postoperatively.

Photogrammetric Analysis

Standardized pre- and post-operative photographs (frontal, lateral, basal views) were taken by the same investigator using identical camera settings and patient positioning.

Anthropometric measurements were performed using Rhinobase software (version 1.1; İzmir, Türkiye, and Chicago, USA) (9). Which automatically calculates angles and linear distances after calibration with a vertical ruler (9). The software has demonstrated a strong correlation with direct anthropometry (10).

After manual identification of the anatomical landmarks, the software automatically generated all anthropometric measurements (Figure 1a-c). Key parameters included were:

- Nasal TP: alar point-nasal tip line.
- Nasal length (NL): nasion-subnasale distance.
- Nasolabial angle (NLA): columella-subnasale-labrale superius angle.

Preoperative anthropometric parameters, including NLA, NL, and TP, were statistically compared between groups to assess baseline comparability. Baseline differences were taken into account during interpretation of postoperative outcomes, and postoperative changes were analyzed within each group to minimize potential confounding effects.

Surgical Technique

All procedures were conducted under general anesthesia using an open rhinoplasty technique. Surgical access was achieved through an inverted-V transcolumellar incision. Standardized operative steps, including dorsal hump reduction, harvesting of septal cartilage, and lateral osteotomies, were applied uniformly to all patients.

Lower lateral (alar) cartilage modifications, including conservative cephalic trim and interdomal suturing when recorded in operative notes, were performed according to individual anatomical characteristics. These maneuvers were applied similarly in both groups and were not used as primary techniques to alter projection or rotation. No additional structural alar grafts, such as lateral crural strut grafts or alar batten grafts, were employed to differentially influence tip support between groups. Therefore, alar cartilage procedures did not represent an independent variable in comparative analysis.

As this was a retrospective analysis, nasal skin thickness was assessed based on preoperative clinical records and

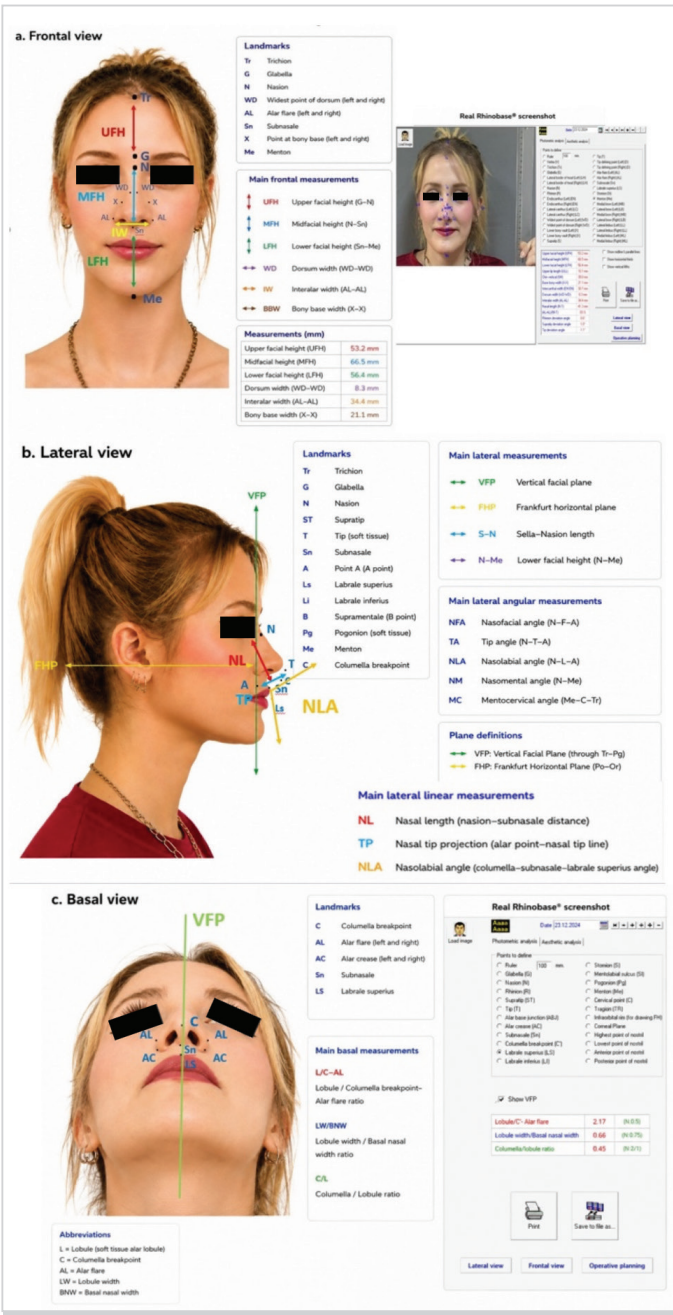

Figure 1. Schematic illustrations and representative Rhinobase® screenshots demonstrating the photogrammetric measurements used in the study. **a)** Frontal view: demonstration of the principal frontal anthropometric measurements and facial landmarks, including upper facial height (UFH), midfacial height (MFH), lower facial height (LFH), dorsum width (WD-WD), interalar width (AL-AL), and bony base width (X-X). **b)** Lateral view: illustration of the principal lateral linear and angular measurements, including nasal length (NL), tip projection (TP), nasolabial angle (NLA), and reference planes vertical facial plane (VFP) and Frankfurt horizontal plane (FHP). **c)** Basal view: illustration of the basal anthropometric measurements and ratios, including the lobule/columella breakpoint-alar flare ratio (L/C-AL), lobule width/basal nasal width ratio (LW/BNW), and columella/lobule ratio (C/L)

standardized photographs. No objective measurement or formal stratification according to skin thickness was performed. Patients with severe soft tissue characteristics requiring advanced structural reconstruction were not included in the comparative evaluation. No differential surgical strategy based solely on skin thickness was applied between groups. The only procedural distinction between the two study groups involved the method used to support the nasal tip. For patients in the SE group, a SE graft was aligned alongside the caudal septum and stabilized with side-to-side sutures. The graft was subsequently anchored to the medial crura to provide structural support (Figure 2d). In the CS group, a CS graft was placed within a prepared soft-tissue pocket between the medial crura and secured directly to these cartilaginous structures (Figure 2e).

In both groups, graft fixation relied on suturing between the graft and the medial crura. Additionally, septocolumellar sutures were applied in the CS group to further refine nasal TP and rotation.

Apaydin et al. (11) previously defined five distinct septocolumellar suture configurations, each capable of modifying nasal TP by increasing, maintaining, or decreasing it. These techniques also influence nasal tip and columellar rotation with varying directional effects depending on the suture type.

Apaydin et al. (11) Classification of Septocolumellar Sutures:

Type 1: The suture is placed between the caudal septum and the soft tissue posterior to the medial crura, providing posterior support for controlled modification of nasal TP.

Type 2: This technique involves fixation between the caudal septum and the inner surface of the medial crura, allowing adjustment of projection with an additional effect on tip rotation.

Type 3: In Type 3 suturing, the caudal septum is anchored to the central portion of the medial crura to achieve balanced control of nasal TP and alignment.

Type 4: The suture approximates the caudal margin of the medial crura to the caudal septum in a tongue-in-groove-like manner, primarily influencing nasal tip rotation and columellar position.

Type 5: This configuration connects the nasal dorsum with the midportion of the medial crura, modifying nasal tip rotation through the ventral septocolumellar relationship.

In our series, all patients were treated using a Type 1 septocolumellar suture, with placement through the soft tissue adjacent to the medial edge of the medial crura, in accordance with the original description (11). Although septocolumellar sutures were used in the CS group to

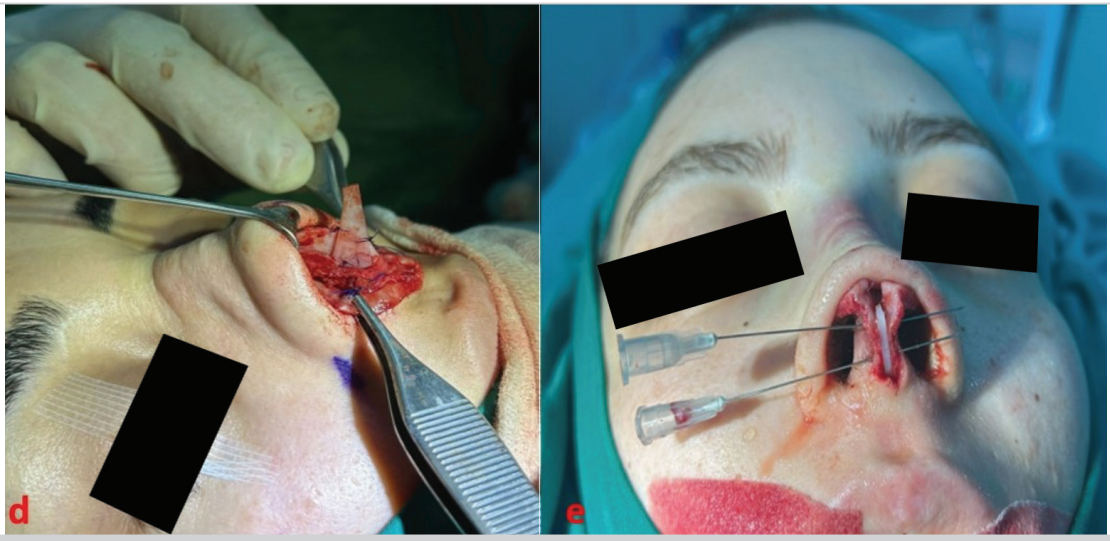

Figure 2. Intraoperative images demonstrating the grafting techniques used for nasal tip support. **d)** Septal extension graft fixation to the caudal septum, **e)** Columellar strut graft placement between the medial crura

improve TP and rotational control, no SE graft was used. Unlike the SE technique, the CS graft was not fixed side-to-side to the caudal septum to establish a rigid septal framework. Therefore, despite their similar effects on TP and rotational control, the two techniques remain structurally and biomechanically distinct.

Ethical Considerations

Prior to initiation of the study, the research design and data collection procedures were reviewed and authorized by the Non-Interventional Ethics Committee of Kırıkkale University (date of approval: 14.11.2024; reference number: 2024.11.02). Participation was voluntary, and written consent was obtained from all enrolled individuals. Separate written permissions were additionally obtained from patients whose clinical photographs are used for scientific publication.

Statistical Analysis

All statistical analyses were carried out using the SPSS statistical package (IBM SPSS Statistics for Windows, version 21, IBM Corp., Armonk, N.Y., USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation for normally distributed data and as median (interquartile range) for non-normally distributed data. Categorical variables were presented as frequencies and percentages. For comparisons between the two independent groups (SE vs. CS), the independent samples t-test was used for normally distributed variables, while the Mann-Whitney U test was applied for variables that did not meet the normality assumption. Within-group comparisons (preoperative vs. postoperative) were performed using the paired samples t-test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed data. Categorical variables, such as sex distribution, were analyzed using the chi-square test. For all analyses, a two-tailed p-value of <0.05 was considered statistically significant.

Results

Sixty patients were included in the analysis, with an equal allocation to the SE graft group (n=30) and the CS graft group (n=30). The two groups were comparable in terms of age (p=0.53), sex distribution (p=0.57), and duration of follow-up (p=0.14), with no measurable differences detected between them. The average postoperative follow-up period was 9.50±2.65 months.

Patient-reported Outcome Measures

Preoperative NOSE scores were similar between the SE and CS groups (p=0.59). After surgery, both groups demonstrated marked improvement in NOSE scores, reflecting better nasal function (p<0.001). Before surgery, FACE-Q scores were lower in the SE group than in the CS group (p=0.003); however, this discrepancy was not observed after the intervention (p=0.487). Improvements in postoperative FACE-Q scores were observed in both groups, as detailed in Table 1 (p<0.001).

Photogrammetric Analysis

Baseline Comparisons

Preoperative anthropometric analysis demonstrated that NL and TP were significantly lower in the SE group compared with the CS group (p<0.001 and p=0.002, respectively), whereas the NLA was comparable between groups (p=0.955). These findings indicate inherent anatomical variation at baseline.

Table 1. Patient demographics, clinical features, NOSE and FACE-Q scores

Parameter	Septal extension	Columellar strut	p
Age	28.43±7.76	27.23±7.12	0.53
Gender (female/male)	22/8	20/10	0.57
Follow-up duration (months)	9.00±2.72	10.00±2.53	0.14
NOSE			
Preoperative	60.17±32.09	64.17±25.66	0.59
Postoperative	21.00±23.35	17.33±23.18	0.54
p	**<0.001**	**<0.001**	
FACE-Q			
Preoperative	34.22±9.86	45.66±17.30	**0.003**
Postoperative	88.27±14.42	85.66±14.24	0.487
p	**<0.001**	**<0.001**	

All scores are given as mean ± SD. Bold values indicate statistical significance. NOSE: Nasal Obstruction Symptom Evaluation Questionnaire, FACE-Q: Facial Aesthetic Quality of Life Questionnaire, SD: Standard deviation

Frontal View

Frontal view photogrammetric measurements are summarized in Table 2. Pre- and post-operative values for upper face height, midface height (MFH), and dorsum width (DW) were significantly lower in the SE group ($p<0.05$). Lower face height (LFH) and intercanthal width (IW) were similar preoperatively but became lower in the SE group after surgery. Bony base width (BBW) remained similar in both groups. Surgery significantly affected MFH, BBW, DW, and IW in the SE group, and MFH and LFH in the CS group.

Lateral View

Lateral view measurements are presented in Table 3. Nasal frontal angle (NFR), nasofacial angle (NFA), NLA, and nasomental angle showed no significant differences between groups. NL, TP, and columella values were consistently lower in the SE group. Preoperatively, projection and infralobule were lower in the SE group but equalized postoperatively. Surgery significantly affected NFA, NLA, NL, TP, projection, and infralobule in the SE group, and NFA, NLA, NL, TP, and infralobule in the CS group.

Basal View

Basal view parameters are shown in Table 4. No significant differences were found between groups in terms of the lobule/columella breakpoint-alar flare ($p=0.932$) and columella/lobule ratios ($p=0.879$). However, the lobule width/basal nasal width ratio was significantly lower in the SE group ($p=0.014$). Surgery led to significant changes in both ratios in the SE group, while only the lobule width/basal width ratio changed significantly in the CS group ($p=0.040$).

Nasal Tip Parameters

Changes in nasal TP, rotation, and NL are summarized in Table 5. Changes in nasal TP, rotation, and NL were observed in both groups; however, these changes were not statistically significant.

Discussion

Nasal tip esthetics play a key role in rhinoplasty, influencing both functional and cosmetic outcomes (12). Achieving stable nasal TP and rotation remains a central surgical objective, and several techniques have been developed to support the nasal tip framework (13). Among these, SE and CS grafts are widely used and well-established options. The choice between the two often depends on the surgeon's experience, the patient's anatomy, and the desired degree of tip control.

In contrast to previous studies, the presented study specifically evaluates CS grafts reinforced with Type 1 septocolumellar sutures, directly comparing them with SE grafts using standardized photogrammetric analysis.

In the presented study, SE grafts and CS grafts reinforced with septocolumellar sutures produced comparable esthetic and functional results. Postoperative FACE-Q and NOSE scores did not differ significantly between the two groups, indicating that both grafts can satisfactorily meet patient expectations regarding nasal appearance and breathing. These findings reinforce the value of patient-reported outcomes in evaluating rhinoplasty results.

The mechanical behavior of SE and CS grafts continues to be a subject of discussion. CS grafts are often favored for their flexibility and ability to provide tip support without excessive rigidity or palpability (14-16). In contrast, SE grafts offer firmer and more predictable control over tip position, often described as providing a "stay-where-you-put-it" stability (4,17). Previous studies generally report superior long-term preservation of projection and rotation with SE grafts. Aldosari et al. (18). demonstrated more consistent tip rotation with SE grafts compared to CS grafts, and similar findings were reported by Sadeghi et al. (19) and Akkus et al. (20). Other authors also highlight the long-term stability associated with SE grafts (21-23). Operating room comparisons by Bellamy and Rohrich (24) further support enhanced projection and rotation control with SE grafts. Likewise, Mookerjee et al. (25) showed that although early postoperative decline in projection and rotation may occur, these parameters stabilize and remain steady for up to two years following SE graft placement. Collectively, these recent prospective and quantitative studies further support the improved long-term stability, flexibility, and projection control achieved with SE grafts compared with traditional CS techniques.

Table 2. Photogrammetric analysis results of the frontal views measurements

		Septal extension	Columellar strut	p
Upper facial height	Preoperative	47.22±7.92	53.61±8.86	**0.005**
	Postoperative	47.74±6.82	53.97±7.81	**0.001**
	p	0.681	0.772	
Middle facial height	Preoperative	61.20±8.96	66.98±8.24	**0.015**
	Postoperative	55.8±6.28	61.76±8.21	**0.002**
	p	**<0.001**	**<0.001**	
Lower facial height	Preoperative	51.9±10.17	52.93±11.56	0.669
	Postoperative	51.15±9.50	58.99±7.84	**0.001**
	p	0.708	**<0.001**	
Base bony width (X-X)	Preoperative	26.16±4.79	25.76±4.53	0.741
	Postoperative	24.38±3.97	25.41±4.20	0.332
	p	**0.009**	0.363	
Dorsum width (WD-WD)	Preoperative	7.74±2.14	9.15±2.57	**0.025**
	Postoperative	6.85±1.79	8.70±1.88	**<0.001**
	p	**0.028**	0.299	
Interalar width (AL-AL)	Preoperative	34.15±5.22	35.72±6.15	0.41
	Postoperative	32.56±4.10	34.98±4.32	**0.027**
	p	**0.028**	0.720	

All scores are given as mean ± SD. Bold values indicate statistical significance. X-X: Lower bony vault (left) (X)-lower bony vault (right) (X), WD-WD: Widest point of dorsum (left) (WD)-widest point of dorsum (right) (WD), AL-AL: Alar flare (left) (AL)-alar flare (right) (AL), SD: Standard deviation

Despite the structural advantages of SE grafts, several reports show that CS grafts can also achieve satisfactory tip control, particularly when combined with adjunctive maneuvers such as septocolumellar sutures or tongue-in-groove techniques (26-29). This suggests that the surgical technique may play an important role in optimizing CS graft performance. Recent studies evaluating septocolumellar sutures and tongue-in-groove modifications further suggest that adjunctive stabilization techniques may contribute to improved TP and rotational control in CS-based rhinoplasty (11,12,28,29).

The presented study addresses a specific gap in literature: it demonstrates that CS grafts reinforced with septocolumellar sutures can achieve short-term outcomes comparable to SE grafts, using objective photogrammetric assessment. This provides novel evidence for surgeons considering alternatives to SE grafts in primary rhinoplasty and emphasizes the importance of adjunctive suturing techniques.

Because several baseline anthropometric parameters differed between the groups, these findings require parameter-specific interpretation. While NLA was statistically similar between the SE and CS groups before surgery, baseline NL, TP, projection, and infralobule showed significant intergroup differences. These differences most likely reflect surgeon-driven technique selection based on baseline nasal anatomy rather than intentional allocation of different patient types to the groups. In routine rhinoplasty practice, patients with shorter nasal structures, weaker projection, or reduced tip support are more likely to undergo SE grafting because this technique provides stronger structural control of the nasal tip. Therefore, the lower preoperative values observed in several length- and projection-related parameters in the SE group may be explained by differences in initial nasal morphology.

For NL, the preoperative difference between groups likely reflects the preferential use of SE grafts in patients with shorter nasal structures. Although postoperative improvement was achieved, NL remained numerically lower in the SE group, suggesting that this difference was mainly related to baseline anatomical characteristics rather than insufficient surgical correction. Thus, the persistent postoperative difference in NL should be interpreted as the continuation of pre-existing anatomical variation rather than failure of either technique to lengthen or support the nasal framework.

Similarly, lower preoperative TP and p-values in the SE group may be attributed to weaker baseline tip support and reduced projection. The comparable postoperative improvement between groups suggests that both techniques were effective in improving projection-related parameters, although absolute postoperative values may still have been influenced by the initial anatomical differences.

Table 3. Photogrammetric analysis results of the lateral views measurements

		Septal extension	Columellar strut	p
Nasofrontal angle	Preoperative	149.9±9.71	146.8±8.87	0.208
	Postoperative	149.2±8.45	146.8±8.49	0.316
	p	0.682	0.885	
Nasofacial angle	Preoperative	29.12±4.26	29.42±4.12	0.701
	Postoperative	32.23±5.32	31.84±3.86	0.794
	p	**<0.001**	**<0.001**	
Nasolabial angle	Preoperative	98.86±13.02	98.81±13.45	0.955
	Postoperative	106.2±15.15	107.1±8.83	0.790
	p	**0.007**	**0.002**	
Nasomental angle	Preoperative	131.1±7.12	130.3±6.32	0.591
	Postoperative	129.9±6.55	130.1±5.30	0.914
	p	0.278	0.903	
Nasal length	Preoperative	37.66±5.99	44.01±6.15	**<0.001**
	Postoperative	33.96±5.75	38.97±5.30	**0.001**
	p	**<0.001**	**<0.001**	
Tip projection (goode ratio)	Preoperative	22.77±3.88	27.32±6.75	**0.002**
	Postoperative	27.99±5.16	31.20±4.24	**0.011**
	p	**<0.001**	**0.001**	
Premaxilla (ABJ-Sn)	Preoperative	6.13±1.96	8.79±4.25	**0.003**
	Postoperative	8.68±1.98	9.48±1.80	0.105
	p	**<0.001**	0.372	
Columella length (Sn-C')	Preoperative	6.95±1.61	8.82±1.99	**<0.001**
	Postoperative	6.94±1.80	8.35±2.25	**0.012**
	p	0.990	0.145	
Infralobule (C'-T)	Preoperative	8.57±2.27	10.26±2.97	**0.022**
	Postoperative	12.30±2.40	13.38±2.39	0.082
	p	**<0.001**	**<0.001**	
Columellar show	Preoperative	5.23±1.66	5.90±1.71	0.180
	Postoperative	5.61±1.68	6.73±1.30	**0.007**
	p	0.316	0.005	

All scores are given as mean ± SD. Bold values indicate statistical significance. ABJ-Sn: Alar base junction (ABJ)-subnasale (Sn), Sn-C': Subnasale (Sn)-columella breakpoint (C'), C'-T: Columella breakpoint (C')-tip (T), SD: Standard deviation

Table 4. Photogrammetric analysis results of the basal views measurements

		Septal extension	Columellar strut	p
Lobule/columella breakpoint-alar flare	Preoperative	1.15±0.39	1.14±0.26	0.874
	Postoperative	1.24±0.34	1.23±0.35	0.932
	p	0.291	0.198	
Lobule width/basal nasal width	Preoperative	0.74±0.05	0.78±0.08	**0.014**
	Postoperative	0.68±0.05	0.72±0.08	**0.04**
	p	**<0.001**	**0.008**	
Columella/lobule ratio	Preoperative	0.93 (0.5-2.27)	0.81±0.26	0.092
	Postoperative	0.79±0.18	0.80±0.20	0.879
	p	**0.028**	0.819	

Data are presented as mean ± standard deviation or median (interquartile range, 25th-75th percentiles), as appropriate. Bold values indicate statistical significance

Table 5. Comparison of changes in tip projection, tip rotation, and nasal length values before and after surgery

Preop-postop change	Septal extension	Columellar strut	p
Tip projection	5.21±4.26	3.88±5.83	0.318
Tip rotation; NLA	7.42±13.99	8.34±13.12	0.796
Nasal length	3.69±3.56	4.98±3.15	0.143

NLA: Nasolabial angle

Interestingly, infralobule, which differed significantly before surgery, became statistically comparable after surgery. This finding suggests postoperative normalization of the infratip-tip contour relationship. In particular, the use of septocolumellar sutures in the CS group may have enhanced rotation and projection control sufficiently to compensate for the structural rigidity advantage traditionally associated with SE grafts. This may explain why a parameter that was initially different between groups became statistically similar after surgery.

Overall, these findings indicate that the observed intergroup differences should not be interpreted solely based on absolute postoperative values. Instead, baseline nasal morphology, surgeon-driven graft selection, and the magnitude of surgical change within each group should be considered together when evaluating the comparative effects of SE and CS grafting techniques.

Our photogrammetric analysis further supports the clinical equivalence of the two graft types. Although postoperative NL and TP values were slightly lower in the SE group, these postoperative differences should be interpreted in light of the lower baseline values in the SE group. Both groups exhibited significant postoperative improvement in NL, TP, and NLA. The finding that CS grafts combined with a septocolumellar suture achieved outcomes similar to SE grafts suggests that the adjunctive suture may compensate for the increased structural rigidity provided by SE grafts.

Another notable observation is the ability of CS grafts to maintain projection while creating a defined infratip break, provided that appropriate suturing techniques are applied. This highlights the critical role of surgical execution, possibly as important as graft selection itself. More recently, Amador et al. (30) conducted a systematic review comparing SE and CS grafts and emphasized that both techniques remain valuable options in rhinoplasty, with graft selection needing to be individualized according to patient anatomy, desired tip characteristics, and surgical goals.

Study Limitations

This study has several limitations. The sample size was modest and derived from a single-center, which may limit generalizability. Additionally, patients were not stratified based on skin thickness, a known factor affecting tip support and postoperative stability. The mean follow-up period was 9-12 months, which allowed assessment of early and mid-term outcomes; however, it may not fully capture long-term nasal tip stability, particularly for SE grafts. Therefore, longer-term prospective studies with follow-up periods exceeding one year are warranted to better evaluate the durability and stability of surgical outcomes. Furthermore, the retrospective design, lack of randomization, baseline anatomical differences between groups, and potential surgeon-selection bias should be considered when interpreting the results. Nonetheless, the use of standardized three-dimensional photogrammetric measurements represents a major strength, enabling objective and reproducible analysis of nasal morphology.

Conclusion

Both SE grafts and CS grafts reinforced with septocolumellar sutures demonstrated comparable functional and esthetic outcomes, with no significant differences in postoperative FACE-Q scores, NOSE scores, NL, TP, or NLA. Although patients in the SE group began with lower baseline values, postoperative results were equivalent between the two groups; however, it should be interpreted with caution given the baseline differences and the adjunctive septocolumellar sutures used in the CS group.

The use of a septocolumellar suture in the CS technique appears to offset the structural advantages traditionally attributed to SE grafts, indicating that CS grafts, when reinforced with appropriate suturing, can serve as an equally effective alternative for tip support and control. It is important to note that the comparison is not purely between SE and CS grafts alone, but between SE grafts and CS grafts combined with septocolumellar sutures, which should be considered when interpreting the findings.

Ethics

Ethics Committee Approval: Prior to initiation of the study, the research design and data collection procedures were reviewed and authorized by the Non-Interventional Ethics Committee of Kırıkkale University (approval no: 2024.11.02, date: 14.11.2024).

Informed Consent: Participation was voluntary, and written consent was obtained from all enrolled individuals.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., B.M.T., Z.Ş., Concept: S.K., L.N.C., N.B.M., B.M.T., Z.Ş., E.C., Design: S.K., L.N.C., N.B.M., B.M.T., Z.Ş., E.C., Data Collection and/or Processing:

S.K., L.N.C., B.M.T., Z.Ş., Analysis or Interpretation: S.K., L.N.C., B.M.T., Z.Ş., Literature Search: S.K., L.N.C., N.B.M., E.C., Writing: S.K., L.N.C., N.B.M., E.C.

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Main Points

- Both surgical techniques achieved comparable improvements in nasal tip projection, rotation, nasal length, and patient-reported functional and esthetic outcomes.
- Reinforcement of the columellar strut graft with a septocolumellar suture provided postoperative results comparable to those achieved with a septal extension graft.
- Septocolumellar suture reinforcement may represent a reliable alternative to septal extension grafting for achieving stable nasal tip support in primary rhinoplasty.

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Systematic Review

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Olfactory Training for COVID-19-Related Olfactory Dysfunction: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

The coronavirus disease-2019 (COVID-19) pandemic has led to a high prevalence of olfactory dysfunction (OD), a debilitating condition that significantly impacts quality of life (QoL). While most patients recover their sense of smell, a substantial number experience persistent COVID-OD. Olfactory training (OT) has emerged as a leading, non-invasive therapeutic strategy. A systematic review and meta-analysis were conducted on evidence retrieved from Web of Science, PubMed, Scopus, CENTRAL, and Embase through June 2025 for randomized controlled trials (RCTs) evaluating OT in patients with COVID-OD. The primary outcome was the change in objective olfactory scores, and the secondary outcome was the change in QoL scores. We used STATA software to pool outcomes using standardized mean differences (SMD) with 95% confidence intervals (CI). Ten RCTs involving 628 patients were included in the analysis. Compared to the control group, OT was associated with a significant improvement in objective olfactory scores [SMD=0.30, 95% CI (0.08, 0.51), p=0.01] and QoL [SMD=-0.40, 95% CI (-0.65, -0.15), p<0.001]. The heterogeneity among studies was low for both outcomes (I^2=33.69% and I^2=37.47%, respectively). OT significantly improves objective olfactory function and QoL in patients with COVID-OD. Despite these positive findings, the results should be interpreted with caution due to heterogeneity in OT protocols and variability among the included studies. Future large-scale, rigorously designed RCTs with standardized OT protocols are necessary to establish definitive clinical practice guidelines.

Keywords: Anosmia, COVID-19, olfactory training, quality of life, meta-analysis

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Introduction

The coronavirus disease-2019 (COVID-19) pandemic has presented a diverse range of clinical symptoms; notably, the abrupt onset of olfactory dysfunction (OD), encompassing anosmia and hyposmia, quickly became a significant diagnostic indicator of COVID-19 (1). The high predictive value of COVID-OD, exceeding that of fever or cough, has led major health organizations and otolaryngology societies to recognize it as a key diagnostic indicator warranting self-isolation (2,3). Early pandemic meta-analyses revealed a substantial pooled prevalence of COVID-OD, affecting approximately 47%; some studies employing objective psychophysical testing reported rates as high as 98% (4,5). Despite a reduction in prevalence with variants such as Omicron, the underlying pathophysiological mechanisms and optimal treatment strategies remain unclear (6).

COVID-OD, unlike the majority of postviral anosmia cases, does not typically arise from direct viral infection of the olfactory sensory neurons (OSNs). Evidence from molecular and autopsy studies suggest that SARS-CoV-2 predominantly infects non-neuronal support cells, particularly sustentacular cells expressing ACE2 and TMPRSS2, leading to secondary disruption of OSN function through inflammatory mechanisms (7-9). The initial insult initiates a cascade of localized tissue damage, an inflammatory response, and non-cell-autonomous disruption of OSN function, including the downregulation of odorant receptor genes, resulting in functionally silent neurons (10). Although most patients recover within weeks to months, approximately 10-20% develop persistent OD, a key feature of long COVID-19 syndrome (11,12). Persistent chemosensory dysfunction significantly impairs quality of life (QoL), affecting nutrition, safety, and psychosocial well-being, and is associated with increased depression and anxiety (13,14).

Lacking proven, effective pharmacotherapies for postviral OD, olfactory training (OT) has become the foremost evidence-based, non-invasive treatment modality (15). OT is a structured rehabilitative intervention involving repeated exposure to predefined odorants, based on the olfactory system's neuroplastic capacity at both peripheral and central levels (16). Pre-pandemic studies have confirmed its effectiveness in treating postviral OD (17).

Accordingly, the substantial global prevalence of persistent OD following COVID-19 necessitates a thorough assessment of the evidence supporting OT to direct clinical practice and future research. Therefore, this systematic review and meta-analysis study aimed to critically synthesize the current evidence from randomized controlled trials (RCTs) on the efficacy of OT for the treatment of COVID-OD.

Methods

Protocol Registration

We registered this systematic review with the International Prospective Register of Systematic Reviews (PROSPERO) with the CRD420251127095. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Handbook for Systematic Reviews of Interventions guided the conduction of this systematic review and meta-analysis (18,19).

Data Sources and Search Strategy

On June 2025, an electronic search was conducted on the following databases: Web of Science (WoS), PubMed, Scopus, CENTRAL, and Embase. The search strategy included the following search entries: ("COVID-19" OR "2019 nCoV" OR "2019nCoV" OR "COVID 19" OR "COVID19" OR "new coronavirus" OR "novel coronavirus" OR "novel corona virus" OR "SARS-CoV-2" OR "SARSCoV2" OR "2019-novel CoV" OR "ncov19" OR "ncov-19" OR "nCov 2019" OR "coronavirus" OR "coronavirus disease 2019" OR "long COVID" OR "coronavirus disease" OR "COVID") AND ("olfactory dysfunction" OR "anosmia" OR "hyposmia" OR "parosmia" OR "olfactory loss" OR "loss of smell" OR "smell disorder*" OR "smell dysfunction" OR "olfaction" OR "olfactory" OR "dysosmia*" OR "phantosmia*" OR "cacosmia*" OR "microsmia*" OR "absent smell" OR "olfactory impairment" OR "smell impairment" OR "sense of smell" OR "smell loss") AND ("olfactory training" OR "smell training" OR "odor exposure" OR "odorants" OR "olfactory rehabilitation" OR "olfactory stimulation" OR "smell therapy" OR "smell retraining" OR "scent training" OR "olfactory retraining" OR "odor retraining" OR "nasal smell training" OR "smell recovery training"). Table S1 provides detailed information on the specific search terms and results for each database. To ensure that no relevant studies were omitted, we comprehensively reviewed the reference lists of all included trials.

Eligibility Criteria

RCTs conducted using the following PICO criteria were included: population (P), patients with post-COVID-19 OD; intervention (I), OT; control (C), placebo or no OT; and outcomes (O): the primary outcome was the change in objective olfactory scores, including the University of Pennsylvania Smell Identification test, Sniffin' Sticks test (threshold, discrimination, and identification score), Connecticut Chemosensory Clinical Research Center olfaction test, and Brief Smell Identification test. The secondary outcome was the change in the QoL scores. Furthermore, our analysis excluded quasi-randomized trials, active comparators like nasal corticosteroids, conference presentations and proceedings, observational studies, *in vitro* research, and review articles.

Study Selection

A thorough screening was performed by two independent reviewers (E.A. and G.A.). Following the elimination of duplicate records, a two-stage screening procedure was executed. The process included an initial screening of titles and abstracts, followed by a full-text review of the remaining articles. The reviewers resolved their disagreements through discussion.

Data Extraction

To design an Excel extraction form, we first conducted a preliminary extraction of eligible publications. This preliminary extraction informed the design of the final extraction form, which included three sections: (1) summary characteristics of the included trials (study ID, country, study

design, sample size, treatment protocols, main inclusion criteria, assessment scores, and OT duration); (2) baseline characteristics of the included participants (age, gender, smoking, diabetes mellitus, and type of OD); and (3) the outcomes sheet (change in objective olfactory scores and change in subjective QoL scores).

Data were independently extracted by two reviewers (G.A. and M.A.), and disagreements were resolved through consultation with a senior author (A.A.). Event rates were used to summarize dichotomous data, while continuous data were summarized using means and standard deviations. Mean and standard deviation were computed using conversion formulas from Wan et al. (20), based on median and interquartile range (or range) data reported in some included studies. According to the Cochrane guideline, we included trials that have not yet been published or are in preprint form (19).

Risk of Bias Assessment

The risk of bias in the included studies was evaluated using the revised Cochrane collaboration tool for RCTs (RoB-2) (21). Each study was reviewed by two independent reviewers (G.A. and M.A.), who assessed aspects such as selection, performance, reporting, and attrition biases, as well as other potential sources of bias. Disputes were resolved through consensus.

Effect Measures and Meta-analysis

Data analysis was conducted with STATA MP version 18 (StataCorp). Continuous outcomes were analyzed using the standardized mean difference (SMD), which was presented with the corresponding 95% confidence intervals (CIs). The SMD was used for both objective and subjective endpoints due to the variability in the scoring systems and the assessment tools used across the included trials. The fixed-effect model constituted the primary methodology. Heterogeneity was assessed among the included studies via the chi-squared test and the I-squared statistic (I^2), where a p-value <0.1 for the chi-square test and an I^2 value of ≥50% suggested noteworthy heterogeneity. Publication bias was not evaluated, given that all assessed outcomes involved fewer than ten RCTs (22). To evaluate the robustness of the pooled estimates, a leave-one-out sensitivity analysis was performed, systematically removing each study to determine its influence on the overall effect size.

Results

Search Results and Study Selection

Following a search of the WoS, Scopus, PubMed, CENTRAL, and Embase databases, 1,486 records were identified. An additional two studies were identified through manual search. After 458 duplicates were removed, 1,030 records were screened. Of these, 993 studies failed to meet the inclusion criteria and were excluded based on their titles and abstracts, leaving 37 full-text articles for further assessment. Following a full-text review, 27 studies were excluded (Table S2), leaving 10 studies (23-32) to be included in the final quantitative and qualitative assessments (Figure 1).

Characteristics of Included Studies

Ten trials and 628 participants were included in our analysis (23-32). Two trials were conducted in Brazil (30,32), two in Canada (24,26), and two in Iran (23,31), with single trials in Denmark (29), China (reference 25), Malaysia (27), and the United Kingdom (28). The follow-up duration ranged from four weeks to 12 months. Intervention details and trial characteristics are given in Table 1. Also, the baseline data of the included patients are outlined in Table 2.

Risk of Bias Summary

Four RCTs showed an overall low risk of bias (23,27,29,31). Still, five studies showed a high overall risk of bias (25,26,28,30,32) due to various issues, including high risk of selection bias (26,32), performance bias (25,28), attrition bias (30,32), and detection bias (24,26,28) (Figure 2).

Objective Olfactory Score

OT significantly improved objective olfactory scores [n=7 RCTs, SMD=0.30, 95% CI (0.08, 0.51), p=0.01] (Figure 3A). Pooled studies showed low heterogeneity (I^2=33.69%), and the leave-one-out sensitivity analysis showed a consistent and significant effect after the exclusion of each individual study, confirming the robustness of our findings (Figure 3B).

Quality of Life

OT significantly improved QoL scores [n=5 RCTs, SMD=-0.40, 95% CI (-0.65, -0.15), p<0.001] (Figure 4A). Pooled studies showed low heterogeneity (I^2=37.47%), and the leave-one-out sensitivity analysis showed the results were significantly affected by a single study, as after the exclusion of Akbarpour et al. (23), there was no significant difference between the two groups (p=0.097) (Figure 4B).

Discussion

This systematic review and meta-analysis of ten RCTs and 628 patients showed that OT was effective in improving olfactory function and QoL. These results align with previous studies supporting OT as an effective, evidence-based treatment for postviral OD (17). OT promotes recovery through peripheral and central neuroplastic mechanisms and is widely recommended as a safe, first-line treatment (16,33).

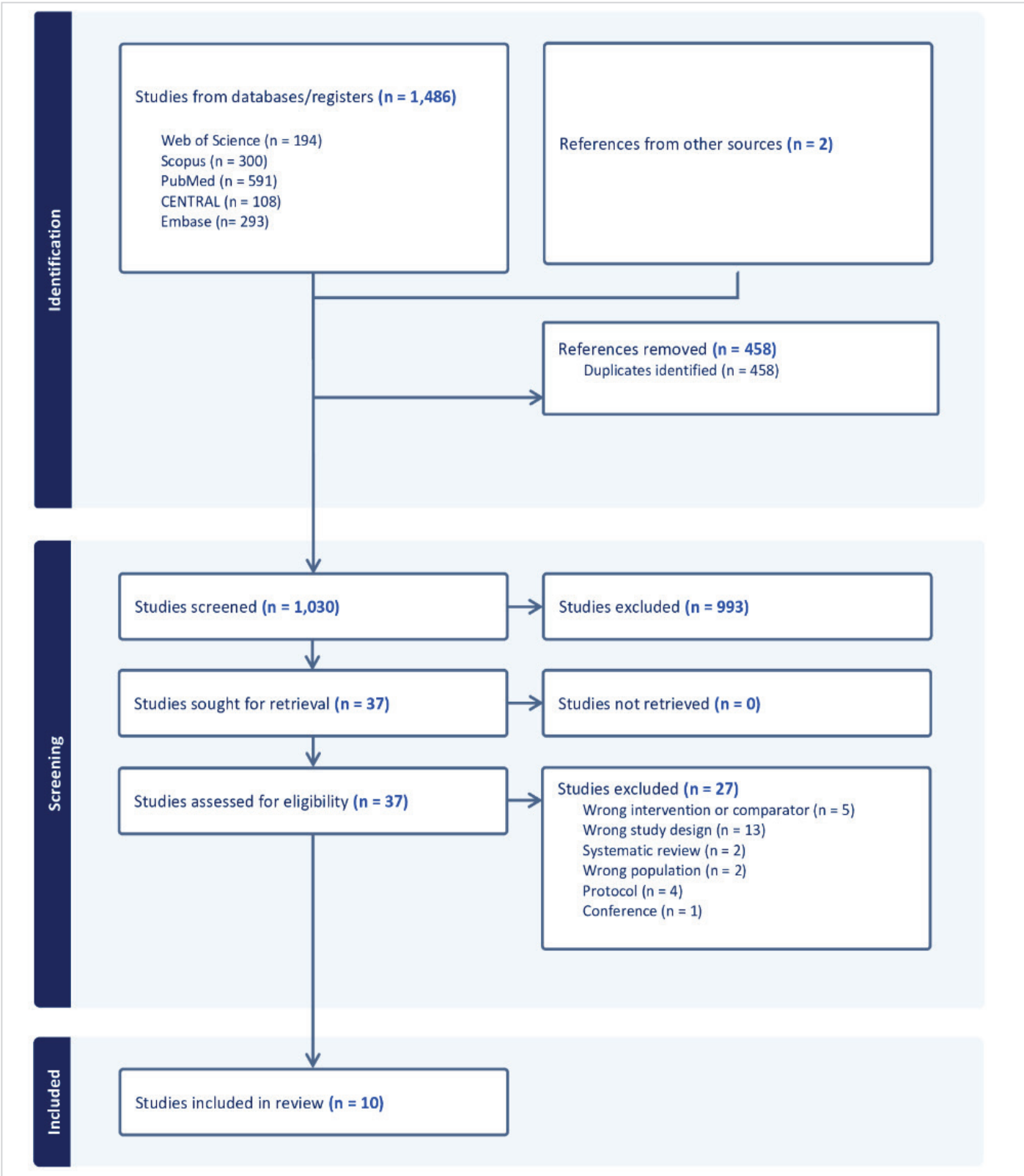

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrates the systematic study selection process

Table 1. Summary information of the included randomized controlled trials

Study ID	Study design	Country	Recruitment	Sample size, n	Patient criteria	Intervention	Control	Olfactory training duration
Akbarpour et al. 2024 (23)	RCT	Iran	Not reported	n=95	Post-COVID-19 olfactory dysfunction	Olfactory training: twice-daily exposure to 4 scents—rose, eucalyptus, lemon, and clove—each for 20 seconds with 10-second intervals.	No olfactory training	6 weeks
Bérubé et al. 2023 (24)	RCT	Canada	May 2021-October 2021	n=50	Post-COVID-19 olfactory dysfunction (≥4 weeks)	Olfactory training: twice-daily training with 4 scents—rose, orange, clove, and eucalyptus—each for 10 seconds with 10-second intervals, using amber vials. Sessions lasted ~5 minutes.	Placebo (odorless vials with propylene glycol)	12 weeks
Chung et al. 2023 (25)	RCT	China	August 2020-11 June 2021	n=13	Post-COVID-19 olfactory dysfunction (≥12 weeks)	Olfactory training: three-times-daily training using diffuser-delivered essential oils—lemon, eucalyptus, geranium, and cedarwood—each for 20 seconds.	No olfactory training	4 weeks
Filiz et al. 2024 (26)	RCT	Canada	Not reported	n=40	Post-COVID-19 olfactory dysfunction (≥8 weeks)	Olfactory training: twice-daily training with 4 scents—rose, orange, clove, and eucalyptus—each for 10 seconds with 10-second intervals, using amber vials. Sessions lasted ~5 minutes.	Placebo (odorless vials with propylene glycol)	12 weeks
Ho et al. 2024 (27)	RCT	Malaysia	January 2022-November 2022	n=21	Post-COVID-19 olfactory dysfunction (≥4 weeks)	Olfactory training: twice-daily exposure to essential oils—rose, lemon, clove, eucalyptus—each for 10 seconds with 10-second intervals; stored in 50 mL jars with cotton pads.	No olfactory training	12 weeks
Lechner et al. 2022 (28)	RCT	UK	May 2020-January 2021	n=63	Post-COVID-19 olfactory dysfunction	Olfactory training delivered using Sniffin' Sticks (Duft-Quartett).	No olfactory training	12 weeks
Mogensen et al. 2025 (29)	RCT	Denmark	June 2022-December 2023	n=49	Post-COVID-19 olfactory dysfunction (≥12 weeks)	Olfactory training: twice-daily exposure to 4 essential oils—orange, lavender, clove, and peppermint—each for 20 seconds with 10-second intervals.	Placebo (odor-free oils)	12 weeks
Paranhos et al. 2025 (32)	RCT	Brazil	May 2021-May 2024	n=114	Post-COVID-19 olfactory dysfunction (≥3 weeks)	Olfactory training: twice-daily inhalation of 4 scents—rose, lemon, eucalyptus, and clove—each for 30 seconds with 30-second intervals.	No olfactory training	12 weeks
Serrano et al. 2025 (30)	RCT	Brazil	June 2020-December 2020	n=123	Post-COVID-19 olfactory dysfunction	Olfactory training: twice-daily 5-minute training with 4 labeled vials—clove, lemon, eucalyptus, and rose—rotating scents every 15 seconds.	Placebo (vials without essential oils)	180 days or until recovery
Taheri et al. 2024 (31)	RCT	Iran	March 2020-March 2021	n=60	Post-COVID-19 olfactory dysfunction (≥2 weeks)	Olfactory training: twice-daily exposure to 4 standard-concentration odors—rose, eucalyptus, lemon, and clove—each for 10 seconds.	No olfactory training	12 weeks

RCT: Randomized controlled trial, COVID-19: Coronavirus disease 2019

Table 2. Baseline characteristics of the included participants and trials

Study ID	Group	Sample size, n	Age (years)	Sex, n [male/female]	Smoking, n	DM, n	Type of OD, n (%)			Assessment tools
							Anosmia	Hyposmia	Parosmia	
Akbarpour et al. 2024 (23)	OT	47	38±12.45	[26/21]	19	NR	47	0	0	QOD-NS
	Control	48	39.1±13.76	[29/19]	16	NR	48	0	0	
Bérubé et al. 2023 (24)	OT	25	44.9±7.4	[9/16]	0	NR	5	20	16	UPSIT, NOSE, and QOD
	Control	25	44.5±10.1	[8/17]	0	NR	5	20	19	
Chung et al. 2023 (25)	OT	8	47.53±14.07	[2/6]	0	0	5	2	3	BTT, and SIT
	Control	5	56.33±8.15	[2/3]	0	1	2	3	0	
Filiz et al. 2024 (26)	OT	20	39.5±9.6	[5/15]	NR	NR	NR	NR	18	UPSIT, SQOD-NS, and QOD
	Control	20	43.5±10.1	[5/15]	NR	NR	NR	NR	16	
Ho et al. 2024 (27)	OT	10	20-60 (range)	NR	3	NR	NR	NR	NR	TIBSIT, and eODQ
	Control	11	20-60 (range)	NR	1	NR	NR	NR	NR	
Lechner et al. 2022 (28)	OT	33	46.25±13.75	NR	NR	NR	NR	NR	NR	BSIT
	Control	30		NR	NR	NR	NR	NR	NR	
Mogensen et al. 2025 (29)	OT	25	47.33±16.30	[6/19]	2	NR	2	7	16	Sniffin Sticks extended TDI test, and NRS
	Control	24	48±27	[8/16]	2	NR	4	8	12	
Paranhos et al. 2025 (32)	OT	70	45.9±12.4	[16/54]	1	5	20	50	10	CCCRC
	Control	44	47.3±13.1	[15/29]	0	2	13	21	2	
Serrano et al. 2025 (30)	OT	68	38.03±10.67	[21/47]	2	4	24	99	NR	CCCRC, QOD-NS, and VAS
	Control	55	37.13±7.93	[10/45]	3	2			NR	
Taheri et al. 2024 (31)	OT	30	42.26±10.98	[14/16]	3	3	9	21	3	UPSIT
	Control	30	40.40±11.84	[14/16]	2	2	21	9	1	

NR: Not reported, DM: Diabetes mellitus, OT: Olfactory training, n: Number, OD: Olfactory dysfunction, UPSIT: University of Pennsylvania Smell Identification Test, CCCRC: Connecticut Chemosensory Clinical Research Center olfactory test, QOD-NS: Brief version of the questionnaire of olfactory disorders-negative statements, VAS: Visual analogue scale, TDI: Threshold, discrimination, identification, NRS: Numeric rating scale, BSIT: Brief smell identification test, TIBSIT: Top international biotech smell identification test, eODQ: English Olfactory Disorder Questionnaire, SQOD-NS: Shortened questionnaire of olfactory disorders-negative statements, QOD: Questionnaire for olfactory disorders, BTT: Butanol threshold test, SIT: Smell identification test, NOSE: Nasal obstruction symptom evaluation

However, these findings should be interpreted with caution.

Our rigorous analysis showed significant improvements in objective smell tests. The mechanism of this improvement arises from the distinct pathophysiology of COVID-19 and the olfactory system's restorative potential. The primary target of SARS-CoV-2 infection in the olfactory epithelium differs from that of other respiratory viruses, as it infects non-neuronal support cells that possess ACE2 receptors, thereby minimizing direct viral damage to OSNs (8). The resulting inflammatory cascade and damage to support cells lead to a secondary, non-cell-autonomous disruption of OSN function, including the loss of cilia and downregulation of odorant receptor genes (8).

OT, involving structured, repetitive exposure to odors, is proposed as a targeted neurorehabilitation method. Peripheral stimulation is thought to promote the regeneration of the damaged olfactory neuroepithelium; this is achieved by activating basal stem cells and guiding the maturation of new OSNs (34). Centrally, the consistent sensory input drives neuroplastic changes. Neuroimaging studies suggest that OT induces structural and functional changes in olfactory pathways, enhancing odor processing (35). Therefore, the olfactory improvements observed are likely attributable to a confluence of peripheral tissue regeneration and central neural plasticity.

Furthermore, our analysis showed a substantial improvement in QoL. Considerable evidence confirms the profoundly debilitating impact of OD on activities of daily living (5). COVID-19-related OD has a significant impact on daily functioning, including nutrition, safety, and psychosocial well-being (5,14). Impaired gustatory perception may result in nutritional deficiencies or poor dietary habits, while an inability to detect hazards such as smoke, gas leaks, or spoiled food presents a significant safety concern (13). Restoration of olfactory function through OT may improve these domains and reduce associated psychological distress (36). OT directly ameliorates these deficits by restoring, even

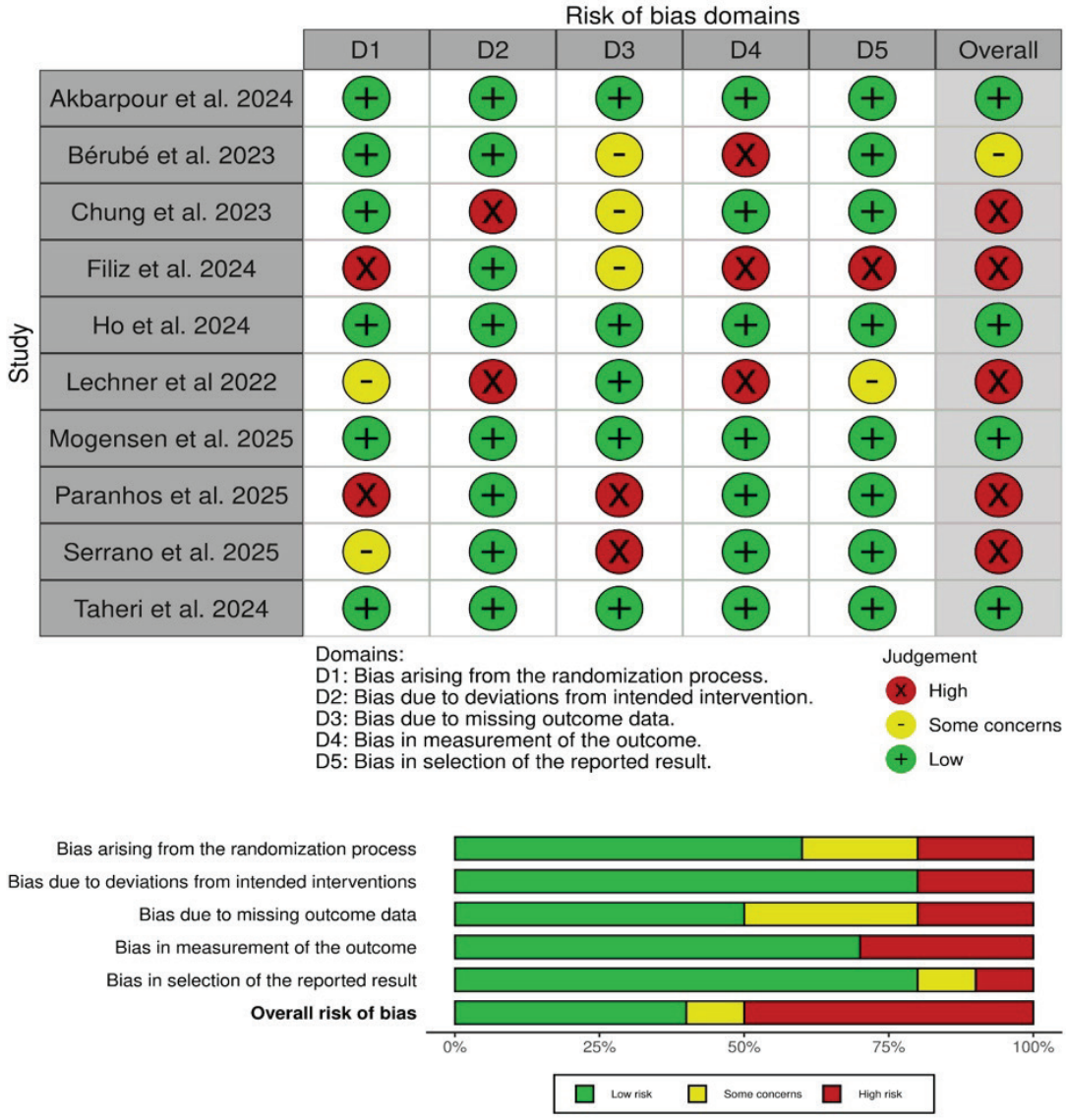

Figure 2. Risk of bias graph and summary of the included randomized controlled trials. The upper panel presents a schematic representation of risks (low=green, some concerns=yellow, and high=red) for specific types of biases of each study in the review. The lower panel presents risks (low=green, some concerns=yellow, and high=red) for the subtypes of biases of the combination of studies included in this review

if partially, olfactory function. Recovery of the sense of smell can lead to renewed enjoyment of food, a restored sense of safety, and improved social confidence, consequently reducing related psychological distress (37).

Moreover, a significant advantage of OT is its remarkably safe profile. Unlike pharmacological interventions, this non-invasive, non-pharmacological approach avoids systemic side effects (38). Neither the trials included in this study nor broader research have shown any significant adverse side effects from smelling essential oils as administered in OT protocols (39). The excellent safety profile supports its suitability as a first-line treatment for persistent post-COVID-OD. Still, the primary challenge associated with OT is not safety, but rather patient adherence, as data from real-world settings and clinical trials reveal poor adherence (17). Non-adherence remains a challenge, with patients either discontinuing early after partial improvement or abandoning therapy due to perceived lack of benefit (40). The dose-dependent nature of OT's benefits, coupled with the need for prolonged treatment (often 12 weeks or longer) to see results, means that poor adherence significantly hinders its

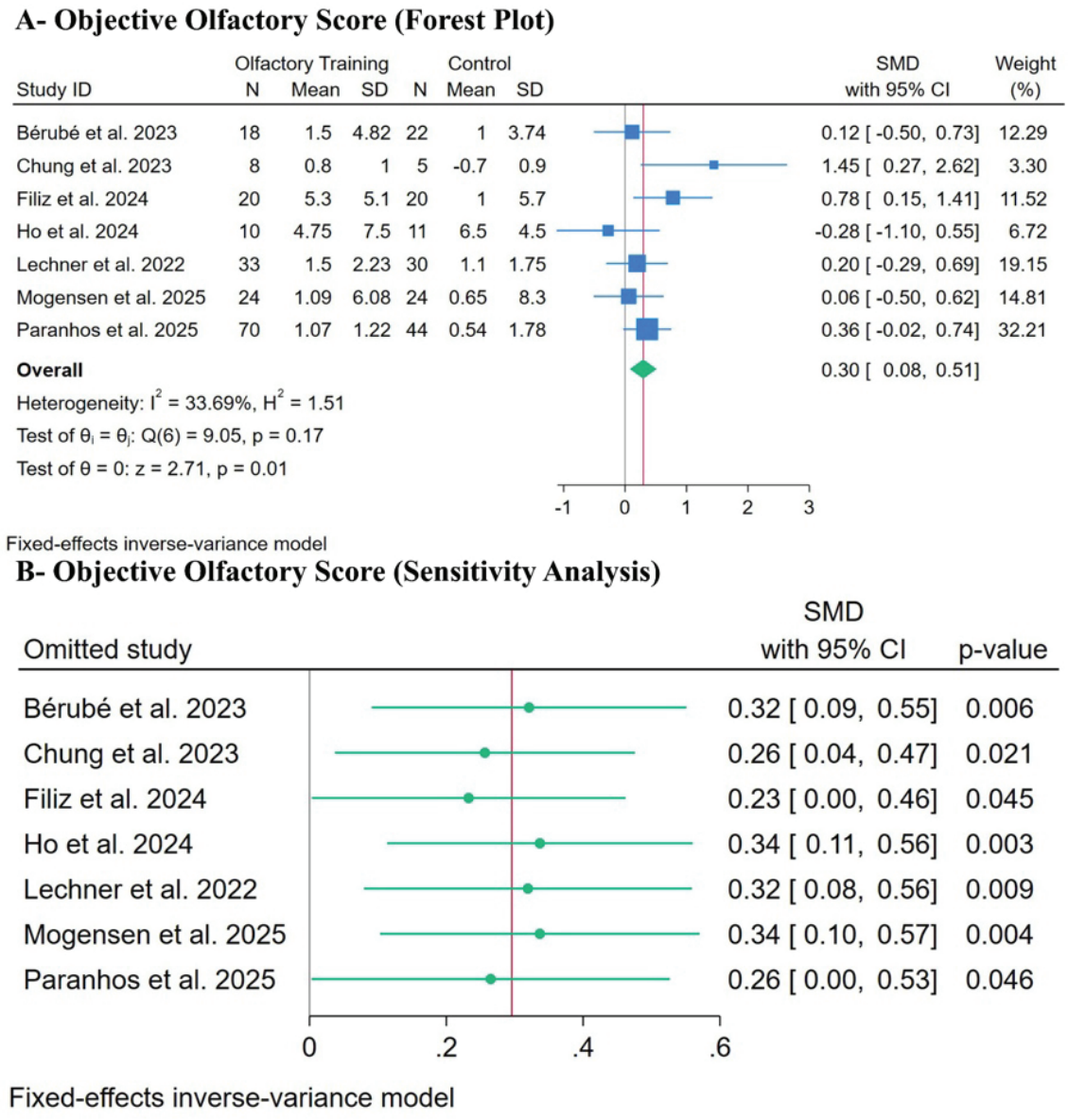

Figure 3. Forest plot and leave-one-out sensitivity analysis of objective olfactory score
SMD: Standardized mean difference, CI: Confidence interval, SD: Standard deviation

real-world efficacy and likely contributes to the small effect sizes reported in certain studies (41).

Study Limitations

This review has several limitations, largely related to the included studies. First, several of the included RCTs had methodological limitations, which may affect the reliability of the estimated effect size. Second, the scores used for olfactory function and QoL varied among the included trials; however, we addressed this limitation by implementing the SMD. Third, there is substantial clinical heterogeneity in the OT protocols employed in the included trials. The studies revealed significant heterogeneity in OT protocols, including duration (ranging from 4 to more than 24 weeks),

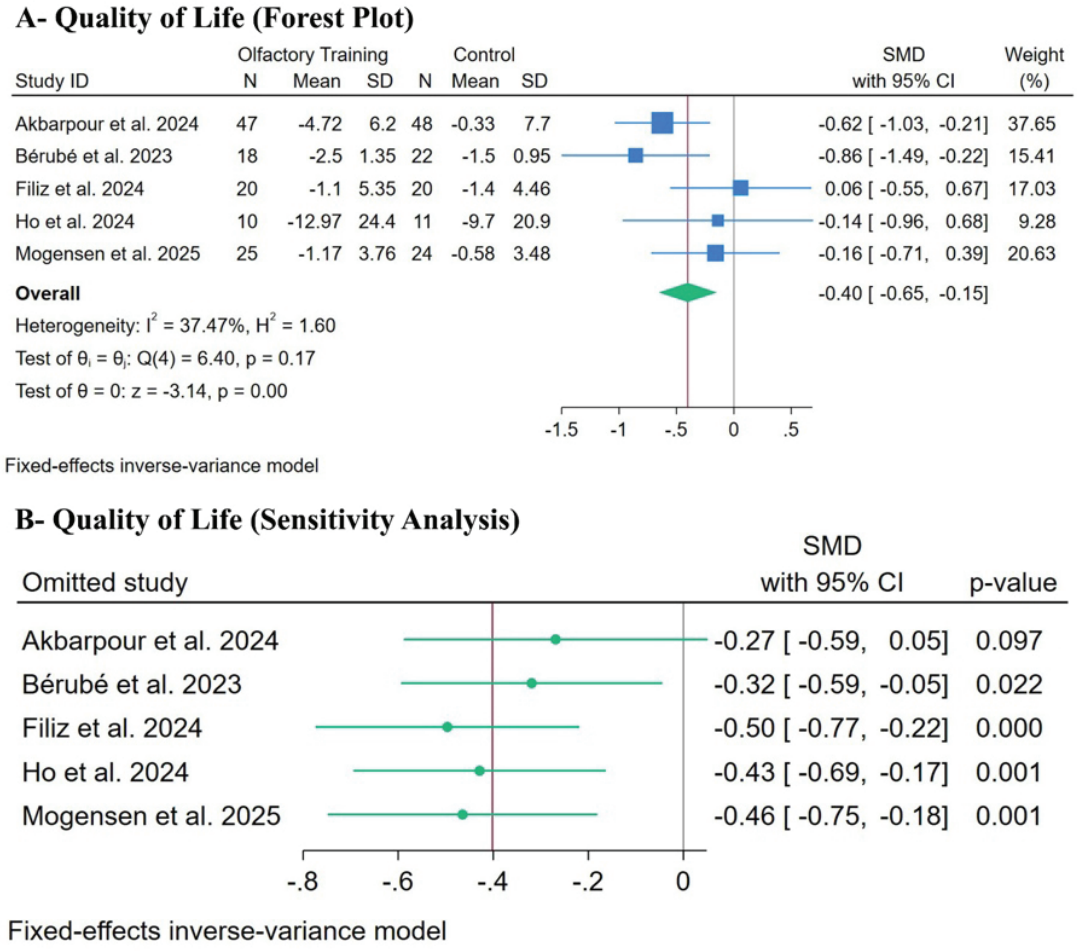

Figure 4. Forest plot and leave-one-out sensitivity analysis of quality of life
SMD: Standardized mean difference, CI: Confidence interval, SD: Standard deviation

the types of odorants used, and the delivery methods employed. The absence of a standardized protocol hinders the recommendation of a definitive, optimized OT protocol, potentially obscuring OT's true potential. Finally, a formal assessment of publication bias was not possible given the limited number of studies per outcome (<10).

Conclusion

OT significantly improved objective olfactory function and QoL in patients with COVID-OD. However, the current evidence should be interpreted with caution due to heterogeneity in OT protocols and the variability among the included studies. Therefore, the development of conclusive, evidence-based clinical practice guidelines urgently requires future research focusing on large-scale, rigorously designed, and standardized RCTs.

Footnotes

Authorship Contributions

Concept: E.A., G.A., M.A., A.H.A., A.A., Design: E.A., A.A., Data Collection and/or Processing: E.A., G.A., M.A., A.H.A., Analysis or Interpretation: E.A., G.A., M.A., Literature Search: E.A., G.A., A.H.A., A.A., Writing: E.A., G.A., M.A., A.H.A., A.A.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: The authors declare that this study has received no financial support.

Main Points

- Olfactory training (OT) has emerged as a leading, non-invasive therapeutic strategy.
- This systematic review and meta-analysis study aims to critically synthesize the current evidence from randomized controlled trials (RCTs) on the efficacy of OT for the treatment of coronavirus disease (COVID)-olfactory dysfunction (OD).
- OT significantly improves objective olfactory function and quality of life in patients with COVID-OD.
- However, these findings should be interpreted with caution due to the heterogeneity of the OT protocols and the variability among the included studies.
- Future large-scale, rigorously designed RCTs with standardized OT protocols are necessary to establish definitive clinical practice guidelines.

Tables S1-2: https://d2v96fxpocvxx.cloudfront.net/d363ec1e-9e5e-4591-a00a-d656bfcabb80/content-images/bb7f969c-6ee8-4379-9c2c-3668dd27cf13.pdf

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Systematic Review

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Predisposing Factors for Congenital Hearing Loss: A Comprehensive Systematic Review

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Abstract

This systematic review aimed to assess and integrate research on risk factors for congenital hearing loss (CHL), emphasizing genetic, infectious, perinatal, environmental, and sociodemographic influences. The review was prospectively registered with PROSPERO (CRD42022372879) and conducted according to PRISMA 2020 and PRISMA-S guidelines. A comprehensive search was performed across PubMed, Embase, Scopus, and Google Scholar using MeSH terms and free-text keywords related to CHL and its risk factors. Observational studies (cohort, case-control, cross-sectional) involving children with CHL and assessing genetic, infectious, perinatal, or environmental exposures were included. Data extraction was done independently by two reviewers, covering study characteristics, diagnostic methods, and measures of association (odds ratio, relative risk). Risk of bias was evaluated using the Newcastle-Ottawa scale for cohort/case-control studies and the Joanna Briggs Institute checklist for cross-sectional studies. Genetic factors such as *GJB2* mutations, a positive family history, and consanguinity were consistently associated with CHL. Infectious etiologies, particularly congenital cytomegalovirus, were prominent across studies, with TORCH infections also commonly implicated. Perinatal risk factors, including neonatal intensive care unit admission, low birth weight, and hyperbilirubinemia, were frequently reported in affected children. Environmental exposures, especially to ototoxic medications, were noted as significant contributors, often acting synergistically with other risk factors like infections or genetic conditions. Sensorineural hearing loss, predominantly bilateral, emerged as the most common type reported. CHL is a multifactorial condition, with genetic and infectious causes being most prevalent. Targeted screening and preventive strategies addressing these risk domains are crucial for early detection and management.

Keywords: Congenital, hearing loss, genetic predisposition to disease, congenital infections, infant, newborn, diseases, ototoxicity, environmental exposure

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Introduction

Congenital hearing loss (CHL) is a critical neurodevelopmental condition that can profoundly impact a child's overall growth, particularly in areas such as speech, language acquisition, cognitive functioning, emotional regulation, and academic achievement (1-5). The absence of adequate auditory input during early life stages disrupts foundational language development, often leading to delays in literacy, educational performance, and social-emotional skills compared to peers with normal hearing (6-10). For decades, research has established a link between certain risk factors and permanent childhood hearing loss, informing early screening and intervention efforts.

On a global scale, hearing loss is emerging as a growing public health concern. According to the global burden of disease study, hearing loss prevalence increased from 1.2 billion

people (17.2%) in 2008 to 1.4 billion (18.7%) by 2017, highlighting the escalating issue (6). The World Health Organization ranks hearing loss as the third leading cause of disability-related years lost, with 39.5 million years of healthy life lost in 2017, up from 27 million in 2000, highlighting its substantial impact (6). In India, estimates suggest that childhood hearing loss affects 6.6% to 16.47% of children, with incidence among high-risk newborns ranging from 7 to 49.18 per 1000 live births, highlighting a significant public health concern (6). Although middle ear infections like otitis media remain a major postnatal cause, congenital origins are increasingly recognized as significant contributors to childhood hearing loss (11-16).

The landscape of childhood hearing loss has evolved considerably. Improvements in vaccination programs and infectious disease control have reduced hearing loss related to post-infectious complications like meningitis (15). Simultaneously, advancements in neonatal care have improved survival rates among preterm and low birth weight infants, who, however, are more susceptible to sensorineural hearing damage due to risk factors like oxygen deprivation, elevated bilirubin levels, and exposure to ototoxic drugs (16,17). At the same time, advances in genetic testing have enabled clinicians to detect a wide range of genetic abnormalities, both syndromic and non-syndromic, responsible for CHL, highlighting the growing importance of hereditary causes.

Considering these trends, identifying CHL risk factors is crucial for effective newborn hearing screening, prevention, and early intervention. This systematic review examines the existing literature on CHL risk factors, including genetic, perinatal, environmental, and sociodemographic aspects, to inform evidence-based practice and guide public health decisions in neonatal auditory care.

Methodology

Research Question

What are the determinants or risk factors for CHL? Which is more prevalent—genetic predisposition or infectious causes?

This systematic review was registered on PROSPERO and approved under the registration number CRD42022372879 and conducted following the PRISMA 2020 and PRISMA-S (search extension) guidelines to ensure methodological transparency and reproducibility.

PICO Statement

Population (P): Children with permanent bilateral or unilateral CHL.

Intervention/Exposure (I/E): Exposure to risk factors potentially associated with CHL, including:

- Genetic factors (e.g., family history, syndromes)
- Infectious causes [e.g., congenital cytomegalovirus (cCMV), TORCH infections]
- Perinatal factors [e.g., low birth weight, Neonatal Intensive care unit (NICU) stay, hyperbilirubinemia, ototoxic drugs]
- Environmental and structural factors (e.g., craniofacial anomalies).

Comparison (C):

- Children without the identified risk factors
- Comparisons across different categories of risk factors (e.g., genetic vs. infectious).

Outcome (O):

- Diagnosis of CHL
- Measures of association such as odds ratios (ORs), relative risks (RRs), or other statistical indicators reflecting the strength of association between risk factors and hearing loss

Search Strategy

A thorough and systematic search of the literature was undertaken to identify the studies exploring the relationship between various risk factors and CHL in children. Multiple databases, PubMed/MEDLINE, PubMed Central, Google Scholar, Embase, and Scopus, were searched using a structured strategy combining Medical Subject Headings (MeSH) and free-text keywords related to CHL, its potential etiological factors, and study design types. Key terms included "congenital hearing loss," "sensorineural hearing loss," "unilateral hearing loss," "genetic predisposition," "family history," "syndromic hearing loss," "TORCH infections," "cytomegalovirus," "rubella," "toxoplasmosis," "perinatal complications," "NICU," "low birth weight," "hyperbilirubinemia," "ototoxic drugs," and "craniofacial anomalies," linked using Boolean operators (and, or) to enhance search precision.

Search filters were set to include only human studies published in English. Only observational studies, including cohort, case-control, and cross-sectional designs, were considered eligible. Interventional studies, case reports, editorials, and narrative reviews were excluded. The inclusion criteria comprised studies evaluating risk factors or determinants of CHL in children. Two reviewers independently screened the titles and the abstracts, and any discrepancies were resolved by discussion or with adjudication by a third reviewer. The search was ended in April 2025.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized, pre-tested extraction form to ensure consistency and reliability. For each eligible study, comprehensive details were systematically documented,

including the first author's name, year of publication, study design, geographical location, sample size, population characteristics, and the specific risk factors investigated. Extracted variables encompassed the type and laterality of CHL (e.g., unilateral, bilateral, sensorineural, or mixed), diagnostic modalities used [such as otoacoustic emissions (OAE) or auditory brainstem response (ABR)], and associations with potential determinants including genetic factors, TORCH infections, perinatal complications, environmental exposures, and consanguinity.

Effect estimates—such as ORs, RRs, confidence intervals, and p-values—were recorded when available to support quantitative synthesis. Any discrepancies arising between reviewers during data extraction were resolved through discussion or adjudication by a third reviewer. All extracted data underwent cross-checking and verification to ensure completeness and accuracy before being synthesized for analysis.

Risk of Bias and Quality Assessment

The Newcastle-Ottawa scale (NOS) was applied to evaluate the quality of cohort and case-control studies, while the Joanna Briggs Institute (JBI) critical appraisal checklist was used for cross-sectional studies. Domains assessed included sample selection, comparability, outcome measurement, and confounding control. Each study was rated as low, moderate, or high risk of bias. No studies were excluded based on quality alone, but methodological limitations were considered during synthesis (Table 1).

Data Analysis

Given the heterogeneity in study designs, populations, and reported outcomes, a meta-analysis was not feasible. Therefore, results were synthesized qualitatively, focusing on the magnitude and consistency of reported associations across different etiological categories.

Results

A total of 17 studies were included in this systematic review, encompassing a wide range of geographic regions, including South Africa, Belgium, Brazil, Sweden, Australia, Iran, India, Japan, Italy, Colombia, the United States, and the United Kingdom. Study designs comprised retrospective cohorts, prospective cohorts, cross-sectional surveys, and case-control studies, with sample sizes ranging from 24 to over 613,000 participants. The age of the participants varied from newborns to children up to 14 years. The review revealed consistent associations of CHL with genetic factors such as *GJB2* mutations, family history, and consanguinity; infectious causes like cCMV and TORCH infections; perinatal risk factors including NICU admission, low birth weight, and hyperbilirubinemia; and environmental exposures such as ototoxic medications. Multiple studies also highlighted the synergistic effects of combined risk factors (e.g., genetic susceptibility and CMV infection). These findings underscore the multifactorial etiology of CHL and the importance of integrated early screening and risk stratification (Figure 1).

Genetic Factors

Genetic contributions to CHL were highlighted in several studies. Khan and Joseph (17) identified *GJB2* mutations (notably 35delG) in 22.1% of their cases. Niu et al. (18) reported syndromic causes in 37.2%, chromosomal anomalies in 21.3%, and *GJB2*-related and X-linked mutations in 8.5% and 1%, respectively. Anastasio et al. (19) also found chromosomal aberrations significantly associated with hearing loss (OR: 4.95). Foulon et al. (20) confirmed a strong association between craniofacial anomalies or syndromes and hearing loss (RR: 24.47), especially when multiple risk factors coexisted. Additionally, Satterfield-Nash et al. (21) noted family history as a major risk factor (OR: 11.47), with consanguinity increasing the risk even further (OR: 12.48) (Table 1).

Infectious Causes

cCMV was the most frequently identified infectious etiology. De Cuyper et al. (22) and Fitzgibbons et al. (23) reported that 100% of their cases had confirmed cCMV infection. Townsend et al. (24) found that 13% of the children with cCMV developed hearing loss. Sabbagh et al. (25) and Verma et al. (6) similarly reported high rates of CMV, followed by rubella, syphilis, toxoplasmosis, and herpes. TORCH infections were frequently included in risk assessments by multiple authors including Umehara et al. (26) and Satterfield-Nash et al. (21), the latter finding congenital infections had an OR of 5.48 for hearing loss (Table 1).

Perinatal Factors

Prematurity, low birth weight, NICU stay, and hyperbilirubinemia emerged as consistent perinatal risk factors. Khan and Joseph (17) observed perinatal risk in 22.1% of their cases. Faistauer et al. (27), Anastasio et al. (19), and Sabbagh et al. (25) reported significant associations with NICU admission, mechanical ventilation, and oxygen use. Satterfield-Nash et al. (21) quantified these risks: NICU stay (OR: 7.21), birth weight <1500 g (OR: 4.40), and bilirubin >10 mg/dL (OR: 5.18). These trends were also supported by findings from Chakrabarti and Ghosh (28) and Fitzgibbons et al. (23) (Table 1).

Environmental Factors

Ototoxic drug exposure, especially to aminoglycosides like gentamicin and amikacin, was a recurring theme. Faistauer et al. (27) and Sabbagh et al. (25) both reported drug-related toxicity in their cohorts, and Satterfield-Nash et al. (21) associated ototoxicity, hypoxia, and fever/seizures with an OR of 3.02. Anastasio et al. (19) found ototoxicity in 45.3% of

their cases, with synergistic effects observed in conjunction with other risk factors such as CMV or syndromes (Table 1).

Other Risk Factors

Additional risk factors included craniofacial anomalies, advanced maternal age, multiple births, and syndromic associations such as Down, Waardenburg, and CHARGE syndromes. Niu et al. (18) and Judge et al. (29) emphasized anatomical abnormalities and caregiver concern. Satterfield-Nash et al. (21) also reported significant associations with seizures, maternal age ≥35 years, and multiparity. Manotas et al. (30) observed a higher prevalence of hearing loss in Muslim populations, possibly linked to sociocultural or genetic clustering (Table 1).

Types of Hearing Loss

Sensorineural hearing loss (SNHL) was the most common type reported across studies, frequently bilateral. Khan and Joseph (17) reported a distribution of 28.5% CHL, 20.1% SNHL, and 7.1% mixed hearing loss. Sabbagh et al. (25) observed 62.5% bilateral and 37.5% unilateral hearing loss. Anastasio et al. (19) noted 75% SNHL and 20.8% auditory neuropathy. Mixed types and conductive hearing loss were reported in fewer studies, such as Niu et al. (18) and Fitzgibbons et al. (23) (Tables 2, 3).

Assessment Method for Hearing Loss

Most studies used objective, standardized methods. Commonly employed tests included OAE, ABR, automated ABR (AABR), auditory steady-state response, tympanometry, and behavioral audiometry. Imaging (computed tomography/magnetic resonance imaging) was occasionally used, as in Faistauer et al. (27) and Judge et al. (29). Townsend et al. (24) also used the Griffiths developmental scale in follow-up assessments. Longitudinal audiological surveillance was adopted in some cohorts [e.g., De Cuyper et al. (22)] (Tables 2, 3).

Timing of Diagnosis/Age at Diagnosis

Timing varied widely. Some studies, such as Townsend et al. (24) and Foulon et al. (20), identified hearing loss by one year of age. Others, like De Cuyper et al. (22) and Sabbagh et al. (25), conducted reassessment at four years or beyond. NICU-based studies like Umehara et al. (26) ensured evaluation before discharge. School-age assessments were seen in Chakrabarti and Ghosh (28) and Judge et al. (29), while Faistauer et al. (27) noted an average diagnosis age of two years (Tables 2, 3).

Prevalence and Associations

The most consistent risk factors across studies were genetic mutations (*GJB2*, syndromic anomalies), cCMV and TORCH infections, perinatal complications (NICU stay, low birth weight, hyperbilirubinemia), and ototoxic drug exposure.

Reported pooled ranges:

- Genetic/family history: OR: 4.0-12.5
- cCMV infection: OR: 5.0-10.3
- NICU admission: OR: 6.8-7.2
- Hyperbilirubinemia: OR: 4.5-5.2
- Ototoxic exposure: OR: 3.0-4.2

These trends were consistent with recent large-scale analyses, such as by Sökmen et al. (31) and Han et al. (32), which identified NICU admission >5 days, ototoxic drug use, and consanguinity as leading risk factors for CHL.

Discussion

Our systematic review demonstrates that CHL is a multifactorial condition influenced by a combination of genetic, infectious, perinatal, environmental, and other clinical and demographic risk factors. Genetic contributions were reported in seven studies, with common findings including syndromic and chromosomal abnormalities as well as non-syndromic mutations such as those in the *GJB2* gene. Family history and consanguineous marriage were also significant predictors of CHL. Infectious etiologies were highlighted in eight studies, with cCMV being the most frequently reported cause, followed by other TORCH infections such as toxoplasmosis, rubella, syphilis, and herpes.

Perinatal risk factors were consistently highlighted across nine studies and included conditions such as prematurity, low birth weight, NICU admission, use of mechanical ventilation, and hyperbilirubinemia, all of which were significantly associated with a higher likelihood of developing hearing loss. Environmental exposures were explored in five studies, with ototoxic agents like aminoglycosides frequently identified as key contributors, often acting in combination with infections or inherited susceptibilities. Additional determinants reported in six studies included craniofacial abnormalities, syndromic features, advanced maternal age, multiple births, and socioeconomic or cultural factors. SNHL emerged as the predominant type, typically bilateral, although some studies also documented mixed or conductive variants. These findings emphasize the critical importance of early risk identification and reinforce the need for universal newborn hearing screening programs coupled with targeted follow-up for infants with known risk factors.

Our findings align closely with recent meta-analyses and systematic reviews, including those by Sökmen et al. (31), Han et al. (32) and Fernández-Rueda et al. (33) which revealed NICU stay, ototoxic exposure, and hyperbilirubinemia as

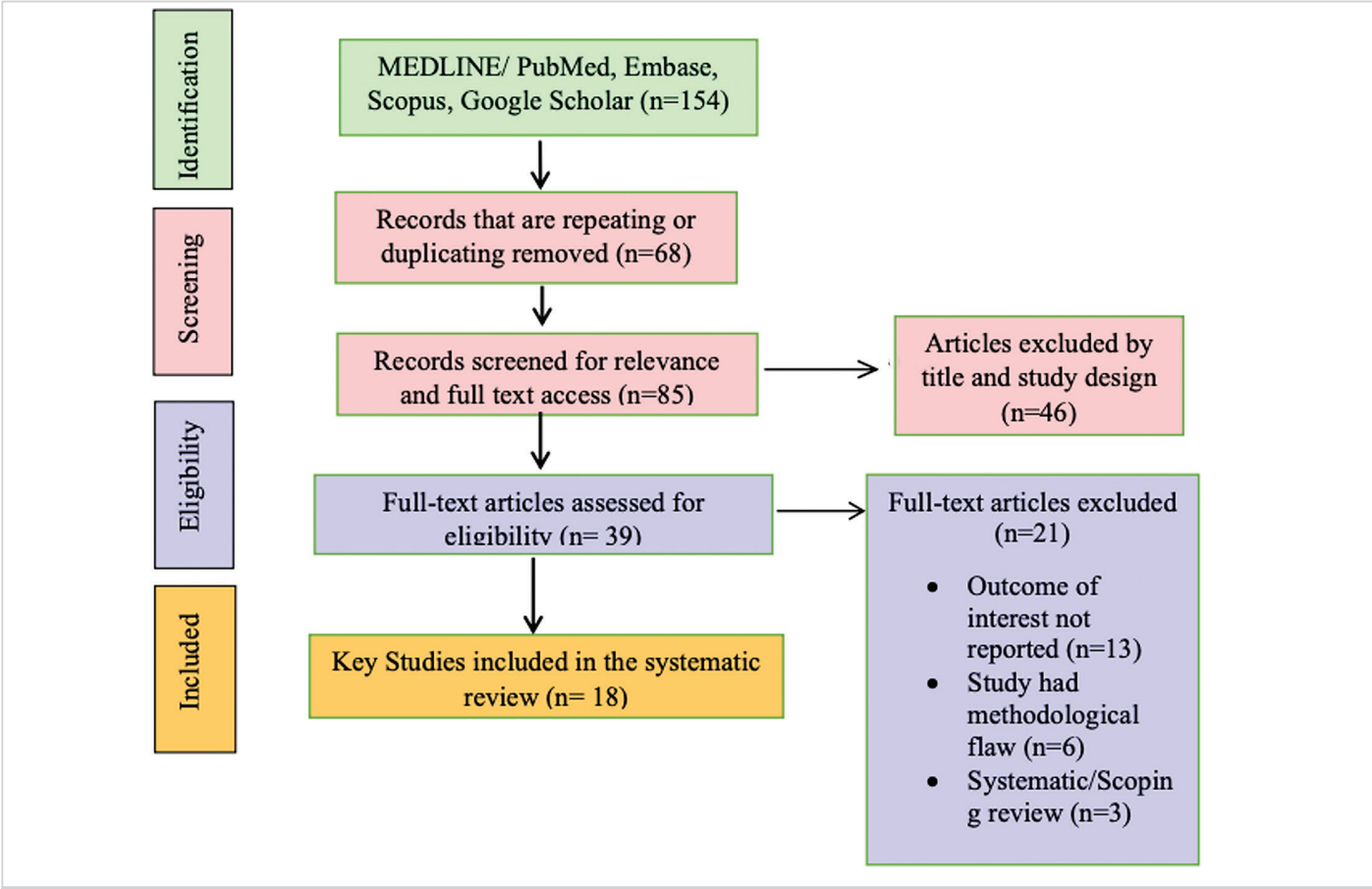

Figure 1. PRISMA flowchart detailing results of literature search and study screening of research studies

consistent determinants of hearing loss in infants. The most frequent genetic contributors were *GJB2* and syndromic mutations, particularly among consanguineous populations (e.g., Iran, India, and Türkiye). Infectious causes, notably cCMV, accounted for up to 32% of the cases, emphasizing the importance of CMV screening within neonatal protocols. Perinatal and environmental factors, such as prematurity, prolonged ventilation, and aminoglycoside use, acted both independently and synergistically with genetic susceptibilities. This convergence supports the concept of gene-environment interaction in CHL pathogenesis (34,35).

Compared to earlier systematic reviews, our review incorporated more recent global datasets (2023-2025) that broaden the contextual understanding of CHL determinants (36-38). For instance, Sökmen et al. (31) highlighted NICU admission, mechanical ventilation >5 days, hyperbilirubinemia requiring exchange transfusion, consanguinity, and family history as the most prevalent risk factors—findings echoed in our analysis. Han et al. (32) provided pooled estimates supporting similar risk magnitudes, strengthening the external validity of these associations.

Verma et al. (6) included 29 studies in their systematic review spanning 1980 to 2020, examining prevalence patterns of hearing loss in neonates, children, and adults. The review identified syndromes and craniofacial anomalies as major genetic contributors, while CMV and other TORCH infections were prominent infectious causes. Perinatal factors frequently cited were NICU stay, low birth weight, mechanical ventilation, and hyperbilirubinemia. Although environmental and consanguinity factors were not extensively detailed, the study highlighted other contributors such as rural residence, advanced age, and limited awareness. The types of hearing loss varied, with SNHL prevalent in children and conductive loss due to otitis media noted in older age groups. Diagnostic approaches included OAE, AABR, ABR, tuning fork tests, and pure tone audiometry, with comparisons made across age brackets and rural vs. urban populations.

Satterfield-Nash et al.'s (21) scoping review across multiple countries focused on children aged under two years and identified through universal newborn hearing screening cohorts. Among 1787 children evaluated for underlying causes, genetic testing was conducted in 933 cases, with attribution rates ranging from 7.7% to 83.3%. CMV testing

was performed in 1021 cases, with causation attributed in 0-32%. While perinatal and environmental factors were not systematically examined, and data on consanguinity were absent, the review offered a comparative perspective on genetic versus CMV-related etiologies. All cases involved SNHL, diagnosed via OAE, ABR, dried blood spot testing, or saliva polymerase chain reaction, generally before two years of age. The importance of differentiating congenital from delayed-onset cases within this age window was emphasized.

Vos et al. (9) developed a systematic review and meta-analysis protocol targeting the identification of permanent unilateral or bilateral hearing loss in individuals aged from birth to 18 years. Although sample size was not specified, inclusion required clearly defined hearing loss and its associated risk factors. Temporary losses, case reports, and gray literature were excluded. The protocol accounted for genetic syndromes, infections like cCMV, meningitis, and toxoplasmosis, and perinatal risks such as NICU stay, hyperbilirubinemia, and ototoxic drug exposure. Environmental exposures were included only if they led to permanent auditory damage. Factors like consanguinity and family history were incorporated when available, along with other contributors like pediatric malignancies. Types of hearing loss included sensorineural, auditory neuropathy, mixed, and permanent conductive loss. Audiologist-confirmed diagnosis was mandatory, excluding cases detected solely by automated tools. Timing of diagnosis was categorized as early-onset (<3 months) or late-onset (>3 months), with comparisons between children with and without specific risk exposures.

Future investigations on CHL should adopt a standardized, multidisciplinary framework to better understand the complex interplay of genetic, infectious, perinatal, environmental, and sociodemographic factors. There is a critical need for large-scale, multicenter prospective cohort

Table 1. Risk of bias analysis for the included studies using the NOS or JBI tool as required

First author (year, country)	Study design	Tool used	Selection	Comparability	Outcome/exposure assessment	Total score	Risk level
Khan and Joseph, (2024, South Africa) (17)	Retrospective descriptive cohort	NOS	3/4	1/2	2/3	6/9	Moderate
De Cuyper et al., (2023, Belgium) (22)	Multicenter longitudinal cohort	NOS	4/4	2/2	3/3	9/9	Low
Faistauer et al., (2022, Brazil) (27)	Cross-sectional study nested in retrospective cohort	NOS	3/4	1/2	2/3	6/9	Moderate
Afshar et al., (2022, Sweden) (34)	Multicenter case-control study (400 cases, 200 controls)	NOS	4/4	2/2	2/3	8/9	Low
Zizlavsky et al., (2022, Indonesia) (37)	Cross-sectional multicenter study	NOS	4/4	2/2	2/3	8/9	Low
Fitzgibbons et al., (2021, Australia) (23)	Population-based retrospective cohort (UNHS database, Queensland)	NOS	4/4	2/2	2/3	8/9	Low
Sabbagh et al., (2021, Iran) (25)	Analytical case-control, population-based neonatal screening	NOS	4/4	2/2	2/3	8/9	Low
Anastasio et al., (2021, Brazil) (19)	Prospective cohort study	NOS	4/4	2/2	2/3	8/9	Low
Niu et al., (2020, Sweden & China) (18)	Retrospective cohort review	NOS	4/4	2/2	2/3	8/9	Low
Umehara et al., (2019, Japan) (26)	Retrospective observational cohort	NOS	3/4	2/2	2/3	7/9	Moderate
Chakrabarti and Ghosh, (2019, India) (28)	Stratified cross-sectional school-based study	NOS	4/4	2/2	2/3	8/9	Low
Foulon et al., (2019, Belgium) (20)	Prospective cohort	NOS	4/4	2/2	2/3	8/9	Low
Palma et al., (2025, Italy) (35)	Retrospective cohort	NOS	3/4	2/2	2/3	7/9	Moderate
Parab et al., (2018, India) (38)	Prospective non-randomized clinical study	NOS	4/4	2/2	2/3	8/9	Low
Barbi et al., (2006, Italy) (7)	Retrospective observational cohort	NOS	3/4	2/2	2/3	7/9	Moderate

NOS: Newcastle-Ottawa scale, JBI: Joanna Briggs Institute, UNHS: Universal newborn hearing screening

studies utilizing consistent CHL definitions and clearly specifying onset, severity, and classification of hearing loss to improve data comparability across different populations. Incorporating genetic testing into diagnostic protocols, particularly in regions with high consanguinity rates, is essential to identify prevalent mutations, syndromic conditions, and guide genetic counseling and prevention efforts.

Research should also delve into gene-environment interactions to explore how genetic susceptibility may influence the impact of perinatal insults or infections such as CMV or ototoxic drug exposure. Additionally, long-term studies are needed to evaluate neurodevelopmental and quality-of-life outcomes in children diagnosed with CHL in early infancy, especially in resource-limited contexts. Comparative studies should assess the cost-effectiveness and outcomes of universal versus targeted newborn hearing screening programs, particularly in countries where implementation remains incomplete. Moreover, research should actively include diverse and underrepresented populations such as rural, low-income, or Indigenous groups who often face limited access to screening and early interventions. Finally, longitudinal follow-up studies evaluating the timing, type, and outcomes of early interventions—including hearing aids, cochlear implants, and speech therapy—are crucial to shaping health policy and optimizing developmental outcomes in children with CHL.

Critical Appraisal

This systematic review is methodologically robust and comprehensive in scope, synthesizing data from 18 observational studies across multiple continents to identify the determinants of CHL. It adheres to the PRISMA 2020 and PRISMA-S guidelines, includes a registered PROSPERO protocol, and employs standardized tools (NOS and JBI checklist) for quality appraisal—enhancing transparency and reproducibility. The clear PICO framework and detailed inclusion criteria lend methodological rigor. By encompassing diverse risk domains, genetic, infectious, perinatal, environmental, and sociodemographic, the review captures the multifactorial nature of CHL and situates its findings within the evolving global landscape of neonatal auditory health.

A major strength of this review lies in its attempt to examine a temporal shift in CHL etiology, exploring whether improved infection control and neonatal care have shifted the burden from infectious to genetic causes. However, this objective was constrained by a lack of high-quality genetic studies, particularly from low- and middle-income countries where access to molecular diagnostics remains limited.

Table 2. Detailed review of studies included in the systematic review

First author (year, country)	Sample size	Age of participants	Genetic factors	Infectious causes	Perinatal factors	Environmental factors	Other risk factors
Khan and Joseph, (2024, South Africa) (17)	1,433 children	Infants and children <12 years	Syndromic: Down's, Usher, Waardenburg, CHARGE	CMV (54%), rubella, syphilis, toxoplasmosis, herpes	Ototoxic medication exposure, recurrent otitis media	All ethnic/ language groups represented	Retrospective data gaps; large multisite cohort
De Cuyper et al., (2023, Belgium) (22)	387 (774 ears)	Newborns to ≥4 years	Not assessed	100% congenital CMV	Prematurity, symptomatic infection predictors	Not discussed	Exclusion of treated cases limits generalizability
Faistauer et al., (2022, Brazil) (27)	140	Up to 12 years (mean 2.0±2.3 yrs)	*GJB2* mutations (22.1%)	CMV 2.9%, syphilis, toxoplasmosis, herpes	Ototoxic exposure	Single-center	Incomplete CMV data, limited representativeness
Afshar et al., (2022, Sweden) (34)	600 (400 cases, 200 controls)	Mean age 8.9 yrs (cases)	Family history (OR=11.47), consanguinity (OR=12.48)	TORCH (OR=5.48), meningitis (OR=4.66)	Ototoxic drugs, hypoxia, seizures	Not specified	Multicenter, robust design
Zizlavsky et al., (2022, Indonesia) (37)	535	Neonates to adolescence (mean 5.5 yrs)	Family history 2-3%	TORCH (17.8%): rubella, toxoplasmosis, herpes	Ototoxic drugs (11.2%), herbal medicine (37.4%)	Herbal exposure during pregnancy	Lower maternal education → delayed diagnosis
Fitzgibbons et al., (2021, Australia) (23)	6,735 infants (from 613,027 screened)	Newborns to early infancy (screened at birth)	Family history of PCHL; syndromic associations with PCHL	Not reported	Craniofacial anomalies	None reported	Female gender; non-Indigenous status; bilateral refer result on newborn hearing screening

Table 2. Continued

First author (year, country)	Sample size	Age of participants	Genetic factors	Infectious causes	Perinatal factors	Environmental factors	Other risk factors
Sabbagh et al., (2021, Iran) (25)	5,500 newborns	3-14 days	Consanguineous marriage of parents	Not reported	Low gestational age (<35 weeks); low birth weight; hyperbilirubinemia; NICU stay; craniofacial anomalies; exposure to ototoxic drugs	None reported	Gestational diabetes; convulsions
Anastasio et al., (2021, Brazil) (19)	11,900 neonates	Newborns (1-215 days)	Craniofacial anomalies/ syndromes (RR=24.47)	Congenital CMV (RR=9.54)	Ototoxic exposure synergistic with infection	Public hospitals	Strong infection-screening link
Niu et al., (2020, Sweden & China) (18)	296 children (221 BHL, 75 UHL)	Mean 13.2±14.3 months	Family history (59 cases); syndromic and chromosomal abnormalities (37.2% and 21.3% of BHL cases)	Congenital CMV and other perinatal infections (minor proportion)	Low birth weight; neonatal complications; NICU admission	Environmental causes (19.1% of BHL; 14.3% of UHL)	Craniofacial anomalies (30.7% of UHL); oxygen therapy; ear malformations (74.3% of UHL)
Umehara et al., (2019, Japan) (26)	1,071 high-risk infants in NICU; 148 had ABR ≥40 dB	Before NICU discharge (1-33 weeks post-delivery)	Oxygen administration; chromosomal aberrations	Perinatal hypoxia	NICU-related complications	Not reported	Among 148 with abnormal ABR, 102 improved, 5 deteriorated, rest unchanged
Chakrabarti and Ghosh, (2019, India) (28)	10,763	6-14 years (school-aged children)	Not detailed	Not analyzed	Not specified	Not discussed	Higher prevalence in Muslim children—suggesting influence of consanguinity and socioeconomic disparities
Foulon et al., (2019, Belgium) (20)	Not specified	Newborns to 4 years	Not assessed	Congenital CMV (symptomatic vs. asymptomatic)	First-trimester maternal infection, prematurity	Not reported	Symptomatic vs. asymptomatic subgroups; maternal infection timing
Palma et al., (2019, Italy) (35)	45 infants (6 HL cases =13.3%)	Neonatal to 8 years	Not assessed	Congenital vs. acquired CMV	Not discussed	Not reported	Before vs. after neonatal hearing screening
Manotas et al., (2019, Colombia) (30)	Not specified	At birth	Not discussed	Not detailed	Not specified	Not reported	Cases with hearing/ visual defects vs. controls
Parab et al., (2018, India) (38)	5,500 newborns	3-14 days	Not discussed	Not specified	Low birth weight, prematurity, hyperbilirubinemia	Not reported	Failed vs. passed newborn screening
Townsend et al., (2013, United Kingdom) (24)	176 CMV, 214 controls	Newborns-5 years	Not studied	Congenital CMV	Not discussed	Not reported	Symptomatic vs. asymptomatic CMV; maternal infection types

HL: Hearing loss, BHL: Bilateral HL, UHL: Unilateral HL, NICU: Neonatal intensive care unit, ABR: Auditory brainstem response, CMV: Cytomegalovirus, OR: Odds ratio, PCHL: Permanent childhood hearing loss, RR: Relative risks

Table 3. Detailed review of studies included in the systematic review (extended)

First author (year, country)	Type of hearing loss	Assessment method for hearing loss	Timing of diagnosis/age at diagnosis	Comparison groups
Khan and Joseph, (2024, South Africa) (17)	CHL (28.5%), SNHL (20.1%), MHL (7.1%)	ABR, OAE, audiometry, tympanometry, case history	Retrospective; age range not precisely detailed in diagnosis	Hearing loss types vs. risk factors; odds ratios used
De Cuyper et al., (2023, Belgium) (22)	SNHL	ABR, audiometry; hearing tracked until ≥4 years	At birth and reassessed at ≥4 years	Improved vs. stable/ deteriorated; with vs. without late-onset HL
Faistauer et al., (2022, Brazil) (27)	Sensorineural or mixed; bilateral	OAE, ABR, audiometry	At first visit, mean age 2 yrs	Etiological categories (e.g., genetic vs. CMV)
Afshar et al., (2022, Sweden) (34)	Severe/profound sensorineural HL	Audiological assessment and medical records (unspecified)	Diagnosed before cochlear implantation (not age-specified)	Cases (HL) vs. Controls (no HL)
Zizlavsky et al., (2022, Indonesia) (37)	Sensorineural, conductive, and mixed types across neonates to adolescents	Audiometry, tympanometry, otoscopic and clinical evaluation; TORCH serology	Neonates to adolescence (mean age 5.5 years)	Children with vs. without identifiable risk factors (family history, TORCH infections, ototoxic drugs, herbal exposure, low maternal education)
Fitzgibbons et al., (2021, Australia) (23)	Sensorineural, conductive, mixed, ANSD	OAE, ABR, tympanometry, ASSR	Within first few weeks after referral	With vs. without risk factors; bilateral vs. unilateral refer; by risk factor
Sabbagh et al., (2021, Iran) (25)	62.5% bilateral, 37.5% unilateral; mostly right-sided	TEOAE, AABR, diagnostic ABR, ASSR, tympanometry	Post-screening at 3-14 days, confirmed via ABR	Cases (refer group) vs. controls (pass group)
Anastasio et al., (2021, Brazil) (19)	Sensorineural (75%), auditory neuropathy (20.8%), 1 conductive	OAE, AABR, diagnostic ABR, immittance, tone-ABR	Confirmed at median age of 115 days (range 22-361)	Low vs. high-risk; isolated vs combined risk factors
Niu et al., (2020, Sweden & China) (18)	SNHL, CHL, Mixed (BHL and UHL analyzed separately)	ABR, ASSR, audiometry, OAE, tympanometry, imaging	Mean 13.2±14.3 months	BHL vs. UHL risk factors and etiologies
Umehara et al., (2019, Japan) (26)	Sensorineural HL (uni- or bilateral)	Auditory Brainstem Response (ABR)	Before NICU discharge (1-33 weeks after delivery)	Improved vs. deteriorated vs. unchanged ABR threshold
Chakrabarti and Ghosh, (2019, India) (28)	Sensorineural hearing loss (severe/profound); higher prevalence in Muslim children	Pure tone audiometry, otoscopy, impedance testing	Diagnosed during school assessment (age 6-14)	None specified
Foulon et al., (2019, Belgium) (20)	Sensorineural hearing loss (unilateral and bilateral)	OAE, ABR, tympanometry, follow-up tests up to 4 years	Within 2 weeks of birth; follow-up until age 4	Symptomatic vs. asymptomatic; maternal infection timings
Palma et al., (2019, Italy) (35)	Sensorineural HL; 6/45 had HL (13%) bilateral & unilateral	TEOAE, ABR, audiological surveillance	Within first weeks; follow-up to 8 years	cCMV vs. aCMV; before vs after neonatal hearing screening
Manotas et al., (2019, Colombia) (30)	Sensorineural or conductive (e.g., microtia); detailed breakdown not provided	Clinical diagnosis and coding via national birth defects registry	At birth	Cases with visual/hearing defects vs. birth defect-free controls
Parab et al., (2018, India) (38)	Bilateral (62.5%), unilateral (37.5%), mostly right ear	TEOAE, AABR, diagnostic ABR, ASSR, tympanometry	Initial screen at 3-14 days; ABR confirmed HL	Case (failed screening) vs. control (passed)
Townsend et al., (2013, United Kingdom) (24)	Sensorineural hearing loss (bilateral/unilateral)	OAE, pure-tone audiometry, ABR, Griffiths developmental scale	All moderate/severe outcomes identified by 1 year of age	Symptomatic vs. asymptomatic CMV; maternal infection types

HL: Hearing loss, BHL: Bilateral HL, UHL: Unilateral HL, NICU: Neonatal intensive care unit, ABR: Auditory brainstem response, CMV: Cytomegalovirus, SNHL: Sensorineural hearing loss, OAE: Otoacoustic emissions, CHL: Congenital HL, cCMV: Congenital CMV, AABR: Automated ABR, ASSR: Auditory steady-state response, MHL: Mixed HL, ANSD: Auditory neuropathy spectrum disorder, TEOAE: Transient evoked otoacoustic emissions, aCMV: Congenital cytomegalovirus infection

The reliance on heterogeneous observational designs precluded meta-analysis, and variability in diagnostic criteria, sample sizes, and reporting standards across included studies introduced potential bias. Despite these limitations, the review effectively highlights ongoing dominance of infectious and perinatal factors while emphasizing the emerging importance of hereditary causes. Overall, it offers a valuable, up-to-date synthesis that not only consolidates global evidence but also identifies critical research gaps especially the need for longitudinal, genotype-phenotype, and gene-environment interaction studies to better define the evolving etiology of CHL.

Conclusion

This systematic review synthesized the current observational evidence on the risk factors associated with CHL, with a focus on genetic, infectious, perinatal, environmental, and sociodemographic determinants. Unlike previous reviews that primarily emphasized congenital infections such as CMV or perinatal complications, our study aimed to explore whether there has been a temporal shift in the etiological spectrum, from infectious causes toward a predominance of genetic and hereditary factors, as universal newborn hearing screening and perinatal infection control have expanded globally. However, the analysis revealed a persistent paucity of high-quality genetic studies, particularly from low- and middle-income countries, where diagnostic access to molecular testing remains limited. Consequently, infectious, and perinatal factors continue to dominate the reported risk landscape, highlighting both regional disparities and research gaps. This broader, integrative review therefore not only consolidates global data up to 2025 but also underscores the urgent need for genotype-phenotype correlation studies to better delineate the evolving causes of CHL in different populations.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: T.L., A.C.A., Concept: S.T., Design: A.C.A., Data Collection and/or Processing: T.L., S.T., Analysis or Interpretation: S.T., Literature Search: T.L., S.T., Writing: T.L., A.C.A., S.T.

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Main Points

- **Multifactorial Risk Factors:** Congenital hearing loss (CHL) is associated with multiple risk domains, including genetic (e.g., *GJB2* mutations, consanguinity), infectious (especially congenital CMV and TORCH infections), perinatal (NICU admission, low birth weight, hyperbilirubinemia), and environmental (ototoxic drug exposure) factors.
- **Predominance of Sensorineural Hearing Loss:** The most commonly reported type of CHL across studies was bilateral sensorineural hearing loss, highlighting the need for early audiological screening and intervention.
- **Emphasis on Early Screening and Prevention:** The findings support the implementation of targeted screening programs and preventive strategies focusing on high-risk populations to enable early diagnosis and timely management of CHL.

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Video Article

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Retrograde Transillumination: A Reliable Guide for Frontal Sinus Opening in Endoscopic Sinus Surgery

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Abstract

To describe and assess the feasibility of a simple, low-cost retrograde transillumination technique for identifying and confirming the frontal sinus opening during endoscopic frontal sinus surgery in a small series of patients. This single-center descriptive surgical series, conducted between November 2024 and January 2025, included five patients who underwent endoscopic frontal sinus surgery. The technique's five steps were standardized: angled endoscopic view (45°) of the frontal recess, probing the probable opening with angled instruments, darkening the room, placing the light source of the endoscope superomedial to the eyebrow, and observing a retrograde endonasal glow at the true ostium. In all cases, localization of the frontal opening was achieved by retrograde transillumination and independently verified with neuronavigation. Representative scenarios included nasal polyposis, pansinusitis, revision surgery (Draf III), and a pediatric patient with complicated sinusitis with epidural abscess. Retrograde transillumination enabled identification of the frontal sinus opening in all five cases and guided the extent of surgery (Draf IIa-b/III as indicated). It proved especially helpful when landmarks were distorted or when frontal recess cell variants obscured the pathway. In this limited series, retrograde transillumination appeared to be a pragmatic, cost-effective adjunct that complemented anatomical expertise, surgical experience, and neuronavigation for intraoperative localization of the frontal sinus opening. Larger comparative studies are needed to further evaluate its accuracy and generalizability.

Keywords: Chronic rhinosinusitis, endoscopic sinus surgery, frontal sinus, transillumination, revision endoscopic sinus surgery

Introduction

The frontal sinus and its outflow tract remain among the most challenging areas to approach in functional endoscopic sinus surgery (FESS) because of their narrow diameter, complex three-dimensional anatomy, and wide range of anatomical variants. The frontal sinus opening represents the narrowest point of this pathway, and scarring, polyps, or bony cell variants can further obscure this region and complicate safe surgical access (1). Detailed preoperative computed tomography (CT) review, ideally with multiplanar reconstructions, improves understanding of frontal recess anatomy (2).

Transillumination of the frontal sinus has been used to define the integrity and boundaries of the frontal sinus since 1930 (3). Caldwell radiography as an external-route framework for frontal sinus surgery was described in the mid-20th century, and with advances in technology, image-guided surgical systems (neuronavigation) have become widely used adjuncts in both endoscopic and open frontal sinus surgeries (4,5).

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Classical transillumination techniques typically illuminate the sinus from within to delineate its borders externally. In contrast, the presented video article describes a retrograde transillumination technique that places the endoscope light source externally at the superomedial eyebrow while the surgeon views the frontal recess endonasally. This approach aims specifically to localize and confirm the frontal sinus opening.

Our objective is to present a standardized five-step use of retrograde transillumination and to illustrate its application in five representative cases in which the ostium identified by this method was verified with neuronavigation.

Patients and Surgical Technique

This study was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University (approval no: OMÜ KAEK 2024/94, date: 29.02.2024). The study was conducted between November 2024 and January 2025 at Ondokuz Mayıs University Faculty of Medicine, Otorhinolaryngology Department with patients undergoing endoscopic frontal sinus surgery. Written consent was obtained from the patients for the use of their demographic and clinical data, as well as their intraoperative photographs and videos in this article.

Our report includes five patients to demonstrate the technique. For consistency and anonymity, patients were identified numerically throughout the text and accompanying media. Preoperatively, 1-mm slice paranasal CT was obtained from all patients. Table 1 summarizes the clinical characteristics of the patients and the surgical procedures performed. In all surgeries, the frontal sinus opening was found with the guidance of retrograde transillumination and confirmed with neuronavigation (Brainlab AG, Munich, Germany).

There are five key steps to the retrograde transillumination technique:

1. View the frontal recess with an angled endoscope (45° was used in our surgeries).
2. Identify the possible frontal sinus opening with angled instruments.
3. Turn the lights off in the operating room.
4. Detach the light source from the endoscope, check that the light source is not hot, and place it superomedial to the patient's eyebrow.
5. Observe retrograde transillumination of the frontal sinus opening on the screen.

Video 1 includes the title, introduction, intraoperative recordings from the five patients who underwent endoscopic frontal sinus surgery in which the retrograde transillumination technique was used, and the key points of the technique.

Patient 1 had nasal polyposis blocking the middle meatus and the frontal recess. After polypectomy, the agger nasi cell was opened and the frontal recess was viewed with a 45° endoscope. With the help of the retrograde transillumination technique, the frontal sinus opening was identified and a Draf IIa procedure was performed (Figure 1, Video 1).

Patient 2 had pansinusitis. Anterior and posterior ethmoidectomy were performed. The frontal recess was visualized with a 45° endoscope, and the potential frontal sinus opening was explored with angled instruments. With retrograde transillumination, a dim light was seen at the right frontal sinus opening (Video 1). The light guided us and we were able to reach the frontal sinus and perform a Draf IIa procedure.

Patient 3 had recurrent nasal polyposis, and this was his third surgery. Bilateral nasal cavities were obliterated with polyps. Following maxillary antrostomy, anterior and posterior ethmoidectomy, sphenoidotomy, and removal of polyps from the frontal recess, the frontal sinus ostium was localized using retrograde transillumination. A Draf III procedure was performed, and traditional transillumination of the bilateral frontal sinuses showed that the polyps and the cells located in the frontal recess and in the diseased frontal sinuses had been adequately cleared (Video 1).

Patient 4 had nasal polyposis, and this was her first surgery. Polyps were blocking the middle meatus. The maxillary sinus ostium was opened, an anterior ethmoidectomy was performed, and the polyps located in the frontal recess were removed. Again, with an angled endoscope and

Table 1. Demographic and surgical characteristics of study group

	Age	Sex	Indications	Surgery performed
Patient 1	39	Female	Polyposis	Draf IIa
Patient 2	32	Male	Polyposis	Draf IIa
Patient 3	61	Male	Recurrent polyposis (third surgery)	Draf III
Patient 4	51	Male	Polyposis	Draf IIa
Patient 5	10	Male	Pansinusitis (complicated)	Draf IIa

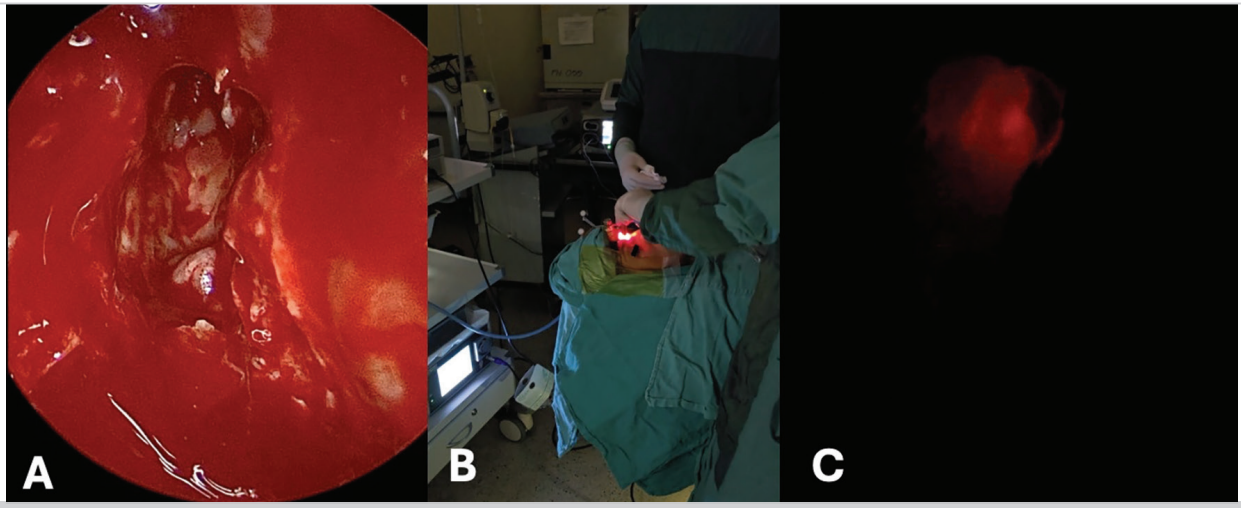

Figure 1. Identifying the frontal sinus opening with retrograde transillumination in patient 1. A, B, and C represent the view before the technique, the application of the technique, and the view after completing the frontal sinusotomy, respectively

angled instruments, the frontal sinus opening was searched. Retrograde transillumination became a guiding light to find the frontal sinus opening and a Draf IIa procedure was performed (Figure 2, Video 1).

Patient 5 was admitted to the pediatric emergency department with fever and confusion. After detailed examination and radiological imaging, an epidural abscess was detected in the right frontal lobe. After abscess removal by neurosurgeons, we performed endoscopic maxillary, ethmoid, and frontal sinus surgery. In this patient, a suprabullar cell made identification of the frontal sinus opening more difficult. In such cases, retrograde transillumination can help surgeons to find the frontal sinus opening; in our case, the light guided us directly to an opening located at the superior lateral aspect (Video 1).

Discussion

In this video article, we demonstrate that retrograde transillumination can be used as a practical adjunct to identify and confirm the frontal sinus opening during FESS. In five illustrative cases, including primary and revision surgeries, nasal polyposis, pansinusitis, and a pediatric patient with complicated sinusitis with epidural abscess, the technique allowed us to localize the ostium and tailor the extent of the frontal sinusotomy, with neuronavigation serving as an independent intraoperative reference.

Our observations build on the long history of frontal sinus transillumination. Campbell (3) first described transillumination of the frontal sinus nearly a century ago. In other fields, intraoperative transillumination has also been used to determine the frontal sinus extent during subcranial approaches to the anterior skull base, emphasizing its

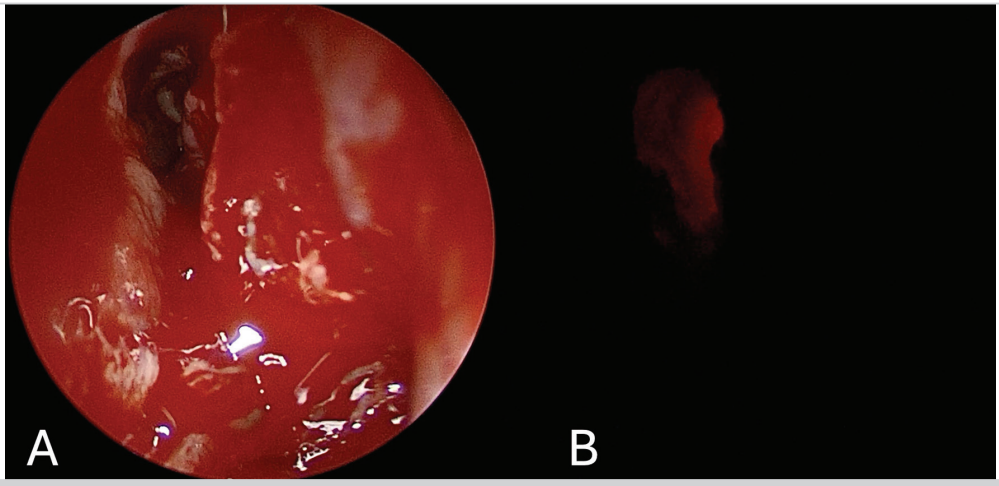

Figure 2. Identifying the frontal sinus opening with retrograde transillumination in patient 4. A and B represent the view before and after frontal sinusotomy, respectively

practical value as a real-time adjunct when landmarks are limited (6).

With advances in imaging, external-route techniques and radiographic approaches for frontal sinus surgery were reported in the mid-20th century, and modern image guidance has become an established adjunct in both open and endoscopic frontal sinus surgery (4,5). In a cadaver study of osteoplastic frontal sinus surgery, Melroy et al. (7) compared the CT guidance, Caldwell radiographs and the transillumination method and found that CT guidance most accurately predicted the frontal sinus borders, followed by Caldwell radiography and transillumination. Friedman et al. (8) later combined transillumination with neuronavigation to assess frontal sinus patency and reported that transillumination was useful for identifying the frontal sinus in 185 of 200 patients.

A conceptually related approach is diaphanoscopy after transcutaneous frontal sinus puncture. Al Kadah et al. (9) reported four revision cases of acute frontal sinus pyocele with bone defect following prior open frontal sinus surgery, in which the frontal sinus was accessed transcutaneously through a pre-existing bony defect using an endoscopic system; the resulting intraluminal illumination enabled clear endonasal identification of the frontal sinus floor by diaphanoscopy and guided a targeted endonasal opening (Draf IIb) in all patients. In contrast, our patients did not have a pre-existing anterior table defect; therefore, we used an external light source placed superomedial to the eyebrow to generate retrograde transillumination as a non-invasive cue for ostium localization without transcutaneous instrumentation.

Compared with these reports, our contribution is to apply the principle of transillumination in a retrograde fashion specifically to localize the frontal sinus opening during endoscopic surgery. By placing the endoscope light source externally at the superomedial eyebrow, the surgeon observes a focal glow at the ostium while simultaneously viewing the frontal recess endonasally. This technique does not replace preoperative CT analysis, where multiplanar reconstructions can improve depiction of the frontal sinus and the recess anatomy, or the detailed knowledge of frontal recess anatomy, or navigation; instead, it offers a simple, low-cost visual cue that may be particularly valuable when anatomical landmarks are distorted, when the frontal cells mimic the drainage pathway, or in centers where navigation is unavailable.

Our study also has limitations. Firstly, this is a small descriptive series without a control group or quantitative outcome measures; therefore, we cannot estimate the diagnostic accuracy or the long-term patency rates. Secondly, retrograde transillumination is less effective when the frontal sinus is filled with dense polyps, granulation tissue, or thick mucosa, which may block or diffuse the light. In addition, the anterior table thickness, the frontal sinus size, and individual variations in the frontal cells may influence the intensity and localization of the glow. Finally, we verified the technique using neuronavigation in all patients, but we did not perform systematic comparisons of procedure time or complication rates with and without the technique.

Future studies with larger patient cohorts and prospective designs are needed to investigate the utility of the technique across different cell configurations to evaluate its validity and reliability (10). Such studies could compare its accuracy with that of navigation alone, assessing interobserver agreement.

Conclusion

In summary, retrograde transillumination may serve as a simple, low-cost adjunct to help localize the frontal sinus opening during endoscopic frontal sinus surgery, especially in challenging or revision cases and in settings without access to neuronavigation. The technique should be used together with thorough preoperative CT evaluation and anatomical knowledge, and its performance should be further validated in larger comparative studies.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University (approval no: OMÜ KAEK 2024/94, date: 29.02.2024).

Informed Consent: Written informed consent was obtained from all adult patients and from the parent or legal guardian of the pediatric patient for the use of demographic and clinical data, as well as intraoperative photographs and videos included in this article.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.K., E.D., M.Ç., Concept: Ö.K., E.D., M.Ç., Design: Ö.K., E.D., M.Ç., Data Collection and/or Processing: Ö.K., E.D., M.Ç., Analysis or Interpretation: Ö.K., E.D., M.Ç., Literature Search: Ö.K., E.D., M.Ç., Writing: Ö.K., E.D., M.Ç.

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Main Points

- Frontal sinus opening can be difficult to localize in endoscopic sinus surgery, especially in revision cases and when frontal recess anatomy is distorted.
- We describe a simple five-step retrograde transillumination technique using the endoscope light source placed superomedial to the eyebrow to identify and confirm the frontal sinus opening intraoperatively.
- In five illustrative cases (nasal polyposis, pansinusitis, revision Draf III surgery, and pediatric complicated sinusitis with epidural abscess), retrograde transillumination enabled reliable localization of the frontal sinus opening and guided the appropriate extent of frontal surgery.
- Retrograde transillumination is a pragmatic, low-cost adjunct that complements anatomical expertise and neuronavigation, and may be particularly useful in centers without navigation systems or for less experienced surgeons.

Video 1. The video includes the title, introduction, intraoperative recordings from five endoscopic frontal sinus surgeries in which the retrograde transillumination technique was used, and key points of the technique.

Video 1 Link: https://youtu.be/qkwcgLMaQGM

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Case Report

Turk Arch Otorhinolaryngol 2026; 64(2): 122-125
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Otorrhagia in Chronic Otitis Media: An Unexpected Presentation of Internal Carotid Artery Rupture

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Abstract

Internal carotid artery rupture in the middle ear is very rare and can be life-threatening. We report the case of a 78-year-old male with a history of chronic otitis media who presented with spontaneous, high-volume otorrhagia. Computed tomography imaging revealed a dissection of the petrous segment of the internal carotid artery with an associated pseudoaneurysm. As the rupture of the pseudoaneurysm was considered the cause of otorrhagia, endovascular stenting was performed. After hospital admission for monitoring and antibiotic treatment, the patient underwent subtotal petrosectomy, with no further episodes of hemorrhage.

Keywords: Chronic otitis media, internal carotid artery, otorrhagia, pseudoaneurysm, case report

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Introduction

Internal carotid artery dissection occurs when blood enters the tunica media through a tear in the tunica intima, creating an intramural hematoma that may compromise the integrity of the arterial wall (1). Although uncommon, this process can, in certain situations, progress to arterial rupture, particularly in intracranial segments where the vessel wall is thinner and has less elastic support, leading to the formation of a pseudoaneurysm that cannot withstand high arterial pressures (2).

Otorrhagia in chronic otitis media is considered a relatively common finding due to the persistent mucosal inflammation characteristic of this condition. However, rupture of the internal carotid artery within the middle ear represents an exceptionally rare and severe complication, with only a few cases documented in the literature (3).

High-resolution computed tomography (CT) angiography is the first-line diagnostic modality in this context, which may be complemented by magnetic resonance angiography. Digital subtraction angiography remains the gold standard and offers the advantage of simultaneous therapeutic intervention (4). Management is usually medical, although endovascular or surgical approaches may be required in selected cases (4-6).

We describe the case of a patient with chronic otitis media who presented with otorrhagia, later found to be caused by a rupture of the petrous segment of the internal carotid artery

following a pseudoaneurysm that developed after carotid dissection. Although rare cases of otorrhagia due to internal carotid artery bleeding from carotid canal erosion by chronic otitis media have been described, our report highlights the acute and life-threatening nature of this presentation.

Case Presentation

We report the case of a 78-year-old male with a history of non-cholesteatomatous chronic otitis media of the right ear with approximately a decade of evolution, characterized by intermittent otorrhea, for which surgical treatment had been previously recommended at another institution but declined by the patient. No prior radiological imaging of the temporal bone was available. His additional medical history included medically controlled arterial hypertension, dyslipidemia, and type 2 diabetes mellitus. The patient presented to the emergency department with spontaneous (i.e., without trauma) high-volume otorrhagia from the right ear, unresponsive to compressive measures.

CT angiography revealed an interruption of the bony cortex in the right carotid canal, involving the medial wall of the tympanic cavity. Additionally, irregular filling of the internal carotid artery was observed, extending from just above the common carotid bifurcation to the petrous carotid canal over a length of 58-mm, suggestive of dissection of the internal carotid artery with an associated pseudoaneurysm measuring 1.3-mm at the level of the petrous segment (Figures 1-3).

For this reason, diagnostic angiography was further performed, followed by endovascular stenting with a PK Papyrus covered stent (4×15 mm; Biotronik AG, Berlin, Germany), a balloon-expandable, cobalt-chromium, single-layer covered stent with a polyurethane membrane (Figure 4).

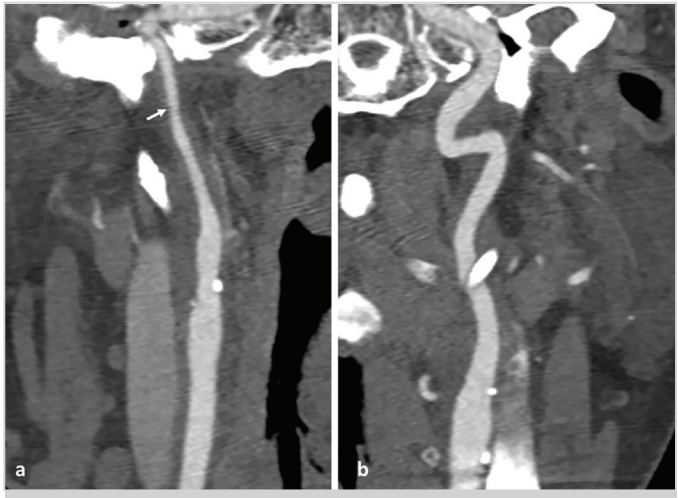

Figure 1. Computed tomography angiography reconstruction of the right (a) and left (b) internal carotid arteries, showing a diffuse thinned lumen in the former, suggestive of a carotid dissection (arrow), when compared with the contralateral carotid artery

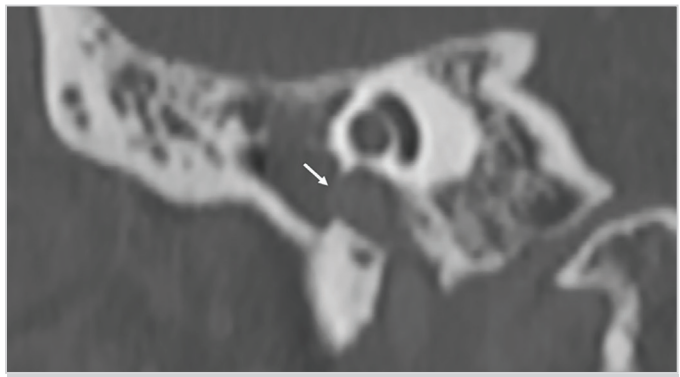

Figure 2. Coronal CT section of the right temporal bone showing dehiscence of the petrous carotid canal (arrow)
CT: Computed tomography

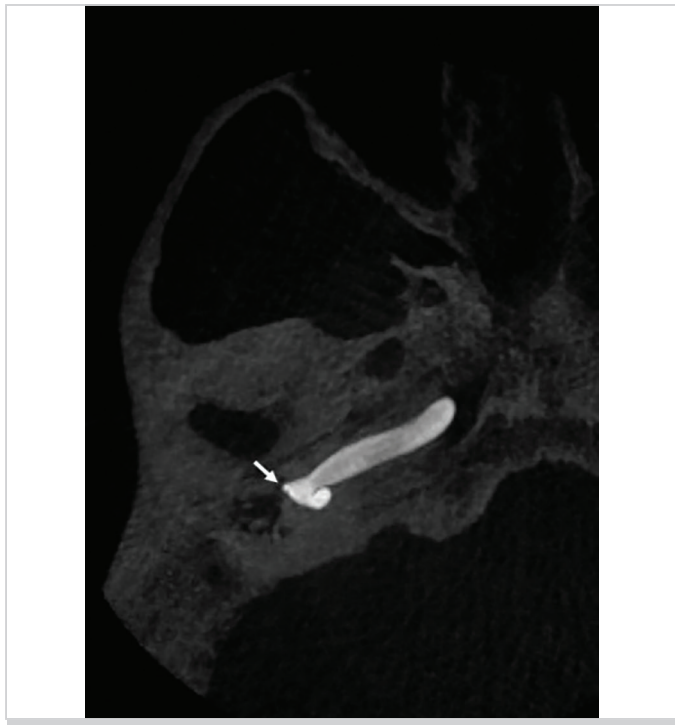

Figure 3. Digital subtraction angiography-maximum intensity projection, 8.5 mm, showing a tiny pseudoaneurysm (arrow) as the probable cause of the carotid rupture

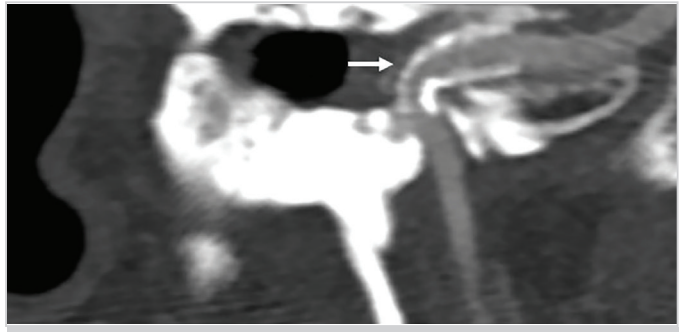

Figure 4. Computed tomography angiography reconstruction showing the carotid stent (arrow)

Following hospital admission for monitoring and antibiotic treatment, no further hemorrhagic episodes occurred. Audiometric evaluation during hospitalization revealed a profound mixed hearing loss in the right ear. Ear examination revealed a pars tensa perforation of the tympanic membrane, accompanied by inflamed middle ear mucosa, while the external auditory canal was normal, without inflammatory tissue or bony exposure.

The patient subsequently underwent a subtotal petrosectomy, which confirmed the bony dehiscence of the carotid canal, with exposure of the petrous segment of the internal carotid artery (Figure 5). The dehiscent area was reinforced using bone pâté and fibrin glue, the Eustachian tube was obliterated, the external auditory canal was closed, and the petrosectomy cavity was obliterated with abdominal fat.

After receiving loading doses of 300 mg of both clopidogrel and aspirin, the patient was maintained on dual antiplatelet therapy (clopidogrel 75 mg daily and aspirin 150 mg daily) for three months, followed by aspirin 150 mg daily as single therapy. His postoperative course was uneventful, and he remained asymptomatic for six months; however, he subsequently suffered a stroke secondary to occlusion of the right internal carotid artery, ultimately resulting in his demise.

Written informed consent was obtained from a family member acting as the patient's legal representative for the publication of this case report in accordance with institutional and ethical standards.

Discussion

Internal carotid artery dissection with an associated pseudoaneurysm in the petrous segment is an extremely rare but potentially life-threatening condition (3). In this case, the initial presentation with spontaneous otorrhagia was unusual and posed a diagnostic challenge. Imaging studies, particularly CT angiography and digital subtraction angiography, were essential for the accurate diagnosis and timely intervention with endovascular stenting, effectively controlling the bleeding and stabilizing the vessel.

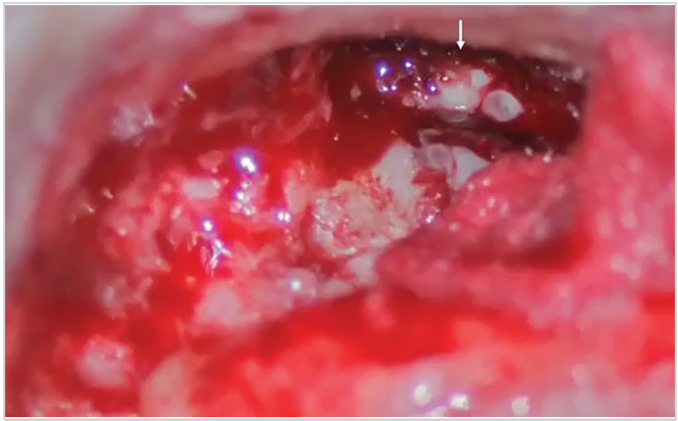

Figure 5. Right petrosectomy cavity showing a dehiscent carotid canal with exposure of the internal carotid artery (arrow)

Surgical management through subtotal petrosectomy was crucial in providing long-term protection of the exposed carotid artery (7,8). Given the bony dehiscence and proximity of the internal carotid artery to the middle ear, the risk of external aggressions, including trauma and recurrent infections, remains significant. The petrosectomy allowed complete exclusion of the middle ear cavity, thus isolating the artery from these potential hazards. This approach represents the only reliable method to safeguard the carotid artery in such anatomical circumstances, as conservative management alone would not eliminate the risk of recurrent hemorrhage or vessel injury.

Although surgical intervention is invasive and reserved for selected cases, in this context it was justified by the need to prevent further complications, ensuring vascular protection and patient safety, as well as to definitively controlling chronic otitis media in an ear without functional hearing.

The patient's risk factors, together with antiplatelet therapy alone, may have been insufficient to prevent the fatal thrombotic event. Furthermore, although the patient remained asymptomatic, scheduled follow-up imaging at 3-6 months could have provided valuable information on stent patency and early detection of any in-stent stenosis, thereby guiding further management.

Conclusion

Otorrhagia in the setting of a pseudoaneurysm rupture of the internal carotid artery is extremely rare and unusual, making it a bizarre clinical manifestation that can easily be overlooked. Early diagnosis and combined endovascular and surgical management are paramount for optimal patient outcomes. Subtotal petrosectomy can be regarded as an essential surgical procedure to protect the internal carotid artery in the setting of petrous segment dissection with subsequent pseudoaneurysm formation and bony dehiscence exposing the vessel to the middle ear. At the same time, it allows definitive treatment of the underlying chronic otitis media. By excluding the middle ear, this surgery effectively shields the carotid artery from external insults, such as trauma and infections, while also eliminating the chronic infectious focus, thereby reducing the risk of potentially fatal hemorrhagic events.

Ethics

Informed Consent: Written informed consent was obtained from a family member acting as the patient's legal representative for the publication of this case report in accordance with institutional and ethical standards.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.M.F., D.R., M.S.B., Concept: A.M.F., Design: A.M.F., Data Collection and/or Processing: A.M.F., G.M.R., F.A.F., M.Q-N., Analysis or Interpretation: A.M.F., M.Q-N., Literature Search: A.M.F., M.S.B., Writing: A.M.F., G.M.R.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: The authors declare that this study has received no financial support.

Main Points

- Spontaneous otorrhagia can be the first sign of a petrous internal carotid artery dissection with pseudoaneurysm, even in patients with simple chronic otitis media.
- Computed tomography angiography and digital subtraction angiography are essential for accurate diagnosis and timely endovascular intervention.
- Balloon-mounted covered stenting provides immediate vessel stabilization while preserving the parent artery in fragile or dissected segments.
- Subtotal petrosectomy offers long-term protection of the exposed carotid artery, excluding the middle ear from trauma or infection and definitively treating chronic otitis media.

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Case Report

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Bench Pressing Related Traumatic Laryngeal Fracture

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Abstract

Laryngeal fracture is a rare but potentially life-threatening injury requiring prompt recognition and management due to the risk of airway compromise. We present the case of a 42-year-old man who presented to a tertiary center with symptoms of dysphonia and neck pain following blunt trauma sustained when a barbell fell on him while bench pressing without assistance. Computed tomography (CT) imaging confirmed a displaced fracture of the thyroid cartilage. He was managed conservatively with corticosteroids and high dependency unit airway monitoring. He recovered well and later resumed weightlifting with appropriate supervision. This case outlines the stages of assessment and management of laryngeal fractures, including airway evaluation, CT imaging and ear nose and throat (ENT) involvement. We discuss the benefit of conservative management in selected cases even when there are significant clinical findings and the importance of public health messaging to prevent such injuries. A high index of suspicion is essential for emergency physicians and ENT specialists when evaluating patients with neck trauma and voice changes.

Keywords: Laryngeal fracture, larynx/injuries, neck injuries, dysphonia, airway management, weight lifting/injuries, case reports

Introduction

Laryngeal fractures are rare but life-threatening, especially in cases of trauma. The degree of injury varies from mild non-displaced fractures to severe laryngotracheal separation. The incidence of laryngeal fractures is about 1 in 30,000 emergency department presentations (1). Blunt force trauma is the most common cause of laryngeal injury, often associated with high-impact incidents such as road traffic collisions, especially when there is hyperextension of the neck during impact with the body of the vehicle, such as the steering wheel or the dashboard. This hyperextended position more commonly causes laryngeal injuries than when the neck is in a relaxed position, where the larynx is protected by the cervical spine posteriorly, the sternum inferiorly, and the mandible bone anterosuperiorly (1-3). Bench-press-related laryngeal fractures are very rarely reported in the literature.

There is a rise in the incidence of lower-impact etiologies causing laryngeal fractures, such as sport-related injuries, including basketball, combat sports, ice hockey, or self-inflicted hanging injuries. These are all examples of where there is a high force of impact over the small surface area of the anterior neck (3,4). Whilst men tend to have shorter and wider necks that can protect their larynx, they make up a larger proportion of these injuries; this is thought to be due to their increased likelihood to take part in combat or violent sports (4).

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We present the case of a patient who self-admitted to the emergency department with neck pain and dysphonia. He was found to have suffered a thyroid cartilage fracture after his barbell fell on his neck whilst exercising at his local gym.

Case Presentation

We present the case of an otherwise healthy 42-year-old man, with no past medical history and a lifestyle inclusive of regular exercise. He is a non-smoker and does not drink regularly. He self-presented to the emergency department with dysphonia and neck pain after an incident a few hours earlier. While at the gym, performing a bench press unassisted, he dropped a 180 kg weight onto his chest, which then rolled up to his neck. With help from bystanders, he was able to move this off and immediately described a sensation of neck pain, neck swelling, and difficulty breathing.

On initial assessment in the emergency department, he was unable to speak in full sentences, had a hoarse voice, neck pain, and odynophagia (painful swallowing) with difficulty swallowing his own saliva. He maintained his oxygen saturations on room air and was assessed to have a Glasgow Coma Scale of 15/15. Examination revealed some external neck swelling, neck bruising, no palpable surgical emphysema, and a good range of neck movement. His chest examination was unremarkable.

Due to the high-impact nature of his injury, an urgent neck and chest contrast-enhanced computed tomography (CT) was performed. This showed a comminuted fracture of the right thyroid cartilage, with the fracture fragment displaced medially. Adjacent soft tissue swelling suggesting haematoma, and visible anterior gas locules in the anterior commissure suspicious for laryngeal rupture (break in integrity of the larynx) (Figure 1).

After receiving a verbal report of the injury from the radiology team, the case was discussed with the ear, nose, and throat (ENT) team. They reviewed the images and assessed the patient using flexible nasolaryngoscopy, which was described as unremarkable with findings of symmetrical vocal fold mobility bilaterally, no significant mucosal disruption and no visible cartilage in his airway. In view of the injuries, the patient was admitted for close airway monitoring. He was managed as per local guidelines with intravenous dexamethasone 6.6 mg as an anti-inflammatory agent to reduce his risk of laryngeal edema and worsening neck swelling.

After a night of close observation, he underwent repeat nasolaryngoscopy with local anaesthetic approximately 11 hours later to formally assess his airway. Similar to his initial examination, this showed normal findings of symmetric vocal fold mobility bilaterally, no mucosal disruption, and no visible exposed cartilage. In addition to this, he also reported no difficulty swallowing, and his voice returned to normal. His steroids were discontinued after a single dose, and he was discharged from the hospital one day after admission.

On follow-up, he had no lasting signs of trauma or voice change. Although he was given safety advice on discharge, he

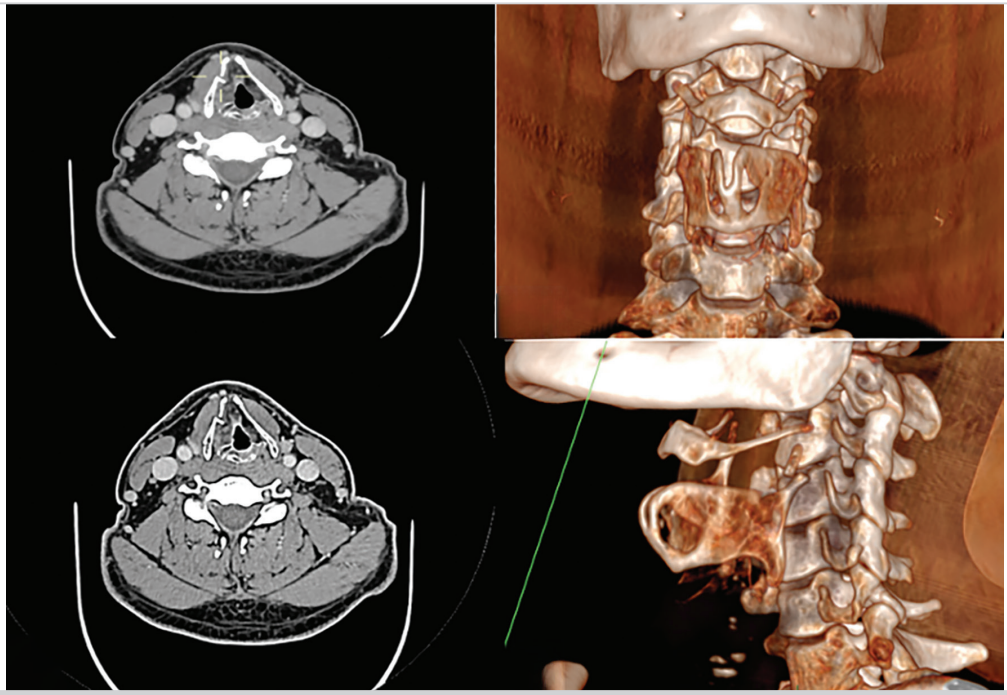

Figure 1. Computed tomography images of displaced comminuted fracture of the right thyroid cartilage with a fracture fragment displaced inwards

reported a return to his hobby of gym exercise. He reported that he now uses a spotter when attempting heavy lifts or maximal efforts during training to prevent further accidents while bench pressing. Written and verbal consent was taken from the patient.

Discussion

With the increasing focus on a healthy lifestyle and personal body image, weightlifting-related injuries will likely become a more problematic issue. A 2024/25 United Kingdom fitness report indicated a sustained increase in gym memberships compared to 2023. This rise can be attributed to growing public awareness of the importance of healthy lifestyles, the benefits of exercise on mental health as highlighted during the pandemic, and the increased availability and affordability of gyms (5).

As illustrated in our case, the risk of injury during a bench press occurs when a weighted bar is held above the chest while the individual is in a supine position with their neck extended. In addition, the thyroid cartilage is thought to be at increased risk in adults above the age of 20 years, as this cartilage progressively ossifies to the bone, and the lack of elasticity diminishes its ability to tolerate trauma (6).

Accurate history-taking and examination of such patients are important in evaluating laryngeal injuries; however, this can be complicated by dysphonia and aphonia, where reliance on collateral history becomes necessary. This cohort of patients will usually present with a history of trauma, dysphonia, dysphagia, neck pain, or stridor (7). When assessing patients with suspected laryngeal injury, the first step is to establish a stable airway. If the patient is able to speak and there is no additional noisy breathing, conservative management should be considered. If there is concern of a compromised airway, the primary aim is to place a cuffed airway tube to keep the trachea open and protected. This can be achieved via intubation, tracheostomy, or cricothyroidotomy. The following signs and symptoms suggest airway compromise and increase the necessity of intubation or tracheostomy: respiratory distress, neck haematoma, significant bleeding, subcutaneous neck emphysema, stridor, hoarseness, hemoptysis, thrill, bruit, and distorted neck anatomy (3). If there is no immediate concern for a compromised airway but symptoms or signs are suggestive of laryngeal injury, urgent referral to ENT is still vital. Edema can develop progressively, and airway compromise may be delayed.

The choice of method for securing the airway can be challenging, as intubation in the presence of laryngeal fracture is technically difficult and carries the risk of converting a partially obstructed airway into a completely lost airway. This highlights the need for a multidisciplinary approach, including the early involvement of surgical specialists. In cases of a compromised airway with a displaced laryngeal fracture, a tracheostomy under local anaesthetic or a cricothyroidotomy is recommended (1).

If there is concern regarding the airway with no immediate compromise, the patient should be assessed by a physician knowledgeable in endoscopy, such as an ENT specialist. If the patient is stable and a fracture is of concern, then CT scans have been recommended in the literature to visualize the cartilaginous and bony structures of the larynx (7). This has been shown to have an advantage of early surgical intervention and removes the possibility of missed diagnosis due to the rare frequency of laryngeal fractures (Figure 2).

A literature search in PubMed revealed that thyroid cartilage fractures resulting from bench pressing are exceedingly rare, with only two comparable cases reported involving weights of at least 100 kg falling onto the neck. The first case involved a 49-year-old man who sustained his injury after a 100 kg barbell fell onto his chest and rolled onto his neck. He was assisted by bystanders and assessed in hospital with an immediate neck CT and repeat nasolaryngoscopy. He was managed conservatively with airway observation and later discharged (4). The second case involved a healthy 55-year-old man with no past medical history who was bench-pressing 180 kg, the same weight as in our case. He suffered a vertical thyroid fracture while bench-pressing this weight alone in a private gym. He was unable to receive assistance and died at the scene. His findings were identified on postmortem CT (8).

The management of laryngeal fractures is based on the severity of the fracture and its associated injuries. The American Otolaryngology Society advises the use of the Schaefer classification system for laryngeal trauma, as it incorporates clinical examination and imaging findings to guide treatment decisions (Table 1). According to the Schaefer classifications, thyroid cartilage fractures that are non-displaced with no evidence of injury on endoscopy are managed with a range of non-surgical management options. These include head elevation, voice rest, humidified oxygen, steroids, and anti-reflux medication (Table 2) (3).

Although our patient had a displaced thyroid fracture, flexible nasolaryngoscopy demonstrated no visible laryngeal hematoma, mucosal disruption, or exposed laryngeal cartilage, and he demonstrated no signs of immediate airway compromise. Based on these findings, the injury lay between group 2 and 3 of the Schaefer classification. Given his stable clinical presentation, he was categorized as group 2 despite the presence of a displaced fracture, and conservative management was therefore chosen. This decision was made with the caveat that close monitoring and re-assessment would be undertaken, with consideration for surgical intervention should clinical deterioration occur.

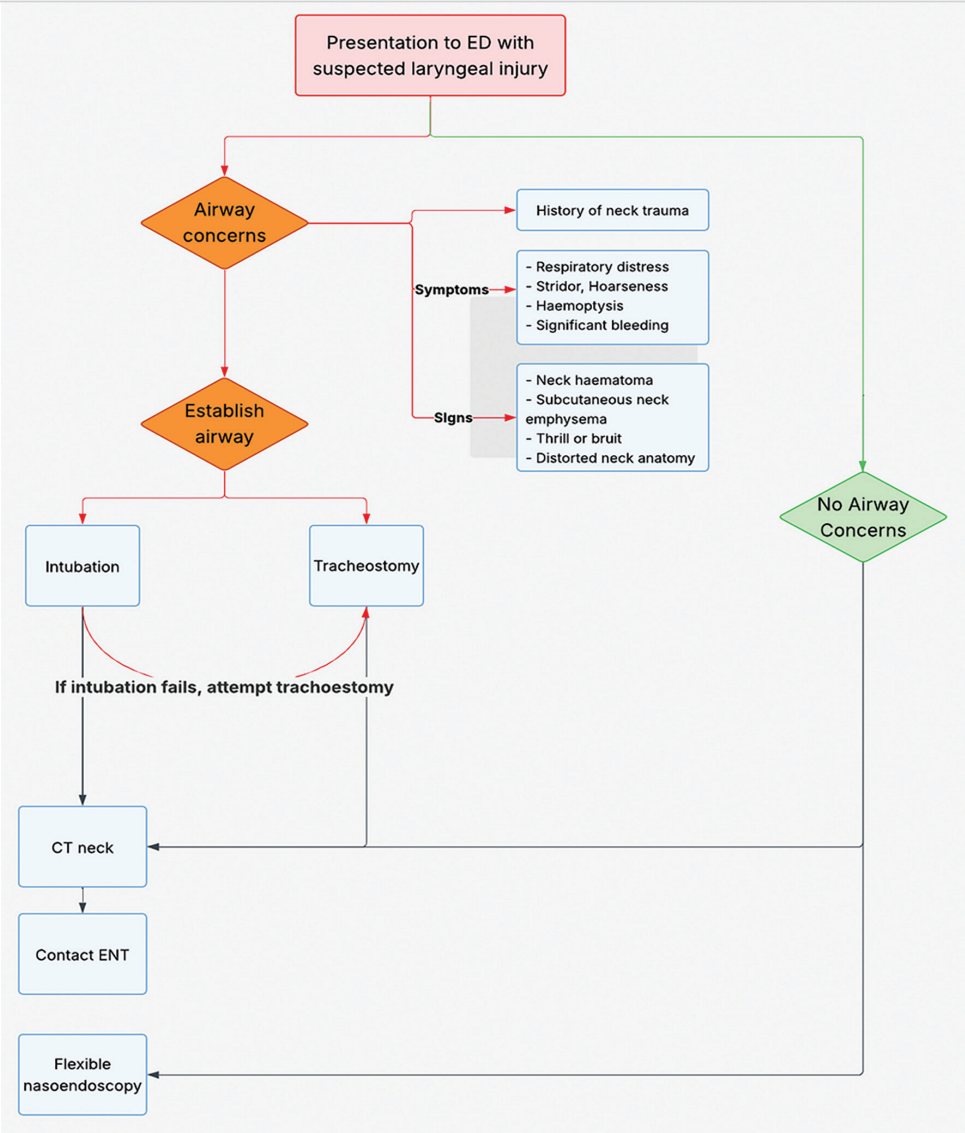

Figure 2. Flowchart of laryngeal injury assessment and management in the emrgency department
ED: Emergency department, ENT: Ear, nose and throat, CT: Computed tomography

Table 1. The Schaefer classification of laryngeal injuries

Group	Severity of injury
1	Minor laryngeal hematomas or lacerations without detectable fractures
2	Severe edema, hematoma, minor mucosal disruption without exposed cartilage, or non-displaced fractures
3	Severe edema, large mucosal lacerations, exposed cartilage, displaced fractures, or vocal cord immobility
4	Same as group 3, but more severe with disruption of anterior larynx, unstable fractures, two or more fracture lines, or severe mucosal injuries
5	Complete laryngotracheal separation

Table 2. Overview of conservative management strategies for laryngeal injuries and their rationale

Management type	Rationale
Head elevation	Improves venous return, reducing laryngeal edema and hematoma formation
Humidified oxygen	Moistens the mucosa to aid healing and prevent further laryngeal damage
Corticosteroids	Reduce laryngeal edema
Voice rest	Prevents further laryngeal trauma and promotes healing by minimizing vocal cord movement
Medication for acid reflux	Protects healing tissues from exposure to stomach acid

He was managed with high dependency unit-level airway observations, monitoring for late-onset laryngeal edema. After his repeat nasolaryngoscopy and full voice recovery during his time in the hospital, he was discharged approximately 24 hours after admission.

Comparing the cases identified in the literature review and our own, the primary determinant of survival following a bench-pressing neck injury in the pre-hospital setting is external assistance. Recommendations for the safe use of the bench press in the United Kingdom and the United States emphasize the importance of having a spotter who can lift the barbell if the lifter reaches their limit, thereby preventing injuries to the neck and chest. Additional safety measures include the use of safety catches to prevent bar descent onto the body, the use of Smith machines with integrated locking mechanisms, and appropriate gym induction to ensure users are adequately informed about safe training practices (4,9,10).

Conclusion

Laryngeal fractures are rare but can progress to potentially fatal complications. Patients typically present with a history of neck trauma accompanied by dysphonia and dysphagia. In those displaying signs of respiratory distress, prompt airway management is crucial. In all cases, CT imaging in conjunction with endoscopic evaluation serves as the gold standard for establishing a diagnosis of laryngeal fracture. Early ENT referrals are essential to facilitate further assessment and monitoring, with the Schaefer classification used to determine injury severity and guide management. While a high index of clinical suspicion is essential given the rarity of these injuries, prevention strategies must also be adopted to reflect the changes in the exercise habits of the general population. With an uptake in gym memberships of the public, education on safe techniques is paramount. As with other widely accepted public safety precautions such as mouth guards in contact sports and seatbelts in cars, having a supervising partner or spotter should be encouraged to prevent life-threatening injuries when weightlifting in vulnerable positions. By enhancing clinician awareness and promoting prevention strategies among individuals lifting weights over the body, the incidence of laryngeal injuries may be reduced and patient outcomes improved. Going forward, future research should focus on the efficacy of these safety interventions in gym environments.

Ethics

Informed Consent: Written and verbal consent was taken from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.K. M.S., Concept: M.K. M.S., Design: M.K. M.S., Data Collection and/or Processing: M.K., H.I., Analysis or Interpretation: M.K., H.I., Literature Search: M.K., H.I., Writing: M.K., H.I., M.S.

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Main Points

- Laryngeal fractures are rare but life-threatening injuries with the potential of evolving.
- Whilst thyroid cartilage fractures have a significant morbidity rate, in a stable patient there is a role for conservative management with close observation and assessment.
- In the interest of public health, when exercising with heavy weight, it is good practice to have supervision.

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Case Report

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Decade-Long Progression of Localized Amyloidosis from the Larynx to the Nasal Cavity-A Case Report

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Abstract

Localized amyloidosis of the upper aerodigestive tract is an uncommon and benign condition characterized by extracellular amyloid deposition. While the larynx is the most frequently involved site, progressive, multifocal mucosal involvement remains exceedingly rare. We report the case of a 58-year-old male initially diagnosed with localized laryngeal amyloidosis confirmed via Congo red staining. The initial laryngeal lesions were excised using conservative endoscopic surgery to both confirm the diagnosis and alleviate symptoms. However, no additional treatment was recommended by the rheumatology department since the patient's further evaluations did not indicate a diagnosis of systemic amyloidosis. Over an 11-year follow-up period, sequential progression to the nasopharynx was observed after five years and to the nasal cavity after 11 years. The patient remained free of systemic involvement throughout, confirmed by comprehensive evaluations including serum and urine immunofixation, renal and hepatic panels, and 24-hour urine analysis. Symptomatic relief was achieved with a series of conservative surgical interventions addressing airway and auditory symptoms. The patient remains under active surveillance. This case highlights a rare, progressive pattern of localized amyloidosis involving contiguous mucosal sites in the upper aerodigestive tract. It underscores the importance of long-term follow-up, systematic evaluation to exclude systemic disease, and the efficacy of conservative surgical management. To our knowledge, this is the first reported case of progressive, segmental spread of localized amyloidosis involving the larynx, the nasopharynx, and the nasal cavity over more than a decade.

Keywords: Amyloidosis, larynx, nasopharynx, nasal cavity, upper aerodigestive tract, disease progression, case reports

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Introduction

Amyloidosis represents a disorder in which misfolded proteins accumulate within the extracellular matrix, leading to progressive tissue dysfunction. The condition is broadly divided into two clinical entities: systemic and localized variants (1,2). When limited to the upper airway region, the larynx is the site most frequently involved, comprising approximately 0.2-1.2% of benign laryngeal lesions (3). Diagnosis relies on histopathological demonstration of amyloid material that exhibits a distinctive apple-green birefringence under polarized light after Congo red staining (4). These deposits exhibit structural diversity, and several amyloid subtypes have been identified: (i) AL or light-chain amyloid, often linked with plasma-cell dyscrasias and appearing in either systemic or localized forms; (ii) AA or amyloid-associated type, a reactive form secondary to chronic inflammatory processes; and (iii) Aβ or beta-amyloid type, predominantly observed within the central nervous system (4,5). A definitive diagnosis requires histopathological examination, and determining the type of amyloidosis is essential for evaluating systemic

or secondary involvement. Localized forms are managed with conservative surgeries, while systemic forms may require chemotherapy. Thus, confirming amyloid presence alone is insufficient; subtype identification is equally critical, as it directly guides treatment and prognosis.

In this case report, we present the long-term follow-up of a patient with segmental progression of amyloid involvement in the larynx, the nasopharynx, and the nasal cavity.

Case Presentation

A 58-year-old male patient presented to our clinic with a complaint of dysphonia. He had no known comorbidities, no history of malignancy, or previous radiotherapy. Endoscopic examination of the nasal cavity and nasopharynx was unremarkable; however, endoscopic laryngeal evaluation revealed bilateral, orange-colored mass lesions on the ventricular bands, raising suspicion of malignancy and prompting a biopsy as shown in Figure 1a. Thus, biopsy specimens were obtained via conservative surgical excision. Excision was performed for diagnostic purposes; therefore, surgical margins were not evaluated.

The laryngeal biopsy showed amorphous and homogenous, pale pink-colored deposits in the extracellular spaces. The biopsy specimen exhibited classic apple-green birefringence under polarized light with Congo red staining, confirming a diagnosis of laryngeal amyloidosis. Positive staining was detected in immunohistochemical staining with Amyloid AA, as shown in Figure 2. To exclude systemic involvement, serum and urine immunofixation electrophoresis revealed no monoclonal components. Kidney and liver function tests were within normal limits, and 24-hour urine analysis demonstrated no significant proteinuria. In the absence of systemic amyloidosis findings, the patient was classified as localized laryngeal amyloidosis and placed under active surveillance.

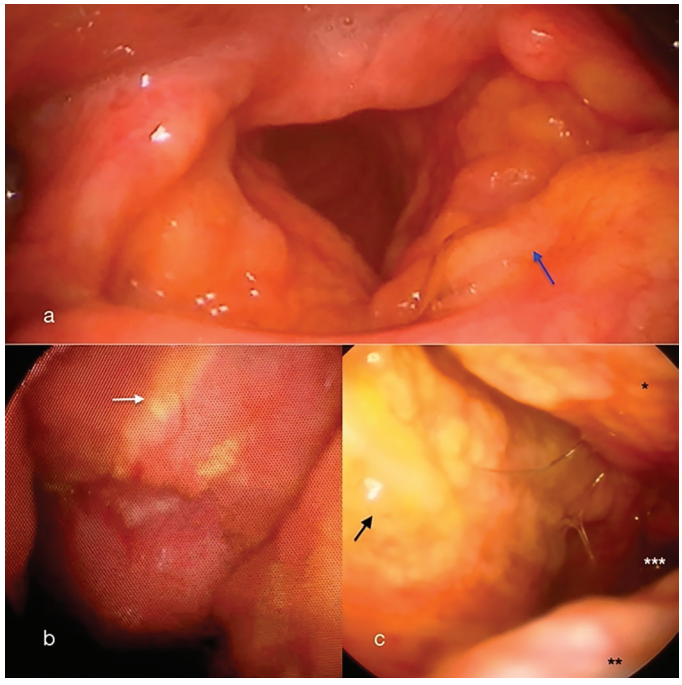

Figure 1. a) Localized amyloid appearance in the larynx at the initial diagnosis. Blue arrow: amyloid deposits, **b)** Amyloid deposits observed in nasopharynx. Five years after initial diagnosis. White arrow: Amyloid deposits in the nasopharynx; **c)** Amyloid deposits observed in the left nasal cavity 11 years after initial diagnosis.
*: Middle turbinate, **: Inferior turbinate, ***: Choana. Black arrow: amyloid deposits on the posterior part of the nasal septum

After 5 years, the patient returned with right-sided hearing loss and a sensation of a foreign body in the pharynx. Examination revealed right-sided otitis media with effusion and a clustered, orange-colored mass around the right torus tubarius and midline in the nasopharynx as shown in Figure 1b, resembling the mucosal features of the previous laryngeal lesion. Amyloid deposits were noted in the ventricular bands and epiglottis with slight progression; though there was no evidence of airway obstruction, as also demonstrated on magnetic resonance imaging (MRI), as shown in Figure 3a. Contrast-enhanced MRI demonstrated soft tissue hypertrophy narrowing the right posterior nasopharynx, a finding that becomes more evident when compared with the patient's initial MRI obtained at presentation (Figure 4a vs. Figure 4b), along with loss of aeration in the right middle ear and mastoid cells. A tympanostomy tube was placed in the right ear. A conservative surgical excision of the mass obstructing the torus tubarius was performed. Similarly, Congo red staining was positive, confirming amyloidosis in the nasopharynx. The patient experienced relief of hearing loss postoperatively. No sign of systemic amyloidosis was detected upon re-evaluation. The patient subsequently missed follow-up due to the coronavirus disease-2019 pandemic and absence of symptoms.

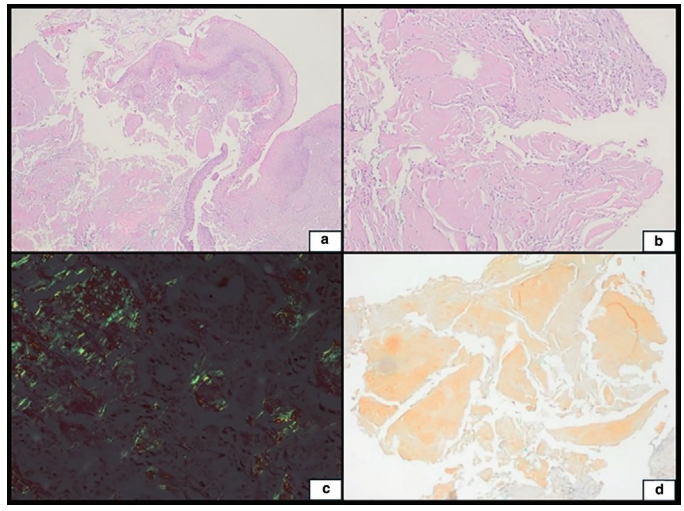

Figure 2. Amyloid deposition in larynx biopsy at the patient's initial presentation. **a)** H&E staining X100, **b)** H&E staining X200, **c)** Congo-red staining x200, **d)** Amyloid AA staining X200
H&E: Hematoxylin & eosin

Eleven years after the initial presentation, the patient returned with nasal obstruction and right-sided hearing loss. Endoscopic examination revealed a nasopharyngeal mass originating from the posterior wall that caused significant anterior narrowing, along with non-bulging mucosal amyloid deposits on the posterior one-third of the nasal septum as shown in Figure 1c. Laryngeal examination showed amyloid deposits extending over the left arytenoid and the laryngeal surface of the epiglottis without airway obstruction. These findings were also visualized on MRI, as demonstrated in Figure 3b. Laryngeal deposits were stable and non-obstructive; therefore, no surgical intervention was performed for the laryngeal component. Surgical excision of the nasopharyngeal and nasal cavity lesions performed to relieve the nasal obstruction. Amyloid deposits were detected via Congo red and amyloid AA staining in the biopsy, as shown in Figure 5. Systemic amyloidosis evaluation was again negative. The patient had an uneventful postoperative recovery and remains under surveillance. The patient reported being satisfied with the surgical results, noting significant improvements in both breathing and hearing. Written informed consent for publication was obtained from the patient for the data included in this case report.

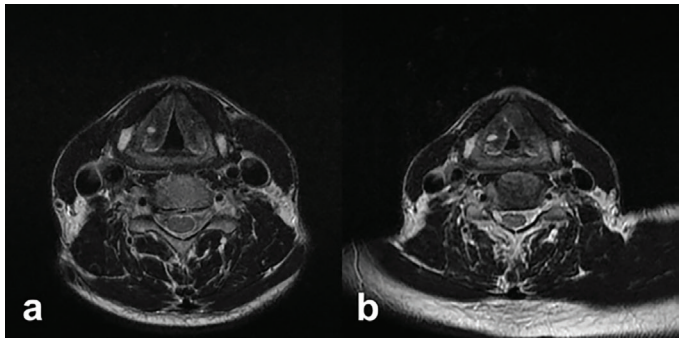

Figure 3. Axial T2-weighted MRI sections of the patient. Although an increase in amyloid deposits was observed during follow-up, no significant airway narrowing was noted. **a)** MRI obtained in initial diagnosis, **b)** MRI obtained in 11 years after initial diagnosis
MRI: Magnetic resonance imaging

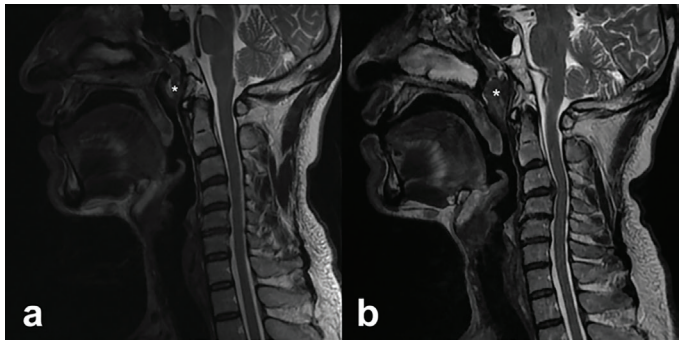

Figure 4. Sagittal T2-weighted MRI images of the patient show soft tissue enlargement in the nasopharynx. **a)** MRI obtained in initial diagnosis, **b)** MRI obtained in 5 years after initial diagnosis.
*: Soft tissue in the nasopharynx, MRI: Magnetic resonance imaging

Discussion

Localized amyloidosis is a benign disease that presents with tumor-like amyloid deposits that may cause site-specific symptoms. Although amyloid deposition in the upper aerodigestive system is rare, the most commonly affected sites include the larynx (60%; the most frequently involved site), the oropharynx (23%), the trachea (9%), and the orbit (4%) (1). Nasal cavity and nasopharyngeal involvement (approximately 3%) represent uncommon manifestations. Sakagiannis et al. (2) reported only 32 patients with nasopharyngeal amyloidosis between 1935 and 2017, while Naidoo et al. (3) found merely 15 patients with sinonasal amyloidosis from 1946 to 2012. In recent decades, case presentations of laryngeal and nasopharyngeal amyloidosis have increased, possibly related to the improvement in diagnostic capabilities through routine endoscopic head and neck examinations and an increase in clinical awareness (4-6).

This case report obviously illustrates the segmental progression of localized amyloidosis in the upper aerodigestive system in the long-term. Initially, the amyloid lesions manifested in the larynx subsequently developed in the nasopharynx after a 5-year interval and ultimately involved the nasal cavity after 11 years of follow-up. This stepwise anatomical progression challenges the conventional view of localized amyloidosis as a static condition, demonstrating its potential for clinically significant advancement along contiguous upper aerodigestive tract mucosa. Although most reported cases generally remain confined to a single anatomical site, emerging evidence of multifocal mucosal involvement corroborates this progressive disease pattern (5,6). In addition, it is important to remember that localized

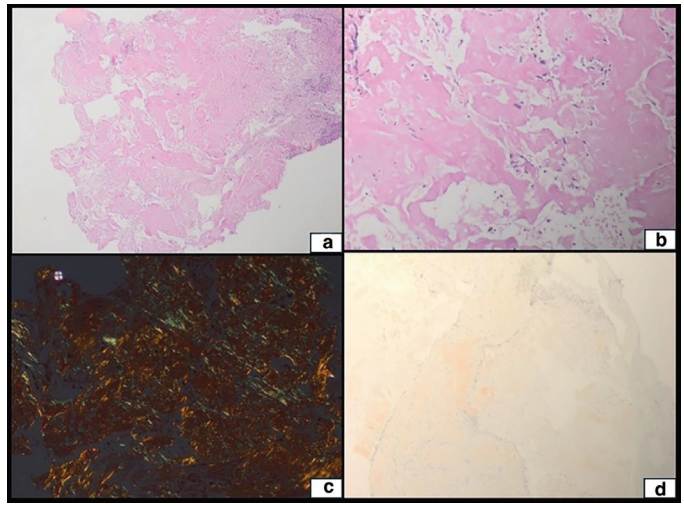

Figure 5. Amyloid deposits in nasopharynx biopsy. **a)** H&E staining X100, **b)** H&E staining X400, **c)** Congo-red staining x200, **d)** Amyloid AA staining X200
H&E: Hematoxylin & eosin

amyloidosis in the upper airway may mimic malignancy, and histopathological confirmation is essential for diagnosis. Amyloid deposits may lead to a variety of symptoms such as hearing loss, epistaxis, dysphagia, globus, and nasal and airway obstruction according to the involved region/s.

While most patients with amyloid deposits involving the upper aerodigestive system have localized disease, systemic or secondary amyloidosis must be excluded both at initial diagnosis and during follow-up particularly when disease progression occurs. Comprehensive evaluation should include serum and urine protein electrophoresis, serum free light chain analysis, renal and liver function tests, and 24-hour urine protein quantification, essential investigations for excluding AL-type amyloidosis (4,7). In our case, systemic evaluation was conducted regularly, and the patient was diagnosed with localized amyloidosis of the larynx, the nasopharynx, and the nasal cavity without evidence of systemic involvement. Systemic surveillance included annual serum and urine immunofixation, renal and hepatic function tests, and 24-hour urine protein quantification to exclude systemic AL amyloidosis.

The mainstay of treatment for systemic amyloidosis is chemotherapy (8). For localized disease, surgical intervention remains the mainstay of therapy (9). The surgical approach should be individualized, ranging from conservative surgeries to more extensive radical resections. Conservative surgeries are generally preferred to relieve symptoms while preserving organ functions. When addressing airway patency, voice quality, or Eustachian tube dysfunction, meticulous tissue preservation is paramount. Radical procedures may be considered for selected patients with recurrent disease following conservative surgeries (1).

Study Limitations

A strength of this case is the extensive long-term follow-up that demonstrates the natural history of progressive localized amyloidosis. The main limitation, however, is the inability to perform serial molecular subtyping of the amyloid deposits, which could have provided additional insights into the evolution of the disease. In the presented case, conservative surgical approaches have effectively achieved symptomatic relief while maintaining anatomical integrity.

Conclusion

To the best of our knowledge, this case represents the first documented example of localized amyloidosis showing a decade-long, stepwise progression from the larynx to the nasopharynx and, subsequently, to the nasal cavity. This rare pattern emphasizes three key clinical points: (i) localized amyloidosis may exhibit progressive, multifocal mucosal spread, (ii) thorough and repeated systemic evaluation is essential to confidently exclude systemic disease throughout follow-up, (iii) conservative surgical approaches can effectively provide durable symptomatic relief while preserving anatomical and functional integrity. Long-term surveillance remains fundamental in managing this uncommon condition.

Ethics

Informed Consent: Written informed consent for publication was obtained from the patient for the data included in this case report.

Footnotes

Authorship Contributions

Concept: U.K., G.E., Design: G.E., Data Collection and/or Processing: U.K., S.E.A., A.T., Analysis or Interpretation: A.T., U.U., G.E., Literature Search: U.K., S.E.A., Writing: U.K., G.E.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: The authors declare that this study has received no financial support.

Main Points

- Localized amyloidosis of the upper aerodigestive tract is rare and may mimic malignancy.
- This case demonstrates sequential progression from larynx to nasopharynx and nasal cavity over 11 years.
- Conservative surgical excision provided effective symptomatic relief while preserving function.
- Long-term surveillance is essential due to the risk of multifocal progression despite localized disease.

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